Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Casgevy 4-13 × 10^6 cells/mL dispersion for infusion

(exagamglogene autotemcel)

PLGB 22352/0019

Vertex Pharmaceuticals (Europe) Limited

LAY SUMMARY

Casgevy 4-13 × 10^6 cells/mL dispersion for infusion
exagamglogene autotemcel

This is a summary of the Public Assessment Report (PAR) for Casgevy 4-13 × 10^6 cells/mL dispersion for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Casgevy in this lay summary for ease of reading.

For practical information about using Casgevy, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Casgevy and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical, and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Casgevy is a cell therapy, which is given to an individual once only as a blood stem cell transplant. It is made from the patient's own blood stem cells and is made specifically for the individual patient. Blood stem cells can turn into other blood cells including red cells, white cells and platelets. Cells are taken from the patient, then are modified and given back to the patient as a cell-based transplant in a hospital.

Casgevy is used to treat:

- **People aged 12 years and older with beta-thalassemia** who need regular blood transfusions. People with beta-thalassemia do not have enough haemoglobin, a protein in the blood that carries oxygen throughout the body. This causes anaemia, and they need regular blood transfusions.

- **People aged 12 years and older with sickle cell disease** who have frequent painful crises (called vaso-occlusive crises). Patients with sickle cell disease have a different form of haemoglobin from other people (sickle cell haemoglobin). It produces abnormal sickle-shaped red blood cells, and these can lead to the blockage of blood vessels, causing vaso-occlusive crises.

How does Casgevy work?
Casgevy works by increasing the production of a special type of haemoglobin called Haemoglobin F (fetal haemoglobin). Having more Haemoglobin F increases haemoglobin levels in the body and improves the production and function of red blood cells. This can mean that people with beta-thalassemia may not need blood transfusions. For people with sickle cell disease, it can also reduce or even stop their vaso-occlusive crises.

How is Casgevy used?
The pharmaceutical form of this medicine is a dispersion for infusion and the route of administration is by slow infusion into a vein (intravenous infusion).

Casgevy is a once-only treatment. The individual patient will not be given Casgevy again.

Casgevy can only be given in an authorised treatment centre (specialised hospital) by doctors with experience in stem cell transplants, and in the treatment of patients with blood disorders such as beta-thalassemia and sickle cell disease.

STEP 1: Before Casgevy treatment, a doctor will give the patient a **mobilisation medicine**. This medicine moves blood stem cells from the bone marrow into the blood stream. The cells are then collected in a machine that separates the different blood cells (this is called apheresis). The entire step may happen more than once, and each time, it takes about one week.

'Rescue cells' are also collected and stored at the hospital. These are the patient's existing blood stem cells and are kept untreated just in case there is a problem in the treatment process.

STEP 2: The patient's blood stem cells will be sent to the manufacturing site where they are **used to make Casgevy**. It may take up to 6 months from the time the patient's cells are collected to manufacture and test Casgevy before it is sent back to the doctor.

STEP 3: Shortly before the stem cell transplant, the doctor will give the patient a **conditioning medicine** for a few days in hospital. This will prepare the patient for treatment by clearing cells from the bone marrow, so they can be replaced with the modified cells in Casgevy. After this medicine is given, the blood cell levels will fall to very low levels. The patient will stay in the hospital at this point and remain in the hospital until after the Casgevy infusion.

STEP 4: One or more vials of Casgevy will be given into a vein (intravenous infusion) over a few hours.

After the Casgevy infusion, the patient will stay in hospital so that the healthcare team can closely monitor the patient's recovery. The length of time for sufficient recovery can vary. A doctor on the team will decide when the patient can go home.

For further information on how Casgevy is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Casgevy have been shown in studies?

β-thalassemia study
Study 111 is an ongoing open-label, multi-centre, single-arm study to evaluate the safety and efficacy of Casgevy in adult and adolescent patients with transfusion-dependent β-thalassemia. After completion of 24 months of follow up in study 111, patients were invited to enrol in study 131, an ongoing long-term safety and efficacy study.

Efficacy results – β-thalassemia
At the time of the analysis used to support the conditional marketing authorisation, 54 patients had been administered Casgevy. Forty-two patients were eligible for the primary efficacy analysis. The median total duration of follow up was 22.8 months from the time of Casgevy infusion.

39 of 42 patients achieved the primary outcome by maintaining a sufficient level of haemoglobin in the blood (Hb ≥9 g/dL) without requiring red blood cell transfusions for at least 12 consecutive months any time after Casgevy infusion.

Three patients did not achieve the primary outcome. These patients had reductions in annualised red blood cell transfusion frequency requirements.

Twenty-three patients have completed study 111 and enrolled into a long-term follow up study.

Sickle Cell Disease
Study 121 is an ongoing open-label, multicentre, single-arm study to evaluate the safety and efficacy of Casgevy in adult and adolescent patients with sickle cell disease. After completion of 24 months of follow-up in study 121, patients were invited to enrol in study 131, an ongoing long-term safety and efficacy study.

Efficacy results – Sickle Cell Disease
At the time of the analysis used to support the conditional marketing authorisation 43 patients had been administered Casgevy. Twenty-nine patients were eligible for the primary efficacy analysis. The median total duration of follow up was 17.5 months from the time of Casgevy infusion.

28 of 29 patients achieved the primary outcome by not experiencing any severe vaso-occlusive crisis (a hallmark of sickle cell disease) for at least 12 consecutive months after Casgevy infusion.

Thirteen patients had completed study 121 and enrolled into a long-term follow-up study.

What are the possible side effects of Casgevy?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.ukor search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Casgevy approved?
Casgevy has been authorised with a conditional marketing authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

Casgevy has also been authorised as a GB Orphan medicine. Orphan medicines are intended for use against rare conditions that are life-threatening or chronically debilitating. To qualify as an orphan medicine, certain criteria, for example concerning the rarity of the disease and the lack of currently available treatments, must be fulfilled.

What measures are being taken to ensure the safe and effective use of Casgevy?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Casgevy. The RMP details the important risks of Casgevy, how these risks can be minimised, any uncertainties about Casgevy (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Casgevy:

Important identified risks	• Longer time to platelet engraftment
Important potential risks	• Neutrophil engraftment failure • Gene editing-related oncogenesis • Medication error due to Casgevy storage and administration
Missing information	• Long-term safety and efficacy • Pregnancy and lactation • Use in patients >35 years of age

The MAH will provide a handling and administration guide, a guide for patients/carers, and a patient alert card.

The MAH will provide final follow up data from the main studies, and carry out studies to collect more information on the long-term safety of Casgevy.

For further information refer to part IV.6 of this report.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Casgevy are continuously monitored and

reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Casgevy
A marketing authorisation application for Casgevy was received on 29 December 2022, and a marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 15 November 2023.

Patient involvement activities
In pursuit of the Agency's commitment to developing its involvement of patients early in the licensing pathway, we wanted to hear the experiences of patients living with sickle cell and transfusion-dependent β-thalassemia. This was to help our assessors better understand the condition and thereby inform their risk benefit assessment as part of the approval process.

The Agency worked with established patient groups to help recruit patient representatives who between them could demonstrate a diverse range of lived experience of both sickle cell and transfusion-dependent β-thalassemia, including the use of different treatments.

Q&A sessions were held with patients; overall, patients took a positive attitude towards the prospect of gene therapy for sickle cell disease and transfusion-dependent β-thalassemia.

Cell mobilisation steps for healthcare professionals
The SmPC includes an instruction to refer to this GB Public Assessment Report for details of cell mobilisation, apheresis, and myeloablative conditioning used in the clinical studies for Casgevy. This information is detailed on pages 46-51 (transfusion-dependent β-thalassemia) and 94-98 (sickle cell disease) of this report.

In March 2023 minor update was made to clarify the use of plerixafor in the cell mobilsiaiton steps for the TDT indication.

The full PAR for Casgevy follows this summary.

This summary was last updated in March 2024.

TABLE OF CONTENTS

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) has authorised a conditional marketing authorisation for Casgevy 4-13× 10^6 cells/mL dispersion for infusion (PLGB 22352/0019).

The product is approved for the following indications:

Transfusion-dependent β-thalassemia
Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

Sickle cell disease
Casgevy is indicated for the treatment of sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype, for whom haematopoeitic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

Mechanism of action
Casgevy is a cellular therapy consisting of autologous $CD34^+$ human haematopoietic stem and progenitor cells edited by CRISPR/Cas9-technology. The guide RNA enables CRISPR/Cas9 to make a precise DNA double-strand break at the critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the *BCL11A* gene.

No off-target editing has been observed based on *in vitro* studies with Casgevy manufactured using either healthy donor or patient cells. As a result of the editing, GATA1 binding is irreversibly disrupted and BCL11A expression reduced. Reduced BCL11A expression results in an increase in γ-globin expression and fetal haemoglobin protein production in erythroid cells, addressing the absent globin in transfusion-dependent β-thalassemia and the aberrant globin in sickle cell disease, which are the underlying causes of disease. In patients with transfusion-dependent β-thalassemia, γ-globin production corrects the α-globin to non-α-globin imbalance thereby reducing ineffective erythropoiesis and haemolysis and increasing total haemoglobin levels, eliminating the dependence on regular red blood cell transfusions.

In patients with severe sickle cell disease, fetal haemoglobin expression reduces intracellular haemoglobin S concentration, preventing the red blood cells from sickling, thereby eliminating vaso-occlusive crises. Following successful engraftment, the effects of Casgevy are expected to be lifelong.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full -dossier application. Where appropriate, non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

Casgevy has been authorised as a conditional marketing authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Casgevy. The CMA for Casgevy, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

This application was evaluated for fulfilment of orphan designation criteria and was examined by the Commission on Human Medicines (CHM) in discussions that took place in April and October 2023. It was concluded that fulfilment of the criteria for approval as an orphan medicinal product was satisfactorily demonstrated for both indications. Please see Annex 1 and Annex 2 for the approval summary of each orphan indication.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100266-PIP01-21 (treatment of sickle cell disease) MHRA-100267-PIP01-21(treatment of beta-thalassemia intermedia and major).

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 27 April 2023, in relation to information concerning quality, non-clinical, clinical & RMP aspects of the dossier and again on 26 October 2023. Following the provision of additional data and information, the CHM were reassured on the quality, safety, and efficacy of the product.

A marketing authorisation application for Casgevy was received on 29 December 2022, and a marketing authorisation was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 15 November 2023.

II QUALITY ASPECTS

II.1 Introduction

What Casgevy contains

Each mL of Casgevy contains 4-13 × 10^6 cells (blood stem cells). The other ingredients are a solution used to preserve frozen cells, which contains sodium, dimethyl sulfoxide (DMSO) and dextran 40.

What Casgevy looks like and contents of the pack

Casgevy is a semi-transparent dispersion for infusion. Casgevy is supplied in vials containing 1.5 mL to 20 mL. One or more vials are packed in a carton. One carton may contain up to 9 vials. The dose for a specific patient may consist of multiple vials and cartons.

II.2 ACTIVE SUBSTANCE

The active substance of Casgevy is a genetically modified autologous $CD34^+$ cell enriched population that contains human haematopoietic stem and progenitor cells edited *ex vivo* by CRISPR/Cas9 at the erythroid-specific enhancer region of the *BCL11A* gene.

1. **rINN: Exagamglogene autotemcel**

Chemical Name: Autologous peripheral blood-derived $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) modified by CRISPR- Cas9- mediated gene editing using SPY 101 guide RNA.

Description of Casgevy

Casgevy contains a genetically modified cellular therapy (Ex-vivo gene therapy) consisting of autologous $CD34^+$ human hematopoietic stem and progenitor cells (hHSPCs)s edited by CRISPR-Cas9 technology. The guide RNA enables CRISPR-Cas9 to make a precise DNA double stranded break at the critical transcription factor binding site (GATA1) in the erythroid specific enhancer region of the BCL11A gene. The resulting insertions and deletions generated during nonhomologous end joining mediated repair of the cut site permanently disrupt GATA1 binding and reduce BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and fetal haemoglobin (HbF) protein production in erythroid cells, addressing the underlying cause of disease and resulting in a one-time functional cure.

Figure 1 provides an overview of critical regions of exa-cel including the GATA1 binding site and DNA cut site by SPY101 performed by exa-cel.

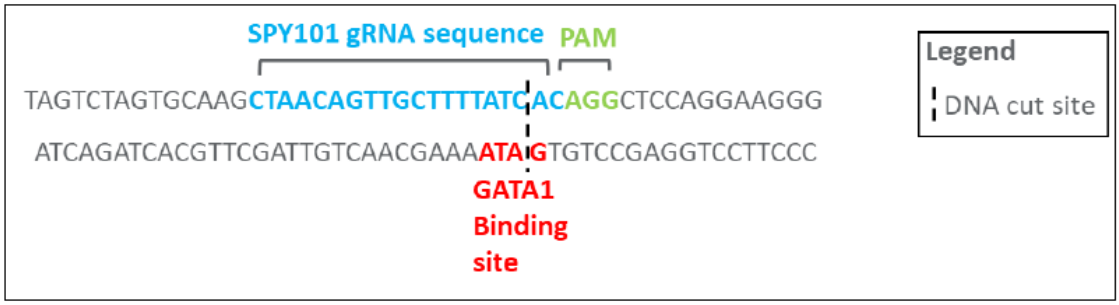


Figure 1: Overview of Critical regions of Exa-cel

Casgevy manufacture

Casgevy (exa-cel) manufacture begins with a portion of the recipients white blood cells, obtained by apheresis. $CD34^+$ cells are selected from the leukopak at the manufacturing site and gene-edited. To edit the cells a complex of SPY101 (specific guide RNA oligonucleotide) and Cas9 (nuclease protein) are introduced into the cells by electroporation. Once inside the cells, the SPY101/Cas9 ribonucleoprotein -RNP- complex migrates to and edits DNA at the desired locus. Following electroporation, the cells are cultured for a short period, pooled, harvested, formulated in CryoStor CS5 (excipient containing 5% DMSO), filled into 20 ml cryovials and stored at ≤-135°C before frozen shipment to the clinical site. The manufacture is a continuous process, with no separate drug substance step, although for regulatory purposes assignment of a drug substance is required (harvested cells post-electroporation). All subsequent steps constitute drug product. Drug product is the frozen vial containing edited cells. The manufacturing process is described in sufficient detail and suitably controlled.

There are three starting materials involved in the manufacture of Casgevy: the patient's leukopak and the gene-editing reagents SPY101 and Cas9. The leukopak is collected at authorised treatment centers and conforms to the requirements of The Human Tissue (Quality and Safety for Human application) Regulations 2007 and current requirements for apheresis collection. Appropriate testing is performed and the cellular material is shipped under validated conditions to the manufacturing site. The suitability of SPY101 and Cas9 for manufacture of Casgevy has been demonstrated through separate sections.

Cas9 is a recombinant protein produced in and purified from *E. coli.* SPY101 is a 100 nucleotide chemically synthesised RNA molecule. In both cases the suitability of these starting materials for the manufacture of Casgevy has been demonstrated.

All other raw materials and components used in the manufacturing process are considered suitable.

The manufacturing process development has been adequately described as have the changes introduced between different process versions (comparability). Process validation is also demonstrated.

Casgevy has been adequately characterised such that sufficient release specifications have been established to ensure product quality. Analytical methods have been appropriated validated. Batch analysis data are provided and are acceptable.

Both drug substance and drug product containers conform to current requirements. Validated transport of Casgevy to patient administration sites is demonstrated.

All excipients have been shown to be suitably for their intended use. No excipients of animal origin are used in the final products.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, the following are acceptable:

Shelf life:
Frozen: 2 years at ≤ -135 °C.
Once thawed: 20 minutes at room temperature (20 °C – 25 °C).

Storage conditions:
Casgevy must be stored in the vapour phase of liquid nitrogen at ≤ -135 °C and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration.

Thaw one vial at a time. Do not thaw until ready to infuse. Do not re-freeze after thawing.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This product falls within the definition of a genetically modified organism (GMO) as per the "contained use" Directive 2009/41/EC and "deliberate release" Directive 2001/18/EC, since the $CD34^+$ hHSPCs contained in CTX001 are cellular entities capable of transferring genetic material, altered in a way that does not occur naturally by mating and/or natural recombination.

Conventional mutagenicity, carcinogenicity and reproductive and developmental toxicity studies have not been conducted. No studies on the effects of Casgevy on fertility have been conducted.

The biodistribution and persistence as well as toxicity and tumorigenicity of Casgevy were evaluated in two studies in sub-lethally irradiated, immunodeficient mice. These studies did not identify evidence of aberrant migration, accumulation, or persistence of $CD34^+$ human haematopoietic stem and progenitor cells in non-target tissues and results were comparable between edited and unedited $CD34^+$ cells. Persistence of edited cells in haematopoietic tissues was confirmed, with comparable overall percent editing of infused $CD34^+$ cells throughout the 20-week duration of study. Treatment with edited $CD34^+$ cells revealed no evidence of target organ toxicity or tumourigenicity.

In vitro studies with exagamglogene autotemcel manufactured from healthy donors and patients showed no evidence of off-target editing. In studies with edited $CD34^+$ cells obtained from healthy donors, no translocations were detected by either karyotyping or sequencing methods.

Compliance with Good Laboratory Practice (GLP) is expected for pivotal safety studies which in this file is the following study: (1) 1016-2465 [Toxicity and tumorigenicity study in NOD/SCID/IL2Rγnull (NSG) mice]. The MAH also conducted a biodistribution study in compliance with GLP, study 1016-2475 [A pivotal biodistribution and persistence study]. In addition, normally, studies into genotoxic potential would be in compliance with GLP. However, in this file, the genotoxicity studies (CTxSR15-24, R263, R264 and RES-IND041 and 042) did not apply the standard methodology for such studies as might be applied for a chemical-based drug, as this is not applicable. The MAH conducted a series of genotoxicity

studies relevant to characterising potential genotoxicity arising from the primary mode of action of exa-cel. These studies are not in compliance with GLP and this can be accepted. Overall, there are no concerns with GLP compliance.

III.2 Pharmacology

Exa-cel is a gene therapy product containing autologous $CD34^+$ cells edited by CRISPR/Cas9 at the erythroid-specific enhancer region of the BCL11A gene aimed at lowering the expression of BCL11A in erythroid cells. Such lowering of BCL11A is expected to result in greater level of fetal haemoglobin, HbF, containing two γ, as opposed to two β subunits in adult haemoglobin, which is known to alleviate symptoms of sickle cells disease and β-thalassemia.

The product contains a guide RNA, SPY101, complexed with Cas9 nuclease, thereby generating the SPY101-RNP complex, which is electroporated into $CD34^+$ cells to edit the BCL11A erythroid enhancer locus.

BCL11A gene

The MAH was asked to discuss what effects in non-haematological systems (e.g., bone, brain or pancreas) might be affected by knocking out the BCL11A gene, notwithstanding that this product is edited ex vivo in $CD34^+$ haematopoietic stem cells. The MAH was also asked to include a summary of evidence on other roles of the BCL11A gene.

Exa-cel is ex vivo edited haematopoietic stem and progenitor cells (HSPC), where the editing components (SPY101-RNP) are present transiently during ex vivo culture and no residual gene editing activity is present in cells delivered back into the body. Moreover, the exa-cel target is an erythroid specific enhancer with no associations outside of the erythroid lineage. For these reasons, gene editing of cells outside the haematopoietic system is not anticipated.

Genetic studies cannot distinguish effects on development (which would not be relevant to modification after birth) to effects later in life (which, in principle, could be relevant to post-natal modification of *BCL11A*). For example, heterozygous mutations in *BCL11A* (outside the erythroid specific enhancer) have been associated with neurodevelopmental defects such as intellectual disability, cognitive impairment, and autism spectrum disorders.[1] However, these are developmental defects and there is no evidence that modification of *BLC11A* after embryonic and fetal development would have effect in the nervous system. Genetic variants of *BCL11A* outside the erythroid specific enhancer have been identified as type 2 diabetes risk alleles.[2] These too may be developmental in nature and there is no human evidence for an impact of modification of BCL11A expression post-natally on diabetes risk. While *BCL11A* germline knockout mice (not involving the erythroid specific enhancer) have effects on skin,[3] conditional ablation of *BCL11A* in adult mice has a different effect of keratinocyte proliferation and rapid closure of excisional wounds.[4] Thus, the effect of modification later in life may have different effects than those in the germline.

In conclusion, exa-cel is manufactured during ex-vivo HSPC culture with transient exposure of gene editing components (SPY101-RNP) in the HSPCs that result in edits at an erythroid specific enhancer. There is no risk of gene editing in other cell types, nor any relevance given the red cell specificity of the enhancer. While *BCL11A* has genetic associations with other

traits, these fall outside the erythroid specific enhancer and may be developmental in nature without relevance post-natally.

References:

1 Simon R, Wiegreffe C, Britsch S. Bcl11 transcription factors regulate cortical development and function. Front Mol Neurosci. 2020;13:51.
2 Simonis-Bik AM, Nijpels G, van Haeften TW, Houwing-Duistermaat JJ, Boomsma DI, Reiling E, et al. Gene variants in the novel type 2 diabetes loci CDC123/CAMK1D, THADA, ADAMTS9, BCL11A, and MTNR1B affect different aspects of pancreatic beta-cell function. Diabetes. 2010;59(1):293-301.
3 Li S, Teegarden A, Bauer EM, Choi J, Messaddeq N, Hendrix DA, et al. Transcription factor CTIP1/ BCL11A regulates epidermal differentiation and lipid metabolism during skin development. Sci Rep. 2017;7(1):13427.
4 Bhattacharya N, Indra AK, Ganguli-Indra G. Selective ablation of BCL11A in epidermal keratinocytes alters skin homeostasis and accelerates excisional wound healing in vivo. Cells. 2022;11(13):2106.

The MAH conducted a range of *in vitro* and *in vivo* studies to demonstrate mechanism of action and efficacy of exa-cel in increasing the level of HbF in $CD34^+$ hHSPC.

The *in vitro* studies showed that, in healthy $CD34^+$ hHSPC donors, SPY101-RNP generated high allelic editing frequencies (mean editing frequency 80%, SD ± 6%, n=10) at the target erythroid-lineage specific enhancer region of the BCL11A gene. Also, the treatment with SPY101-RNP showed a similar editing rate across all subpopulations within the $CD34^+$ hHSPCs, including long-term repopulating HSCs. The SPY101-RNP editing in all tested donors was associated with upregulation of γ-globin mRNA and HbF protein; increases in γ-globin transcript correlated with the number of alleles edited, with bi-allelic edited cells having the highest induction, followed by mono-allelic edited and unedited cells, respectively.

Overall, similar allelic editing frequencies, γ-globin mRNA expression levels, and HbF protein upregulation was observed in edited $CD34^+$ hHSPCs: i) manufactured at research and clinical scale (process development and process qualification runs), ii) sourced from single agent mobilisation (plerixafor only) and dual-agent mobilisation (G-CSF and plerixafor), and iii) sourced from SCD and β-thalassemia patient-derived samples. It is noted that the expression level for γ-globin in cells derived from healthy donors and cultured in bulk appears highly variable. The variability is likely due to small number of samples, and should be taken into account when assessing efficacy of the editing in patient cells. However, the increase in protein expression seems higher than in the controls, and similar to the positive control, therefore this is not overly concerning. Also, TIDE analysis results over time indicated that editing effects remain constant throughout the 15-day erythroid differentiation process, suggesting the absence of either positive or negative selection of the edited cell populations, as analysed under the in *vitro* conditions.

It is noted that there was a high variability of editing frequency (42 - 88%) in both SCD patient and healthy donor non-purified peripheral blood mononuclear cell (PBMC) samples. The MAH suggests that, as these studies used patients' PBMCs and bone marrow

mononuclear cells the heterogeneity of cells within the studied cell populations included cells which may be poorly amenable to electroporation and efficient delivery of Cas9-gRNA RNP. The MAH also argues that higher editing frequency (75%) was observed in CD34+ cells purified from PBMCs from both SCD and healthy donors, and in the range seen with purified $CD34^+$ hHSPCs from mobilised blood of healthy donors. As PBMCs is comprised of cells in different stages of differentiation, with varying degrees of chromatin accessibility for CRISPR/Cas9 editing, the MAH's explanation with regards to the variability in this particular sample is considered acceptable.

It is further noted that the MAH made an indirect comparison between editing efficacy in the cGMP and research scale conditions, i.e. the editing efficacy in the manufacturing scale lots was made between the non-edited controls and edited cells, rather than between the same population of cells cultured under different, cGMP or GLP, conditions. Therefore, the direct comparison between the culture conditions was not possible for studies CTxSR-030, CTxSR-037, CTxSR-038 and CTxSR-041. Nonetheless, as the numerical results indicate an acceptable level of similarity between the efficiency outcomes measured, and as the study CTxSR-042 directly compared cells mobilised using two different mobilising agents yielding similar results, the MAH's conclusion that manufacture conditions do not negatively affect the editing efficiency is accepted.

Multilineage differentiation of SPY101-RNP edited $CD34^+$ hHSPCs was confirmed in both *in vitro* and *in vivo* studies. No change in erythroid differentiation dynamics or enucleation post-editing compared to control samples was observed, as assessed by cell surface protein expression. The potential for exa-cel to generate myeloid and erythroid progenitor colonies was comparable to control $CD34^+$ hHSPCs in colony-forming assays.

In vivo non-clinical engraftment studies were performed to test exa-cel and several control samples in the NSG xenotransplant mouse model. In different studies, successful long-term engraftment of exa-cel was observed at 16 and 20 weeks post-transplant, in blood, bone marrow and spleen. The MAH concluded that the proportion of the various haematopoietic lineages derived from the transplanted edited hHSPCs was not affected by the editing process. The following additional results are noted:

- At Week 16, the engrafted $hCD45RA^+$ cells were mainly found in the bone marrow. A smaller proportion was found in the spleen and minimally in the whole blood.
- The $hCD45RA^+$ cells detected at Week 16 necropsy were predominantly B cells among the $hCD45RA^+$ cells and this is in agreement with published data in the literature for the NSG mouse model and the determination of the B cell component within the engrafted $hCD45^+$population (Shultz et al., 2005; Giassi et al., 2008; Ishikawa et al., 2005).
- Inter-donor variation for the different cells population was observed. Although it is not always observed within the same donor, untreated $CD34^+$ cells, overall, exhibited higher absolute counts and concentrations of $hCD45RA^+$ cell populations in all haematopoietic tissues tested, suggesting a potentially deleterious effect of treatment on engraftment. A similar treatment effect was observed for the lineage analyses in the whole blood and bone marrow between untreated and mock- or EGFP-, Cas9-gRNA RNP-edited groups. The lowest absolute counts and concentrations of $hCD45RA^+$ cell populations were found in the SPY101-edited group. Although the MAH suggests that the engraftment between the treated groups was similar, indicating

that the cells treated with Cas9 $^+$ target specific gRNA were not different from mock-electroporated cells or electroporated with a control (non-human GFP) gRNA, and therefore that that the proportion of the various haematopoietic lineages derived from the transplanted edited hHSPCs was not affected by the editing process, such a conclusion is not considered to be robust, based on the available statistical analysis. The statistical analysis compared each treated group with the non-treated cells, rather than the treated groups being compared to one another. Nonetheless, given that numerical differences between the treated groups appear small, and that the therapeutic success of exa-cel will depend on the sufficient amount of γ-globin being produced in the edited cells, the presented data demonstrate the efficacy of exa-cell to an acceptable degree.

Karyotyping
The MAH stated that karyotyping in healthy donor $CD34^+$ haematopoietic stem and progenitor cells (HSPCs) is adequate to assess for chromosomal abnormalities. Chromosomal abnormalities could be generated by on-target editing, off-target editing, or the manipulation of the cells ex vivo. Detection of the potential for chromosomal abnormalities from on-target editing and ex vivo manipulation was addressed using healthy donor cells. This is because there is no basis to hypothesise that the genomic variants that cause sickle cell disease and transfusion-dependent beta-thalassemia or the disease state of the patient would influence the karyotyping result. Off-target editing would need to occur to potentially generate chromosomal abnormalities. The potential for off-target editing in healthy donor cells and patient cells was comprehensively evaluated in the nonclinical off-target data package. This extensive analysis is more sensitive (detection down to 0.2%) compared to karyotyping. This argument was accepted.

Concerning secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug-drug interaction studies, these are agreed as either not needed or as being adequately addressed elsewhere (e.g. in the general toxicity evaluations).

In conclusion, the MAH demonstrated the primary mechanism of action of exa-cel to a satisfactory level.

III.3 Pharmacokinetics
Flow cytometry methods were used to determine engraftment of $CD34^+$ hHSPCs in mouse tissues with use of markers of common leukocyte antigens (hCD45RA, hCD45 and mCD45). Quantitative polymerase chain reaction (qPCR) was applied to detect human cells in mouse tissues. Amplicon next-generation sequencing (NGS) was performed on DNA from $CD34^+$ hHSPCs prior to transplant and on tissues from treated mice to establish overall percent editing and to characterise the indel spectrum. Some samples were analysed by a qualified immunohistochemistry (IHC) method for detecting hCD45-positive cells in mouse tissues. The suitability of methods applied was accepted.

In a study over 20 weeks, the biodistribution and persistence study of exa-cel was studied and compared with these profiles of unedited cells. The methodology used irradiated immunodeficient mice to allow engraftment of the human cells given intravenously on one occasion. This use or irradiation does not reflect the clinical use of the product - human

patients will be treated with busulfan – but the aim is the same and the use of irradiation of mice is common in this type of study.

In analyses of engraftment, tissues were categorised as either on-target (whole blood, bone marrow and spleen) or off-target (e.g. brain, heart and lungs): off-target tissues included the reproductive organs (ovary and uterus, and prostate and testes).

There was no difference, overall, between edited cells and unedited cells and exa-cel engrafted into its target cells (whole blood, spleen and bone marrow). There was a reduction in % chimerism between weeks 8 and 20 over the study but it is probably not possible to study whether this fall continues beyond the 20 week period, due to the condition of these mice: any longer follow up to explore further reduction in chimerism will likely be compromised by limitations on mouse survival.

Exa-cel-derived (including progeny cells) persisted in the haematopoietic system and maintained a similar indel spectrum to input cells, indicating polyclonal haemopoiesis. This did not change over time.

Exa-cel was detectable in non-target tissues but at notably lower levels than in targeted, haematopoietic, tissues with maximal value of ~2.4% human cell chimerism in highly vascularised tissues (lung, liver, kidney). In the reproductive organs, there was <0.3% chimerism.

The absence of other studies (into absorption, metabolism, excretion and drug-drug interactions) is appropriate as these studies are not applicable to cell therapies.

Overall, the characterisation of the distribution, persistence and indel spectrum of exa-cel is considered suitable and no questions are raised.

III.4 Toxicology

Two general toxicity study reports were provided: one was a method development study using a cell line expected to result in tumour development – this was done with the intent to test whether the method could detect tumours; the other used exa-cel and assessed both toxicity and tumourigenicity in vivo.

Overall conclusions on toxicology

The general toxicity study, including assessment of potential tumour formation, did not identify toxicity of significant concern and is considered, overall, likely to be a suitable assessment of the potential general toxicity of exa-cel. The study design included assessment of expected measures (eg in-life evaluations, haematology and clinical chemistry parameters, macroscopic and microscopic observations) and no concerns were identified. There were unscheduled deaths of some mice in this study but the pattern of these does not suggest any link to exa-cel as a causative agent. In a study involving 120 immunodeficient mice, all irradiated, a small number of unscheduled deaths might be expected. The MAH assigned a no observed adverse effect level from the toxicity study of 3.33 x 10(7) cells/kg: this is higher than the clinical dose proposed (3 x 10(6) cells/kg).

In the general toxicity study, cells were sourced from 3 healthy donors and in the target tissues of bone marrow and spleen, one of these had higher human cell engraftment than the other two. With this number of samples, it is not clear whether this variation is typical, or if this is a biologically meaningful difference. Testing of cells from further donors could provide an answer to this, but it is not clear that more such testing is needed, as there seems to be no evidence in what is presented either of a related safety concern or of a concern that this variation could be linked to a lack of therapeutic response.

The study included a positive control of HL-60 cells for cell-derived tumours and this confirmed sensitivity of the method to detect tumours in some mice. These were not seen in mice given exa-cel and this is encouraging. The absence of any tumour in exa-cel-treated mice is evidence that the product is not inherently genotoxic / tumourogenic, but this study is not, on its own, sufficient evidence to support an absence of concern for a cancer arising in a treated patient.

The genotoxicity studies contribute further to this assessment. CRISPR/Cas9 genome editing consists of an RNA guide molecule that targets the gene of interest by base pairing, and Cas endonuclease, an enzyme that cleaves that targeted sequence: this generates a double stranded break (DSB) in the edited DNA. There seems to be potential for genotoxicity inherent in this action. Incorrect targeting of the host DNA sequence by CRISPR, and incomplete repair of DBSs, can result in *on-target* and *off-target* errors, including random insertions and deletions, and even large DNA defects such as chromosome shattering. The risk of exa-cel resulting in such errors was examined using a set of complementary techniques in HSPC samples from healthy donors and patients. The combined sensitivity of these methods from the published literature is ~0.12 % (i.e. demonstrating the ability to detect 1.2 erroneous events in every 1000 cells). Results from these studies in healthy donors demonstrated that SPY101-RNP editing resulted in a high precision of editing, with the overall rate of *on-target* indel formation of 88% and the majority (88.4%) of indels shorter than 30 bp in size. These results are consistent the editing efficacy demonstrated in the primary pharmacology studies. Further analysis showed that SPY101-RNP did not cause detectable *off-target* editing, whereas karyotyping analysis did not detect translocations after editing with SPY101-RNP.

The risk of *off-target* editing due to genetic variation in patient population (three SCD and three TDT patients) was addressed using a broad nomination of candidate *off-target* regions, namely a variant-aware homology search, followed by a patient-specific GUIDE-seq and ultra-deep hybrid capture sequencing to quantify indel formation in primary $CD34^+$cells from patients.

The *on-target* site editing, with median indel formation ranged from 60.8% to 71.9% in the treated samples, was similar to that in the healthy donor population (49.4% to 61.0% across four healthy donors). Across the analyses for each of the six patients, 249 *off-target* sites were identified and evaluated, with a total of four *off-target* regions demonstrated a $\geq 0.2\%$ difference between the untreated and median treated indel rate, including one region which met this threshold in two different patients. All four of the identified off-target regions were located in a small intergenic ~500-bp window of the chromosome 3 centromere (chr3:93470361-93470784), with two of the candidate cleavage sites in this centromeric window passing nominal significance ($P < 0.05$). Further manual review indicated that these

regions lacked the hallmarks of CRISPR-Cas9-induced editing. Therefore, the MAH concluded that no evidence of *off-target* editing by SPY101-RNP in either SCD or TDT patients was revealed, which is consistent with the results of studies performed in healthy donors. The MAH further concluded that these results of safety evaluation support the safety profile of exa-cel in patient population. This conclusion was accepted.

It is acknowledged that the conducted genotoxicity studies appear to convey a low risk of detrimental off-target effects or larger gene and chromosome rearrangements. Also, that recent ultra-deep sequencing to detect extremely rare mutations from off-target effects at 523 cancer-relevant genes after CRISPR/Cas9 editing in human haematopoietic cells, showed that this approach did not cause off-target effect on any of the cancer genes tested (Cromer MK et al. Nat. Commun.2022). It is important to note however, that the genome, contains billions of bases, hence the editing mistakes are still possible, even if not detected in the produced set of experiments. Also, natural genetic variation in human population represents an added level of complexity which should be taken into account, as unforeseen events may occur. Specifically, a recent computational analysis that considered single-nucleotide polymorphism (SNP) to nominate and prioritize off-target sites in the GATA1 binding motif of BCL11A (Cancellieri S et al. Nat Genetics, vol. 55. January 2023, p 34–43), identified putative off-target candidates in individuals carrying SNP alleles commonly found in African-ancestry populations (MAF 4.5%). This study demonstrated that allele-specific off-target editing risk is not equally distributed across population groups, and that, in case of BCL11A in patients with SCA, can be concentrated in patients of African ancestry where this genomic variation is most pronounced. However, based on the below reasons, it was concluded that there is no increased risk of *off-target* editing in individuals of African-ancestry and these reasons, as listed below are accepted.

- The computational nomination of off-target candidates conducted by the MAH used computational method similar to that described by Cancellieri et al.

- This nomination included the candidate off-target site overlapping sequence, rs114518452, which was the SNP identified by Cancellieri et al. as a variant of potential concern with regards to off-target effects in individuals of African ancestry;

- Further detection of off-target editing by the MAH was then performed empirically using ultra-deep hybrid capture sequencing, which provided experimental confirmation of the absence of off-target editing by exa-cel across all studies;

- The above approach was applied to samples of both healthy donors and patients with sickle cell disease and transfusion-dependent beta-thalassemia;

- The examined patient population (Study 121) was representative of the SCD population, and included 86% of subjects of Black or African American ancestry;

- And finally, any theoretical off-target editing of the putative risk sequence rs114518452 is not predicted to have any functional consequence, given that this sequence is found in an intron of a non-canonical transcript of the gene CPS1 (an enzyme involved in nitrogen metabolism primarily expressed in the liver), that the

rs114518452 variant has no known association with any trait, and that CPS1 is not an oncogene.

Reproductive and developmental toxicity studies were not conducted for exa-cel. The MAH justified this with reference to the general toxicity study in which it determined that there were no exa-cel-related microscopic changes in the reproductive organs and also in relation to the distribution study in which it determined that there was very low distribution of exa-cel to reproductive tissues. The MAH also noted that the product is autologous in nature and the editing ex vivo is of high specificity and there is no use of integrating vectors. These factors all contribute to the absence of a dedicated reproductive toxicity study being adequate for this file. Patients will have treatment with busulfan too as part of their conditioning regimen: this is to reduce the patient's granulocyte mass to allow better engraftment of exa-cel when it is given. Busulfan is a potential teratogen and will not to be used in pregnant patients in the context of use of exa-cel as there is a requirement in the proposed SmPC for a negative pregnancy test prior to initiating the conditioning treatment. There may yet be a risk to reproductive health of exa-cel, but if so, this is controlled by the proposed measures in the SmPC and a study in pregnant animals, which would again need to be immunodeficient and, likely, irradiated, is not required.

III.5 Ecotoxicity/Environmental Risk Assessment

A full Environmental Risk Assessment (ERA) was submitted with this application.

This product contains a genetically modified organism. A summary of the MAH's environmental risk assessment for Casgevy is given below.

Exa-cel $CD34^+$ hHSPCs are manufactured ex vivo by CRISPR-Cas9 editing system: the editing complex is not present in the drug product and there is no risk of editing the cells of a non-target human in the event of accidental transfer.

Assessments of biodistribution and persistence in mice demonstrated comparable engraftment in on-target tissues between exa-cel (edited) and unedited $CD34^+$ hHSPCs and did not identify evidence of unwanted migration, accumulation, or persistence in non-target tissues, nor was any toxicity identified. SPY101-RNP editing does not cause detectable off-target editing in $CD34^+$hHSPCs obtained from either healthy donors or patients. This profile indicates no special concerns.

If transferred to non-target humans, exa-cel could only permanently persist by engrafting in a bone marrow niche; this could only occur if the non-target human was HLA-compatible and had also received myeloablative conditioning to open a bone marrow niche for the $CD34^+$ hHSPCs and immunoablative conditioning to prevent immune rejection of exa-cel. Even if this unlikely scenario occurred, there would be no harmful effect because HbF is naturally occurring and would not be immunogenic.

Blood donation

Another concern could be of use of blood donated by a treated patient: however, this seems unlikely; patients are to be prohibited from donating blood, tissues or organs.

Conclusions on Ecotoxicity/Environmental Risk

In conclusion, the likelihood is that the hHSPCS present in exa-cel cannot survive for any significant period either outside the human body or outside an environment specially created to maintain them. This suggests the risk to the environment from this product is low; however, there is a risk of accidental injection of cells, including by a needle stick injury. In an otherwise healthy subject, this would likely lead to cells from exa-cel being cleared with no longer term lasting effect. If the accidental exposure was to a patient with a compromised immune system, this could be unfortunate, but the evidence from the mouse toxicity studies does not support there to be a specific reason for concern.

The effects of the finished product on the environment have been fully characterised, in-line with current guidance. No further action regarding the environmental fate of this product is required.

III.6 Discussion on the non-clinical aspects

Conventional mutagenicity, carcinogenicity and reproductive and developmental toxicity studies have not been conducted. No studies on the effects of Casgevy on fertility have been conducted.

The biodistribution and persistence as well as toxicity and tumorigenicity of Casgevy were evaluated in two studies in sub-lethally irradiated, immunodeficient mice. These studies did not identify evidence of aberrant migration, accumulation, or persistence of $CD34^+$ human haematopoietic stem and progenitor cells in non-target tissues and results were comparable between edited and unedited $CD34^+$ cells. Persistence of edited cells in haematopoietic tissues was confirmed, with comparable overall percent editing of infused $CD34^+$ cells throughout the 20-week duration of study. Treatment with edited $CD34^+$ cells revealed no evidence of target organ toxicity or tumourigenicity.

In vitro studies with exagamglogene autotemcel manufactured from healthy donors and patients showed no evidence of off target editing. In studies with edited $CD34^+$ cells obtained from healthy donors, no translocations were detected by either karyotyping or sequencing methods.

The grant of a marketing authorisations was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The safety and efficacy of exa-cel is being evaluated in 3 clinical studies (Table 1).

Table 1 Exa-cel Clinical Studies Providing Efficacy and Safety Data in TDT and SCD Subjects

Study/Module	Objective	Population	Design	Duration
Module 5.3.5.2/ CTX001-111 (Ongoing)	Phase 1/2/3, pivotal study to evaluate the efficacy and safety of exa-cel	TDT subjects 12 to 35 years of age (inclusive) β^0/β^0 and non-β^0/β^0 genotype	Single arm, single dose, multi-center	2 years after exa-cel infusion
Module 5.3.5.2/ CTX001-121 (Ongoing)	Phase 1/2/3, pivotal study to evaluate the efficacy and safety of exa-cel	Severe SCD subjects 12 to 35 years of age (inclusive) β^S/β^S, β^S/β^0, or β^S/β^+ genotype	Single arm, single dose, multi-center	2 years after exa-cel infusion
Module 5.3.5.2/ CTX001-131 (Ongoing)	Phase 3, LTFU to evaluate the long-term safety and efficacy of exa-cel	TDT or SCD subjects who were dosed with exa-cel in Studies 111 or 121	Long-term follow-up	Total follow-up of 15 years after exa-cel infusion

Source: Module 5.2
exa-cel: exagamglogene autotemcel, formerly CTX001; LTFU: long-term follow-up; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

There are also studies 141 and 151 recently started in subjects in the paediatric age range. All studies are on-going.

The conditional Marketing Authorisation was supported by clinical data from two of the studies listed in the table above, studies 111 and 121. The MAH has enrolled subjects from these studies (who have completed or discontinued) into long-term follow-up study 131 it is considered that there are too few subjects with too short a follow-up to permit a formed view on study 131 to be created at this stage.

Studies 111 and 121 studies were conducted in line with current Good Clinical Practice (GCP).

IV.2 CLINICAL ASPECTS *Continued*

The next sections of this public assessment report cover clinical pharmacology, including pharmacokinetics and pharmacodynamics.

IV.3 CLINICAL PHARMACOLOGY ASPECTS

No dedicated clinical pharmacology studies were conducted given that exa-cel is a cell and gene therapy. This summary document includes relevant pharmacology data from 2 pivotal studies (Studies 111 and 121) and an open-label long-term follow-up study (Study 131) as follows:

- Study 111 is an ongoing single-arm, open-label, multi-site, single-dose, Phase 1/2/3 study in subjects aged 12 to 35 years (inclusive) who have TDT (transfusion-dependent β-thalassemia) evaluating the safety and efficacy of a single dose of exa-cel

- Study 121 is an ongoing single-arm, open-label, multi-site, single-dose, Phase 1/2/3 study in subjects aged 12 to 35 years (inclusive) who have severe SCD (sickle cell disease) evaluating the safety and efficacy of a single dose of exa-cel
- Study 131 is an ongoing multi-site, open-label, rollover study designed to evaluate the long-term safety and efficacy of exa-cel in subjects who received exa-cel in a parent study, including Studies 111 and 121.

Studies 111 and 121 also included evaluation of parameters pertinent to busulfan myeloablation.

For cell-based therapies where conventional ADME assessment cannot be conducted, pharmacokinetic assessment should be conducted where feasible to monitor viability, proliferation/differentiation, tumourigenicity, immunogenicity, body distribution, ectopic foci, tissue tropism/migration, and functionality during the intended viability of the cells/products. In the context of exa-cel treatment, the following efficacy endpoints evaluated in Studies 111, 121, and 131 were considered as pharmacodynamics (PD) assessments: HbF (absolute and %); proportion of alleles with intended genetic modification in the exa-cel drug product, in the peripheral blood, and in the $CD34^+$ cells of the bone marrow; and the proportion of circulating erythrocytes expressing γ-globin (HbF; F-cells).
No clinical pharmacology studies were conducted. According to the guideline on human cell based medicinal products CBMP (Doc. Ref. EMEA/CHMP/410869/2006), alternative approaches in the clinical development plan might be acceptable. Therefore, the lack of dedicated clinical pharmacology studies in the current submission is justified.

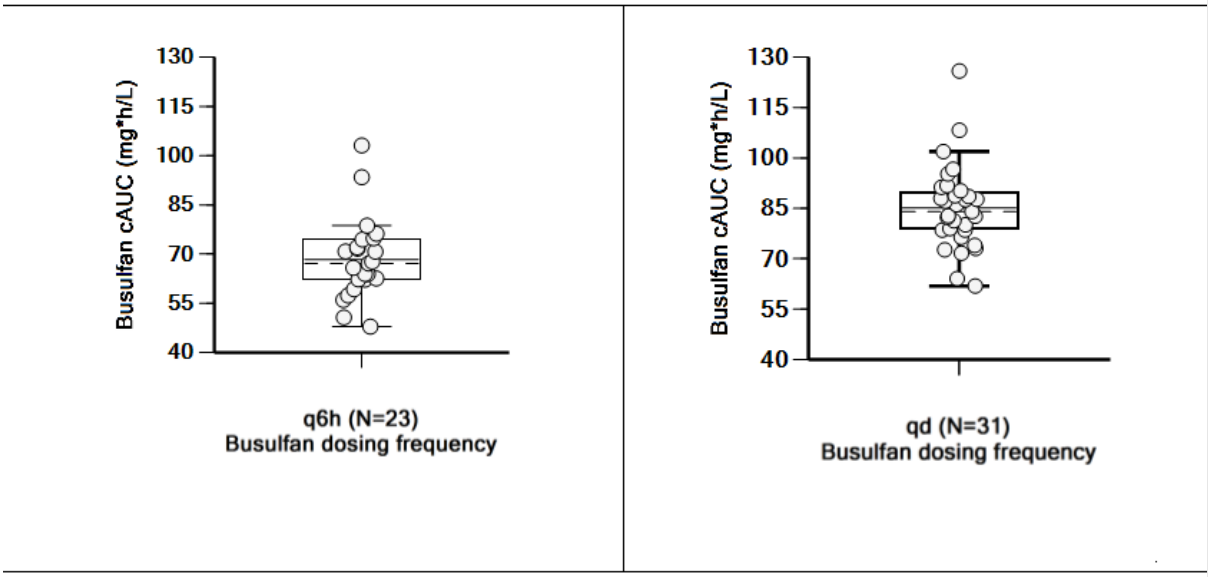
IV. 3 a. Pharmacokinetics

Pharmacokinetics data in terms of exposure (e.g. Cmax and AUC) were not submitted in the current procedure.

Pharmacokinetics of Myeloablation Regimen

Busulfan was used as single agent for myeloblative bone marrow conditioning in exa-cel studies either once daily for four consecutive days and adjusted at 3.2 mg/kg (qd) or every 6 hours at 0.8 mg/kg (q6h), with the dose adjusted based on PK from days 1 and 3. Protocol appears adequate as all subjects achieved profound neutropenia. Caution should be taken with dose adjustments as therapeutic window of busulfan is low.

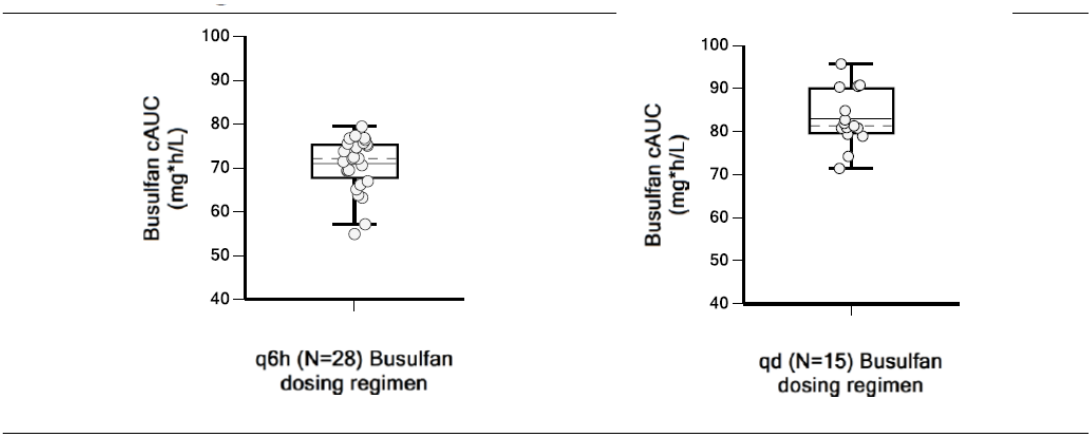
In Study 111 (TDT Subjects), 17 (74%; N = 23) subjects receiving the q6h regimen and 17 (55%; N = 31) subjects receiving the qd regimen were within the protocol-specified busulfan cAUC target range (**Figure 6**).



Source: Figure 14.4.2.1 (data cutoff date of 16 April 2023)
cAUC: cumulative area under the concentration versus time curve; IQR: interquartile range; N: total sample size; q6h: every 6 hours; qd: once daily
Note: Solid lines represent the mean; dotted lines represent the median; box represents the IQR; whiskers represent the observed minimum and maximum up to ±1.5 × IQR; symbols represent individual subjects busulfan cAUC.

Figure 6, Distribution of individual subject observed busulfan cAUC (cumulative area under the concentration curve) by dosing regimen in study 111 (subjects with TDT)

In Study 121 (SCD Subjects), 36 (84%; N = 43) subjects were within the protocol-specified busulfan cAUC target range across both regimens. Twenty-six (93%; N = 28) subjects receiving the q6h regimen and 10 (67%; N = 15) subjects receiving the qd regimen were within the protocol-specified cAUC target range. With the q6h regimen, 2 subjects had an exposure below the target range. With the qd regimen, 1 subject had an exposure below the target range and 4 subjects had exposures above the target range. The observed number of subjects with busulfan cAUC above or below the cAUC target range were as expected for pharmacokinetically adjusted myeloablative busulfan conditioning see (**Figure 7**) on overleaf.



Source: Figure 14.4.2.1 (data cutoff date of 16 April 2023)
cAUC: cumulative area under the concentration versus time curve; IQR: interquartile range; N: number of subjects; q6h: every 6 hours; qd: once daily
Note: Solid lines represent the mean; dotted lines represent the median; box represents the IQR; whiskers represent the observed minimum and maximum up to ±1.5 × IQR, and symbols represent individual subjects busulfan cAUC.

Figure 7, Distribution of individual subject observed busulfan cAUC (cumulative area under the concentration curve) by dosing regimen in study 121 (subjects with SCD)

Following exa-cel dosing, G-CSF use was permitted to support neutrophil engraftment in both Study 111 (TDT) and Study 121 (SCD), if needed. However, the post-dose use of G-CSF was not recommended within the first 21 days after exa-cel dosing to avoid confounding the assessment of neutrophil engraftment. Successful neutrophil engraftment was observed in all subjects who had sufficient follow up time, across Study 111 and Study 121. Therefore, G-CSF use after exa-cel dosing is not anticipated to interfere with neutrophil engraftment or the function of exa-cel. Furthermore, there is no association between G-CSF use after exa-cel dosing and ultimate clinical outcome

IV. 3 b. Pharmacodynamics

Exa-cel is designed as a one-time treatment acting by permanent, irreversible, and precise edits created with the ribonucleoprotein (RNP) complex composed of Cas9 and the highly specific guide RNA, SPY101, target a critical binding site of the transcription factor GATA1 in the non-coding erythroid lineage-specific enhancer region of the BCL11A gene on chromosome 2. BCL11A codes for a transcriptional repressor of γ-globin. The reduction of BCL11A gene transcription and subsequent decrease in BCL11A protein level leads to concomitant increases in γ-globin expression, and, upon erythroid differentiation, increased levels of HbF.

The therapeutic advantage of editing BLC11A erythroid-specific enhancer to induce HbF over editing HbA is specificity and safety for gene editing (as in the preceding paragraph), the developability of the HbF approach, and the ability to treat both TDT and SCD. Both strategies have the potential to eliminate disease symptoms, however the exa-cel approach, of upregulating HbF, does not run the risk of causing changes to the HbA gene that could cause thalassemia. Moreover, non homologous end joining (NHEJ) can be achieved at high editing efficiency in the long-term human hematopoietic stem cells (LT-HSPC), whereas homology directed repair (HDR) has not been shown to be successful in the target cells. In fact, the

reported efficiencies for correcting the sickle cell mutation or repairing the β-globin gene are low and may not be above thresholds to provide benefit.

In the [TDT]FAS (full analysis dataset), after exa-cel infusion in Study 111, increases in mean total Hb and HbF levels occurred early (Month 3) and were maintained over time from approximately Month 6 onward, through the duration of follow-up including in Study 131 (48 months). Mean (SD) total Hb levels were 11.40 (2.2) g/dL at Month 3, increased and were maintained with mean ≥12 g/dL from Month 6 through the duration of follow-up. Mean (SD) HbF levels were 7.8 (2.9) g/dL at Month 3, increased and were maintained with mean ≥10 g/dL from Month 6 through the duration of follow-up. Mean (SD) proportion of total Hb comprised by HbF (HbF %) was 67.4% (19.9%) at Month 3, increased and was maintained with mean ≥86% from Month 6 through the duration of follow-up. Consistent with increases in HbF, the mean (SD) proportion of F-cells (an exploratory endpoint) was 74.27% (19.43%) at Month 3, increased and was thereafter maintained with mean ≥95% from Month 6 through the duration of follow-up **(Figure 8)**.

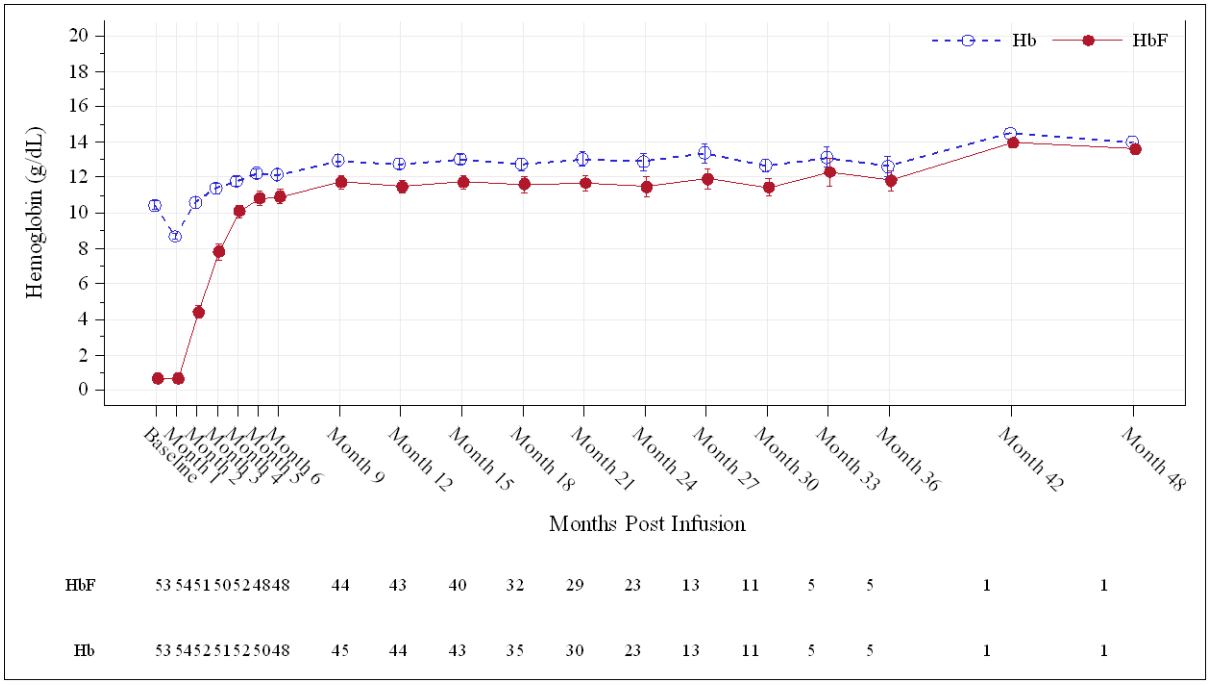


Figure 8, Summary of total Hb (g/dL) and HbF (g/dL) over time (studies 111 and 131, TDT full analysis dataset)

In the [SCD]FAS, after exa-cel infusion in Study 121, increases in mean HbF levels occurred early (Month 3) and were maintained over time from approximately Month 6 onward, through the duration of follow-up including in Study 131 (42 months). Mean (SD) total Hb levels were 12.0 (1.45) g/dL at Month 3, increased and were maintained with mean ≥12 g/dL from Month 6 through Month 24 in Study 121. For subjects who rolled over to Study 131, total Hb levels were maintained after Month 24 with mean ≥11 g/dL over the duration of follow-up in Study 131, reflecting stable levels across Studies 121 and 131 on an individual basis. Mean (SD) HbF levels were 5(1) g/dL at Month 3, increased and were maintained with mean ≥4.0 g/dL from Month 6 through the duration of follow-up. Mean (SD) proportion of

total Hb comprised by HbF (HbF %) was 37.3% (9%) at Month 3, increased and was generally maintained with mean ≥40% from Month 6 through the duration of follow-up. Consistent with increases in HbF, the mean proportion of F-cells (an exploratory endpoint) was 70.38% (14.02%) at Month 3, increased and was maintained with mean ≥93% from Month 6 through the duration of follow-up (**Figure 9**).

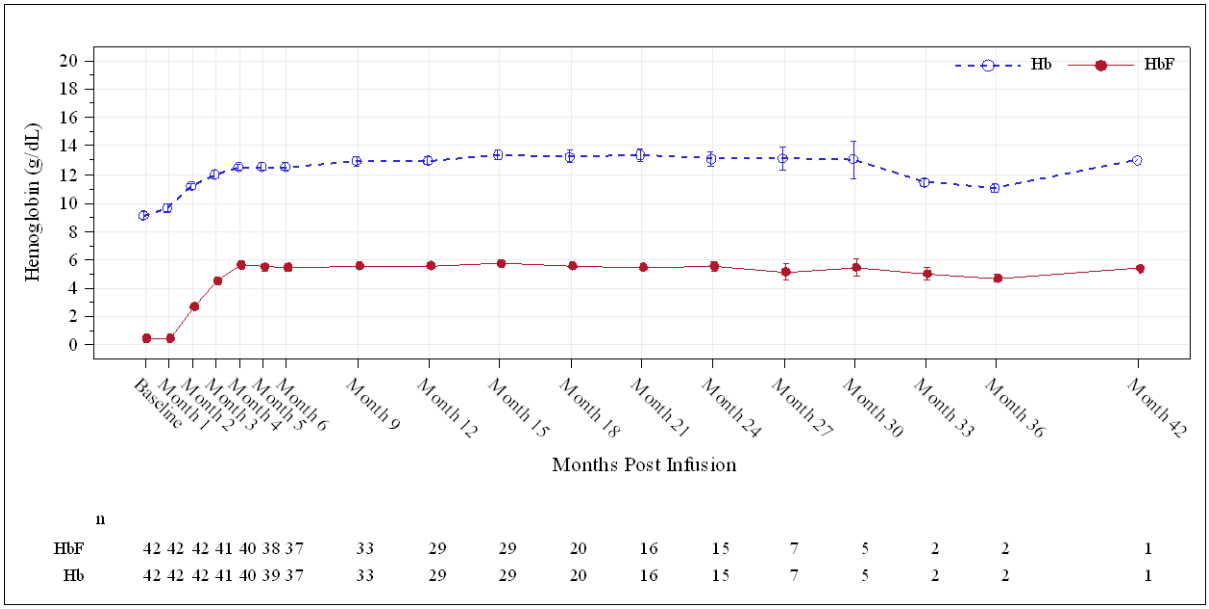


Figure 9, Summary of total Hb (g/dL) and HbF (g/dL) over time (studies 121 and 131, SCD full analysis dataset)

Dose Rationale

The recommended dose of exa-cel is 3.0 × 106 $CD34^+$ cells/kg or greater administered IV for patients with TDT or SCD aged 12 years and older and is weight-based: accepted safe clinical practices regarding the dose of $CD34^+$ cells required to achieve durable long-term hematopoietic reconstitution after autologous transplantation; and an assessment of the clinical data to evaluate the $CD34^+$ cell doses that achieved engraftment and achieved HbF % levels associated with disease amelioration. The dose rationale appears adequate as it does not lead to toxicity or lack of efficacy and leads to successful neutrophil and platelet engraftment, an increase in total Hb and HbF from baseline, and improved clinical outcomes.

Cell Persistence

Persistence of edited cells in subject with TDT was measured as the mean proportion of alleles with the intended genetic modification in the $CD34^+$ cells of the bone marrow and was 78.48% at month 6 and was stably maintained from Month 6 (first timepoint of evaluation) onward (**Figure 1**).

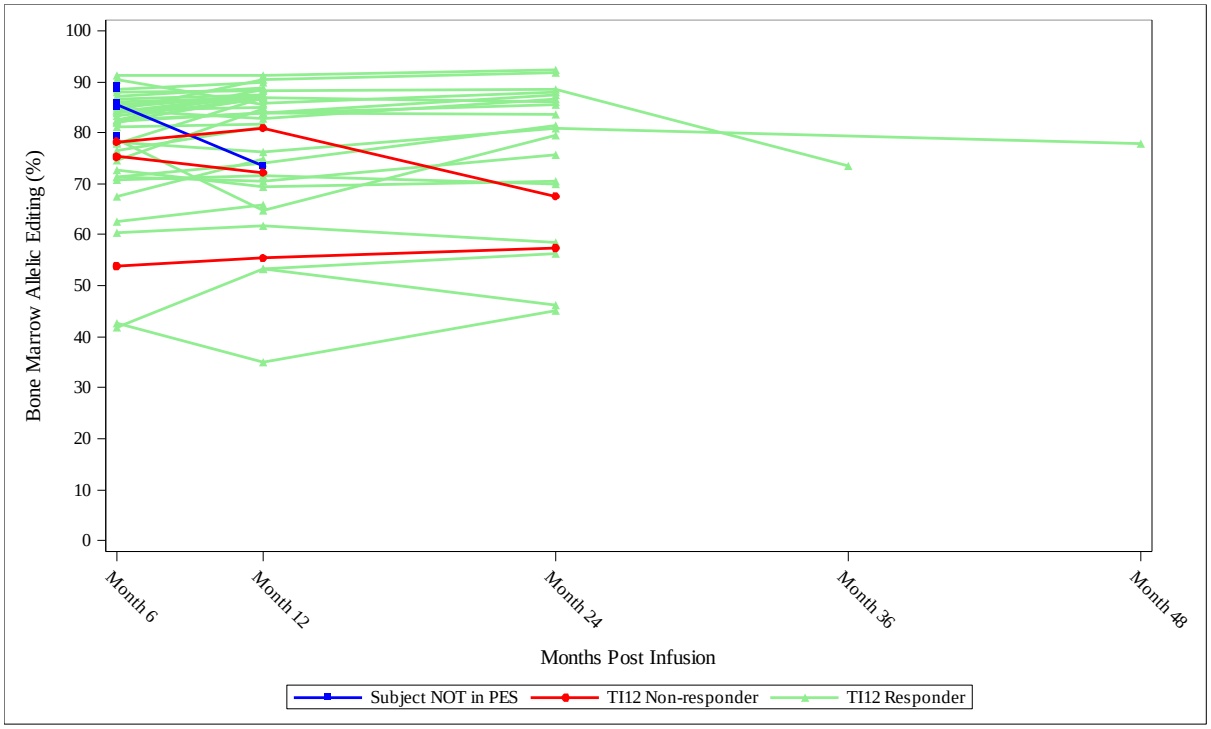


Figure 1, Individual bone marrow allelic editing (%) over time in TDT (study 111, full analysis dataset)

The mean proportion of alleles with the intended genetic modification in peripheral blood was maintained ≥60% from Month 2 onward, through the duration of follow-up in Studies 111 and 131 (**Figure 2**).

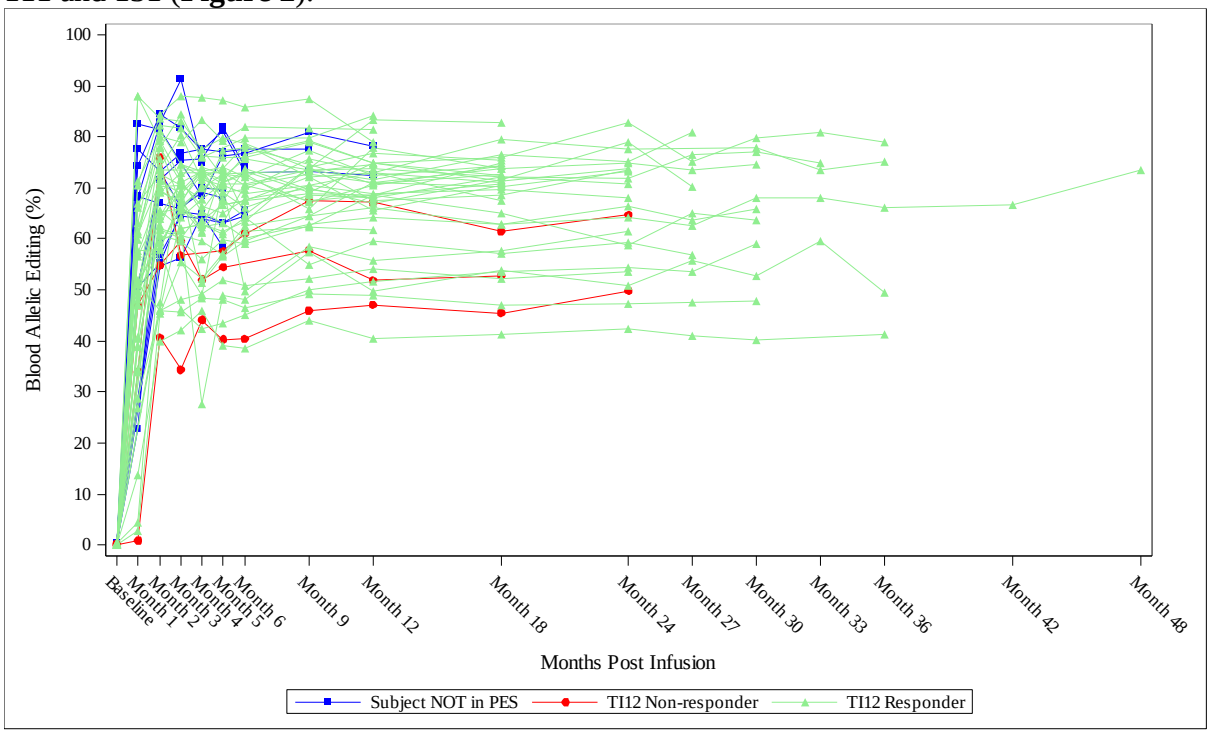


Figure 2, Individual Peripheral Blood Allelic Editing (%) Over Time (Studies 111 and 131, [TDT]FAS)

Persistence of edited cells in subjects with SCD was measured as the mean proportion of alleles with the intended genetic modification in the $CD34^+$ cells of the bone marrow was 86.12% (7.54%) at the first timepoint of evaluation (Month 6) and was sustained with mean ≥85% thereafter through the duration of follow-up in Study 131 (**Figure 3**).

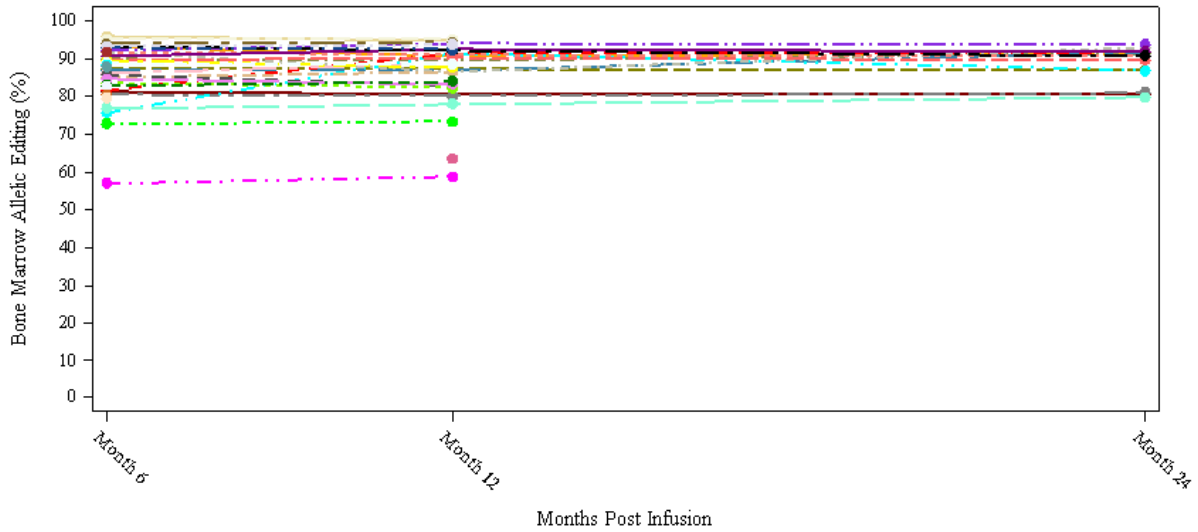


Figure 3, Individual Bone Marrow Allelic Editing (%) Over Time (Studies 121 and 131, [SCD]FAS)

The mean proportion of alleles with the intended genetic modification in peripheral blood was generally maintained ≥70% from Month 2 onward, through the duration of follow-up in Studies 121 and 131, see (**Figure 4**) on overleaf.

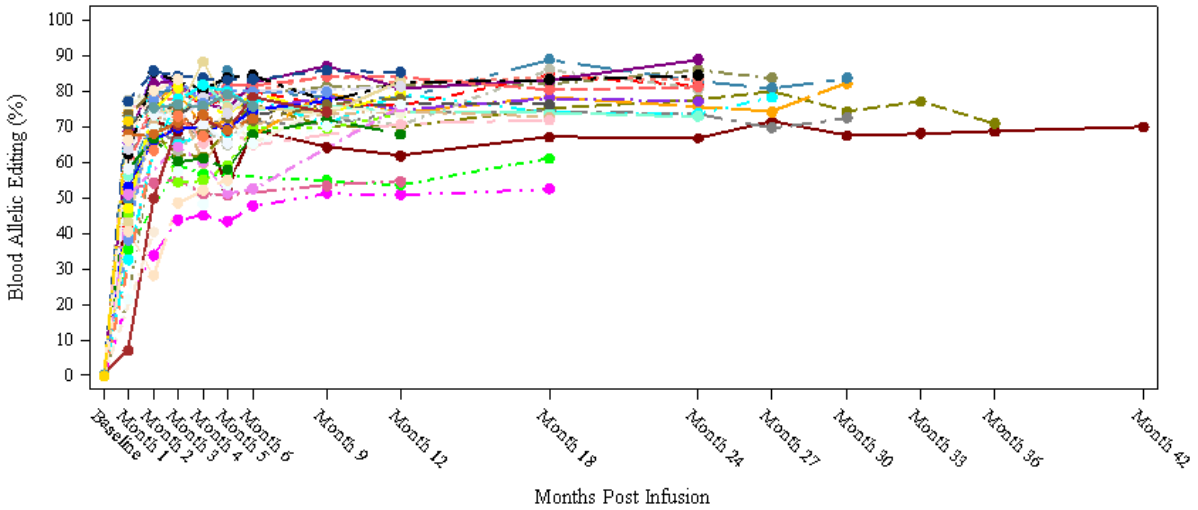


Figure 4, Individual Peripheral Blood Allelic Editing (%) Over Time (Studies 121 and 131, [SCD]FAS)

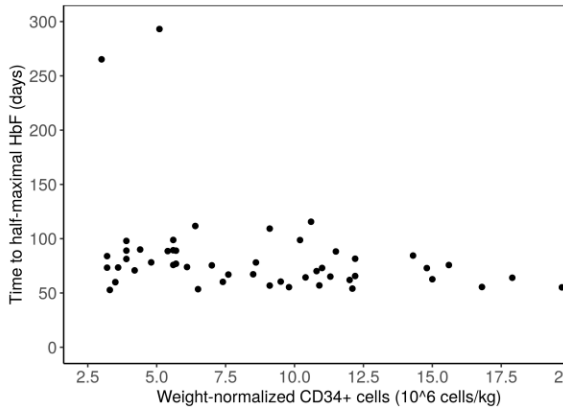
In general, the data appeared to be variable. The bone marrow data was derived from limited time points with no baseline measurements and from limited number of patients making it hard to draw a conclusion about the expansion and persistence of the $CD34^+$ cells with intended genetic modification. The data derived from peripheral blood show trends for

expansion and persistent phases, however, the MAH did not analyse these data in order to characterise these phases using either of non-compartmental or compartmental modelling approaches. Therefore, it is not possible to use these data to support the dose rationale or to estimate the effect of intrinsic and extrinsic covariates. Moreover, the MAH did not characterise the dose proportionality.

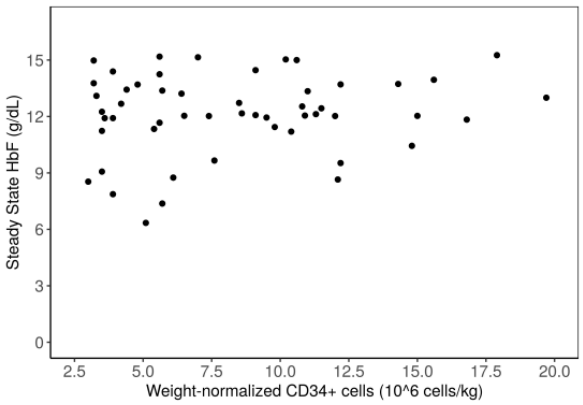
The MAH provided visual representations for the relationship between the exa-cel dose as described by the number of weight-normalised $CD34^+$ cells and either of the expansion phase as described by the time to half maximal HbF or the persistence as described by steady-state HbF. There was no observed visual relationship between exa-cel dose and either the expansion or the persistence phases, see (**Figure 5**) on overleaf.

Expansion **Persistence**

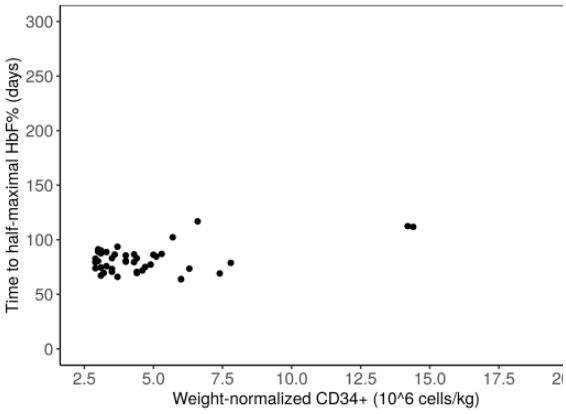
a. Study 111 (TDT)



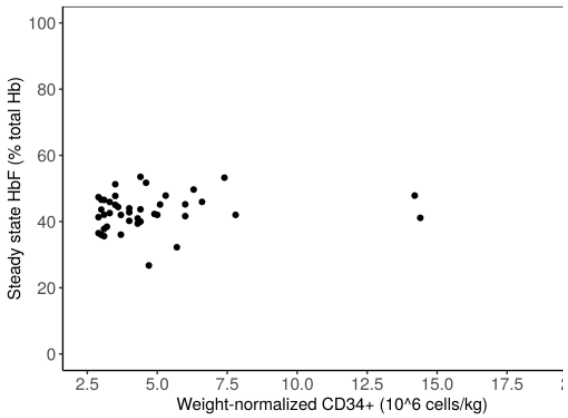
c. Study 111 (TDT)



b. Study 121 (SCD)



d. Study 121 (SCD)



HbF: fetal hemoglobin, SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

Notes: Dose ($CD34^+$ cells /kg) is plotted versus the expansion phase in a) as time to half-maximal HbF (g/dL) for TDT subjects and in b) as time to half maximal HbF (%) for SCD subjects; dose ($CD34^+$ cells/kg) is plotted versus the persistence phase in c) as steady state HbF (g/dL) for TDT subjects and in d) as steady state HbF (%) for SCD subjects.

Figure 5, Dose response relationship in HbF (g/dL; Study 111) and HbF (%; Study 121)

To address the special populations in TDT (transfusion-dependent β-thalassemia) and SCD (sickle cell disease) subjects, the MAH provided a visual analysis based on plotting the changes in mean HbF levels (and 95% CI of HbF g/dL for TDT or HbF [%] for SCD) over

the 24-months treatment period and comparing the observed values between two groups for the different intrinsic factors (age, sex, genotype, and body weight). The MAH concluded that results from these analyses showed no impact of these intrinsic factors on HbF levels (g/dL for TDT or HbF [%] for SCD) and no dose adjustment is needed based on the intrinsic factors assessed. However, it should be noted that these sub-group analyses were based on limited number of observations in the dataset.

The MAH indicated that disease condition did not have impact on the mean levels of Hb and HbF as they were achieved early and maintained over time regardless of disease condition. Although Exa-cel has not been studied in subjects with renal or hepatic impairment, the MAH did not recommend warnings and precautions for patients with hepatic and renal impairment considering that healthcare providers would assess whether these patients are suitable for autologous HSCT.

To address DDIs in subjects with TDT or SCD, the MAH noted that exa-cel does not affect human physiological processes that might alter PK (pharmacokinetics) of co-administered medication. Full myeloablative conditioning with single agent busulfan was a required step in Study 111 (TDT) and Study 121 (SCD) that was completed at least 48 hours prior to exa-cel infusion. Administration of e.g. busulfan at an inappropriate timepoint can cause alterations in bone marrow density, thereby leading to increased risk of drug interactions (DDIs).

IV.4 Clinical efficacy *Transfusion-dependent β-thalassemia – Study CTX001-111*

This section of the public assessment report discusses the clinical data and information to support the following indication:

Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

The clinical information discussed here is based on the interim clinical study report.

Abbreviated Study Numbers
All clinical study numbers conducted with CTX001 are abbreviated to the last 3 digits (e.g. Study CTX001-111 is Study 111).

Definitions of Terms

Term	Definition
Neutrophil engraftment	Neutrophil engraftment was defined as the first day of 3 consecutive measurements of absolute neutrophil count (ANC) ≥500/μL on 3 different days without use of unmodified $CD34^+$ cells after reaching the nadir, defined as ANC <500/μL.
Platelet engraftment	Platelet engraftment was defined as the first day of 3 consecutive measurements of unsupported (no platelet transfusions for the last 7 days) platelets ≥20,000/μL on 3 different days after exa-cel infusion after reaching the nadir (defined as platelets <20,000/μL) or the first platelet transfusion, whichever was earlier. For subjects discharged before reaching platelet engraftment, platelet engraftment was defined as the 7th day after the last platelet transfusion, if there were 3 subsequent and consecutive unsupported measurements of unsupported platelets ≥20,000/μL on 3 different days. This last platelet transfusion refers to the last platelet transfusion that proceeded the 3 measurements.
Intended genetic modifications	Intended genetic modifications are defined as insertions/deletions that modify the sequence of the erythrocyte-specific enhancer in intron 2 of *BCL11A*

Title: A Phase 1/2/3 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified $CD34^+$ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in Subjects With Transfusion-dependent β-Thalassemia

Dates of Study:
Study initiation: 10 Sept 2018 (date first eligible subject signed the informed consent form)
Interim Analysis data cut-off date: 16 Apr 2023
Date of report: 06 Nov 2023

Study objectives
Primary Objective

- To evaluate the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified $CD34^+$ human hematopoietic stem and progenitor cells (exa-cel) in subjects with transfusion-dependent β-thalassemia (TDT)

Secondary Objectives

- To quantify percentage of edited alleles in peripheral blood leukocytes and $CD34^+$ cells of the bone marrow
- To assess the production of HbF after exa-cel infusion
- To assess the effects of infusion of exa-cel on disease-specific events and clinical status

Exploratory Objective

- To assess the ability of biomarkers to characterize exa-cel effect and predict treatment outcomes

Study outcomes

Primary efficacy outcome

1. Proportion of subjects who maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion

Secondary efficacy outcomes

1. Proportion of subjects who maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time after exa-cel infusion

Note: the above secondary efficacy outcome (referred to by the company as an 'endpoint)' is described by the MAH as a 'key' 'endpoint'.

1. Duration being transfusion-free for subjects who achieved the primary efficacy endpoint (where being transfusion-free is defined as maintaining weighted Hb ≥9 g/dL; evaluation started 60 days after last RBC transfusion for post-transplant support or transfusion-dependent β-thalassemia disease management).

2. For subjects who did not achieve the primary efficacy endpoint: relative reduction from baseline in annualised volume of RBC transfusions

3. Absolute and relative monthly reduction from baseline in volume / units / episodes of RBC transfusions

4. Total Hb and HbF

5. Proportion of alleles with intended genetic modification present in (i) peripheral blood and (ii) $CD34^+$ cells of the bone marrow

6. Change from baseline in iron overload

7. Proportion of subjects receiving iron chelation therapy

8. Change from baseline in patient reported outcomes

Exploratory outcomes

1. Hb fractions and change from baseline in proportion of circulating erythrocytes expressing γ-globin (HbF)

2. α-globin and non-α-globin mRNA

3. Assessment of ineffective erythropoiesis in bone marrow analysis compared with baseline over time

Aspects of study design

A single-arm, open-label, multi-site, single dose, Phase 1/2/3 study in subjects 12 to 35 years of age who have transfusion-dependent β-thalassemia.

A single-arm study design was used because of a lack of equipoise with existing standard of care treatments and because of the need for a transplant procedure to deliver exa-cel. The overall process was consistent with procedures used for autologous haematopoietic stem cell transplant in patients with malignant diseases, including mobilization / apheresis and myeloablation. Therefore, the risk associated with the procedures in this study was not expected to be significantly different from the standard risks of these procedures.

A single-arm demonstration study may be understood in the context of subjects with a rare disease who are to be administered a novel therapy; it is acknowledged that the MAH has conducted the autologous haematopoietic stem cell transplant procedure in accord with current clinical practice and so risks are known.

Expansion of enrolment to increase the total number of subjects was based on data monitoring committee review of safety and efficacy data.

Adolescent-aged children were included once efficacy and safety were shown in adults. The rationale for inclusion of adolescent-aged children was that the aetiology and pathophysiology of transfusion-dependent β-thalassemia are similar across age groups.

Transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed red blood cell transfusions in the 2 years before signing the informed consent form.

Recruitment - the population enrolled is considered representative for the claimed indication.

Allocation was not conducted - this is a single arm trial - likely to introduce bias.

Maintenance on product - the product is delivered in a single step and so maintenance is not considered to be an issue.

Blinding was not done - this is an open-label trial - likely to introduce bias.

For outcome in thalassaemia subjects - need for red blood cell transfusion & measurement of units of red cells is considered sufficiently objective.
The use of 'before and after' to assess outcome is considered to introduce bias.

It is not possible to concur with the statistics analysis of the MAH because randomisation was not done; the assessor applies the technique of Bradford Hill and refers to "outcomes" rather than "endpoints".

There were 4 global amendments and 14 country-specific amendments (updates and clarifications in the main) between Nov 2017 and Apr 2022; the MAH provides information on these; the amendments are noted without further comment.

The MAH provides information on important protocol deviations that were, in the main, administrative. The MAH states that "there was no impact of these important protocol deviations to subject safety, data integrity or data interpretation". This is acceptable.

Choice of dose
The study evaluated the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified human haematopoietic stem and progenitor cells (exa-cel).

Autologous transplantation for various indications typically employs a minimum of 2×10^6 to 2.5×10^6 $CD34^+$ cells/kg to support engraftment.
To ensure engraftment in all subjects, a conservative minimum dose of $\geq 3 \times 10^6$ $CD34^+$ cells/kg, which is 20% to 50% higher than the typical minimum dose for autologous transplantation was assessed, and was supported by scientific literature references.

In other gene therapy studies, doses approaching 20×10^6 $CD34^+$ cells/kg, an order of magnitude larger than proposed here, were used in clinical trials with no signs of increased toxicity.

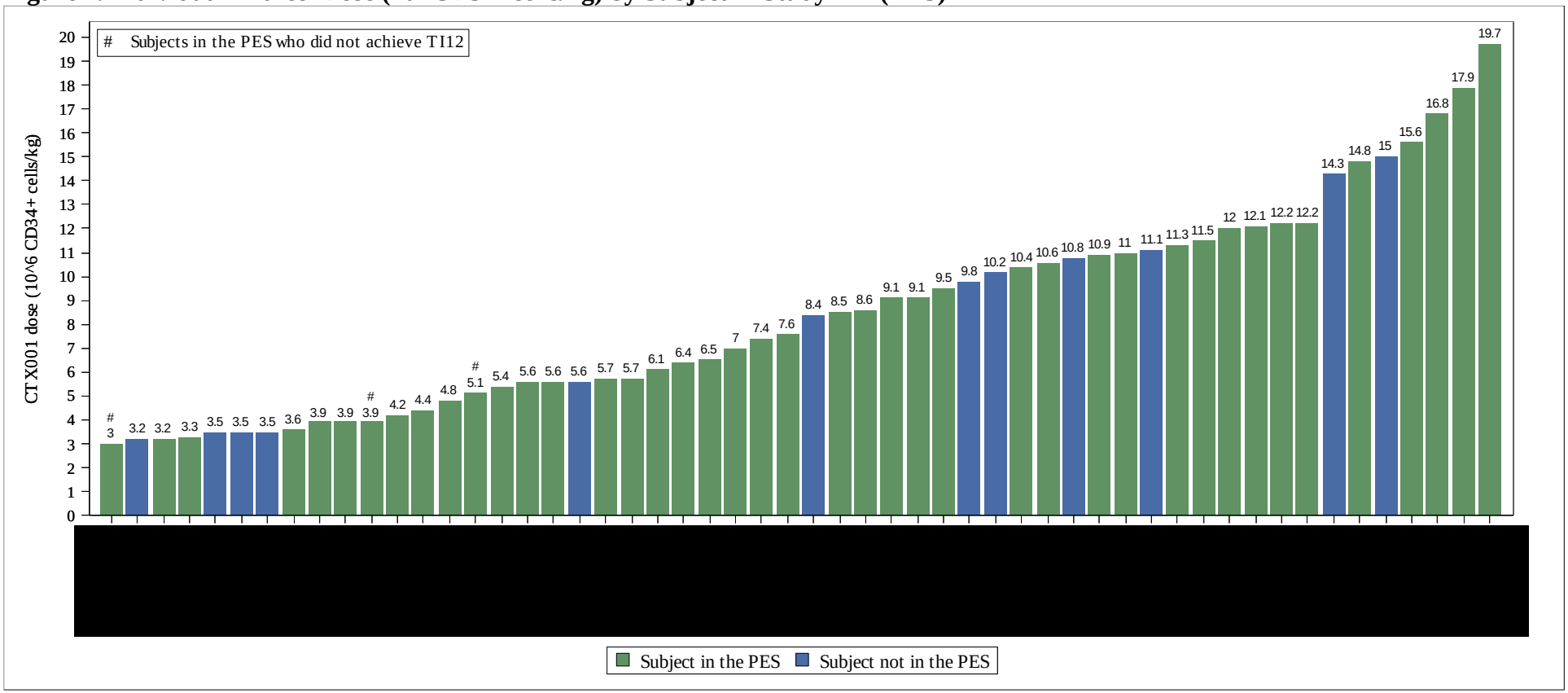
Based on current manufacturing capabilities and projected cell yields, the maximum cell dose limit of 20×10^6 $CD34^+$ cells/kg was selected.

Assessment of choice of dose
The MAH has based its dosing strategy on published information; this may be understood in the context of a study conducted on subjects with a rare condition yet the approach is considered to be a notable deficiency in a study that uses novel technology. Nonetheless, the MAH has agreed to submit data at annual reviews that will aid in the further assessment of sufficiency of number of cells administered to subjects; this is acceptable.

References submitted by the MAH suggest best outcome is achieved with >5 x 10^6 CD34 cells/kg administered.

The MAH has submitted a bar chart with number of patients on the y-axis versus number of cells / kg body weight administered as shown on the following page.

Figure 1. Individual Exa-cel Dose (10^6 $CD34^+$ cells/kg) by Subject in Study 111 (FAS)



CTX001: exagamglogene autotemcel; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; Hb: hemoglobin; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion

Notes: The evaluation of TI12 started 60 days after last RBC transfusion for post-transplant support or TDT disease management. Hb measurements used for the determination of the weighted average Hb were from central laboratory data. Only RBC transfusions adjudicated by an Endpoint Adjudication Committee as meeting the purpose of post-transplant support or TDT disease management were included. Subjects in the PES who did not achieve TI12 are marked. Subjects not marked include subjects in the PES who achieved TI12 and subjects not in the PES

With reference to the figure above: 3/16 (i.e. 19%) administered ≤ 5.5 x 10^6 CD34 cells/kg body weight required red blood cell transfusion [i.e. have not met the primary outcome] whilst 0/38 (i.e. none) administered > 5.5 x 10^6 CD34 cells/kg body weight did not.

It is recognised that number of subjects is small and so opinion is guarded at present; the issue of minimum number of cells administered needed to be sufficient is considered an on-going issue that may be revisited at annual review or at an intervening time point.

Population

Inclusion criteria

1. Subjects 12 to 35 years of age

2. Diagnosis of transfusion-dependent β-thalassemia as defined by:
   a. Documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia / haemoglobin E (HbE).

      Subjects could enrol based on historical data but a confirmation of the genotype using the study central laboratory was required before busulfan conditioning. The β0 and non-β0 genotypes were defined using the HbVar database[1].

   b. A history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the prior 2 years before signing the consent or the last rescreening (if needed).

3. Eligible for autologous stem cell transplant as per investigator's judgment.

4. Access to detailed medical records on packed RBC transfusions, including units and estimated volumes of packed RBCs and associated pre-transfusion Hb values, weight, and in-patient hospitalizations, for at least the 2 years before consent.

The inclusion criteria describe a population of people with thalassaemia who are dependent upon transfusions.

5. Karnofsky performance status of ≥80% for subjects ≥16 years of age.

6. Lansky performance status of ≥80% for subjects <16 years of age.

[1] Comment: The HbVAR database is a database of human haemoglobin variants and thalassemia mutations that is curated by The Pennsylvania State University, a public state-related land-grant (as designated by the Morrill Acts of 1862, signed by Abraham Lincoln) research university with campuses and facilities throughout Pennsylvania, USA. Refer to: HbVar (psu.edu). Reference to the database to define genotypes is considered to be good practice.

Karnofsky and Lansky performance scales are shown:

APPENDIX 2. KARNOFSKY AND LANKSY PERFORMANCE STATUS SCALES

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	60	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	40	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	30	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	20	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	10	Completely disabled, not even passive play

Source: Center for International Blood and Bone Marrow Research. 2009.

The MAH has restricted inclusion to those with Karnofsky and Lansky scores >80%.

Comment: It is considered reasonable to restrict inclusion to those who are able to carry out normal activities (Karnofsky and Lansky scores >80%) in the context of a novel therapy with potentially notable adverse events consequent to the transplant procedure i.e. the enrolled population is sufficiently 'fit'.

Exclusion criteria

1. A willing and healthy 10/10 Human Leukocyte Antigen-matched related donor was available per investigator's judgement
2. Prior allogeneic hematopoietic stem cell transplantation
3. Prior treatment with gene therapy / editing product
4. Subjects with associated α-thalassemia and >1 alpha deletion or alpha multiplications
5. Subjects with sickle cell β-thalassemia variant
6. Clinically significant infection
7. White blood cell (WBC) count <3 × 10^9/L or platelet count <50 × 10^9/L not related to hypersplenism
8. History of a significant bleeding disorder
9. prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder
10. Advanced liver, renal, cardiac or lung disease based on laboratory testing
11. Intolerance, contraindication or known sensitivity to plerixafor, G-CSF products (e.g. filgrastim), or busulfan
12. Positive tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and syphilis. Additional infectious disease markers were obtained and tested as required by local guidance.

Disposition of Subjects

59 subjects were enrolled at 13 sites in the United States, Canada, United Kingdom, Germany and Italy. Subject disposition is summarized in the following table:

Table 10-1 Subject Disposition (Enrolled Set)

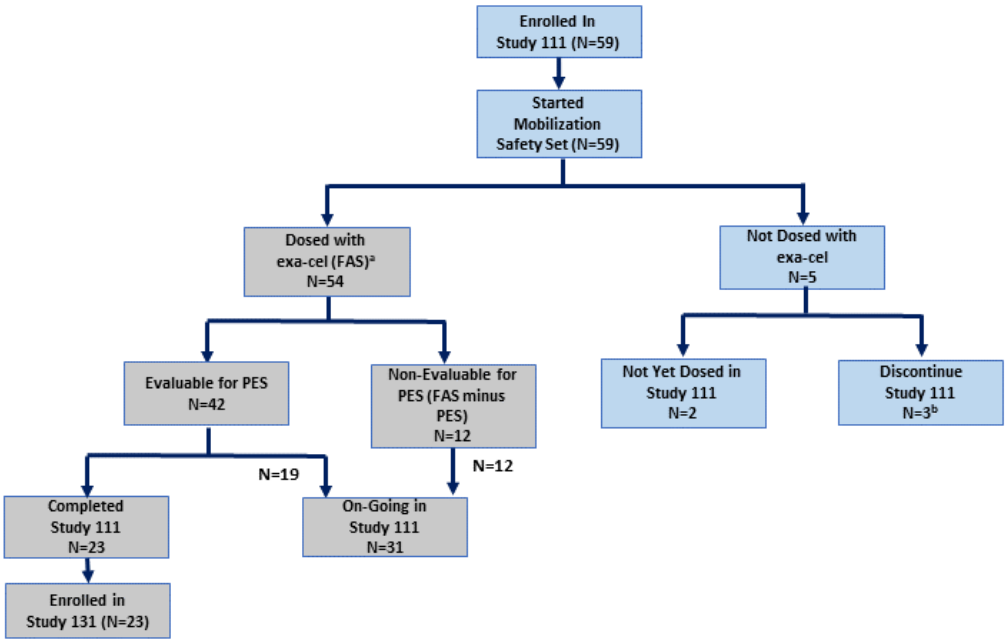
Disposition/Reason	Total n (%)
Started exa-cel infusion	54 (91.5)
Completed exa-cel infusion	54 (100.0)
Not completed exa-cel infusion	0
On study and not yet dosed with exa-cel[g]	2 (3.4)
On study and dosed with exa-cel[g]	31 (52.5)
Completed study[h]	23 (39.0)
Discontinued study after exa-cel infusion	0
Discontinued study after exa-cel infusion and enrolled in long term follow-up study	0

Source: Table 14.1.1 (data cutoff date of 16 April 2023)

[g] On study included all subjects who enrolled and had not yet completed (or discontinued) the study.

[h] Completed study included all subjects who completed the Month 24 visit.

Subject disposition is also summarised in the following figure:



Exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total number of subjects; PES: Primary Efficacy Set; TDT: transfusion-dependent β-thalassemia

Notes: The study was planned to dose approximately 45 subjects. To account for early discontinuations prior to exa-cel dosing, additional subjects were enrolled. Ultimately, 59 subjects were enrolled, and 54 subjects had been dosed at the time of the data cutoff date (16 April 2023). Subjects listed as non-evaluable for PES are included in the FAS minus PES data set.

[a] The FAS included all subjects who received exa-cel infusion.

[b] Reasons for discontinuation: subject did not want to undergo a second apheresis procedure (N = 1), subject had concerns with continued study participation (N = 1), and subject withdrew consent (N = 1).

At the time of this interim analysis:

- all 59 subjects started mobilization and were included in the Safety Analysis Set
- 54 subjects received exa-cel infusion and were included in the full analysis set.
- 3 subjects discontinued from the study – reasons stated in above diagram.
- 42 subjects were evaluable for the primary efficacy set.
- 23 subjects completed Study 111 and all rolled over into the long-term follow-up study (Study 131).

Demographic data

Demographic data for the full analysis set and primary efficacy set are summarised in Table 10-2:

Table 10-2 Subject Demographics (FAS and PES)

Demographics	FAS N = 54	PES N = 42
Sex, n (%)		
Male	29 (53.7)	21 (50.0)
Female	25 (46.3)	21 (50.0)
Childbearing potential[a], n (%)		
Yes	[redacted]	
No		
Age at screening (years)		
n	54	42
Mean (SD)	21.3 (6.6)	21.6 (6.4)
Median	19.5	20.0
Min, max	12, 35	12, 35
Age category at screening, n (%)		
≥12 and <18 years	19 (35.2)	13 (31.0)
≥18 and ≤35 years	35 (64.8)	29 (69.0)
Race, n (%)		
White	18 (33.3)	17 (40.5)
Black or African American	0	0
Asian	23 (42.6)	16 (38.1)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Not collected per local regulations	8 (14.8)	5 (11.9)
Other	2 (3.7)	1 (2.4)
Multiracial	3 (5.6)	3 (7.1)
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	
Not Hispanic or Latino		
Not collected per local regulations		

Sources: Table 14.1.3.1 and Ad hoc Table 14.1.3.3 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; N: total sample size; n: size of subsample; PES: Primary Efficacy Set
Note: Percentages were calculated relative to the number of subjects in the FAS or the PES, unless otherwise specified.
[a] Percentages for childbearing potential were calculated relative to the number of females in the FAS or the PES.

For the 42 subjects in the primary efficacy set: 50% male, 50% female; the median (range) age was 20 (12 to 35) years, with 13 subjects ≥12 and <18 years of age; most subjects were Asian (38.1%) or White (40.5%) [specific weights of participants removed to protect personal data].

At the time of the data cutoff date of 16 Apr 2023, there were 19 adolescent subjects in the full analysis set in Study 111.

Age at Screening for Adolescent Subjects (Study 111 FAS)

Ages of the subjects span the full age range of 12 through 17 years.

Other Baseline Characteristics

Baseline characteristic data (final analysis set (FAS) and primary efficacy set PES) are summarised in the Table below.

Baseline Characteristics	FAS N = 54	PES N = 42
Genotype, n (%)	[redacted]	
β^0/β^0-like		
β^0/β^0		
β^0/IVS-I-110		
IVS-I-110/ IVS-I-110		
Non- β^0/β^0-like		
β^+/β^+		
β^+/β^0		
β^E/β^+		
β^E/β^0		
β^E/β^E		
Other		
Annualized volume of RBC transfusions (mL/kg)		
n	54	42
Mean (SD)	197.6 (62.0)	199.7 (57.2)
Median	205.7	201.0
Min, max	48.3, 330.9	115.2, 330.9
Annualized units of RBC transfusions		
n	54	42
Mean (SD)	36.4 (11.7)	36.5 (10.5)
Median	35.3	35.0
Min, max	11.0, 71.0	20.5, 71.0
Annualized number of RBC transfusion episodes[a]		
n	54	42
Mean (SD)	16.5 (5.2)	17.0 (5.0)
Median	16.5	16.5
Min, max	5.0, 34.5	10.5, 34.5

The Primary efficacy set includes a mix of β0/β0-like and non-β0/β0-like genotypes, as shown.

- 25 subjects (59.5%) had β0/β0-like genotypes.
- 30 subjects had an intact spleen.

For the 2 years before screening:

- the baseline median (range) annualised units of thalassaemia-related RBC transfusions per year was 35.0 (20.5 to 71.0) units
- The baseline median (range) annualised volume of thalassaemia-related RBC transfusions was 201 (115.2, 330.9) mL/kg per year

Table 10-3 Baseline Characteristics (FAS and PES)

Baseline Characteristics	FAS N = 54	PES N = 42
Total Hb concentration (g/dL)		
n	53	42
Mean (SD)	10.4 (1.9)	10.6 (2.0)
Median	10.2	10.2
Min, max	6.9, 14.2	6.9, 14.2
HbF concentration (g/dL)		
n	53	42
Mean (SD)	0.7 (0.9)	0.5 (0.6)
Median	0.3	0.3
Min, max	0.0, 5.8	0.0, 2.2
HbF concentration (%)		
n	54	42
Mean (SD)	6.7 (11.1)	5.1 (5.8)
Median	3.4	3.1
Min, max	0.0, 74.0	0.0, 21.3
F-cell level (%)		
n	54	42
Mean (SD)	14.2 (14.8)	13.0 (12.0)
Median	8.7	8.6
Min, max	2.3, 83.9	2.9, 50.1
Serum ferritin level (pmol/L)		
n	54	42
Mean (SD)	3712.4 (2832.3)	3785.4 (2908.2)
Median	3115.5	3157.0
Min, max	584.2, 10837.3	584.2, 10837.3
Cardiac T2* (msec)[b]		
n	54	42
Mean (SD)	34.2 (9.0)	35.0 (8.9)
Median	34.4	34.8
Min, max	12.4, 61.1	12.4, 61.1
Liver iron concentration (mg/g)[c]		
n	54	42
Mean (SD)	4.5 (3.0)	4.7 (3.2)
Median	3.5	3.8
Min, max	1.2, 14.0	1.2, 14.0
Weight (kg)		
n	54	42
Mean (SD)	55.0 (13.9)	54.6 (14.3)
Median	[redacted]	
Min, max		

Sources: Table 14.1.4.1 and Table 14.1.4.2 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; F-cells: circulating erythrocytes expressing γ-globin (HbF); Hb: hemoglobin; HbF: fetal hemoglobin; ICF: informed consent form; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Baseline volume of RBC transfusions, units of RBC transfusions, and number of RBC transfusion episodes were based on the 2 years before signing of the ICF or the latest rescreening for subjects who rescreened. RBC transfusions were excluded from the baseline calculation if they were not for TDT disease management. Annualized volume = total volume/number of years. Annualized units = total units/number of years. Annualized number of episodes = total number of episodes/number of years. One year = 365.25 days. Hb measurements in this table are from central laboratories.
[a] An RBC transfusion episode was defined as all transfusions within 5 days, starting from the first transfusion in the episode.
[b] Cardiac T2* is the measurement of cardiac iron content.
[c] Liver iron concentration was derived from Liver R2.

Comment:
The primary efficacy set: Subjects had received transfusions in the lead-up to administration of product; data on Hb concentration are noted without additional comment because they are not considered to reflect the underlying disease (subjects were in receipt of transfusions).

The reference range for serum ferritin (differs for men and women and by age) is (about) 600 pmol/L i.e. subjects exhibit high serum ferritin concentration consistent with a status of 'iron overload'.

Cardiac and liver iron content was measured by an algorithm applied to magnetic resonance imaging information; data are noted without additional comment.

Prior and concomitant medications
All subjects were exposed to prior and concomitant medications. The most common concomitant medications were typically used for the management of hematopoietic stem cell transplantation.

G-CSF Usage: Of the 54 subjects in the full analysis set, 20 (37.0%) subjects received filgrastim, 7 (13.0%) subjects received TBO filgrastim, 7 (13.0%) subjects received lenograstim, 1 (1.9%) subjects received G-CSF (PN) and 1 (1.9%) subject received pegfilgrastim.

Comment: The MAH submits an extensive listing of prior and concomitant medications the medications appear 'understood' in the context of subjects with thalassaemia.

There was not a uniform requirement on the nature of the G-CSF; this is considered acceptable because the aim of exposure is to release cells into the peripheral circulation from which they may be harvested (rather than modify the cells) and because it is understood that the G-CSF forms are biosimilar.

Prohibited medications
There were not any prohibited medications.

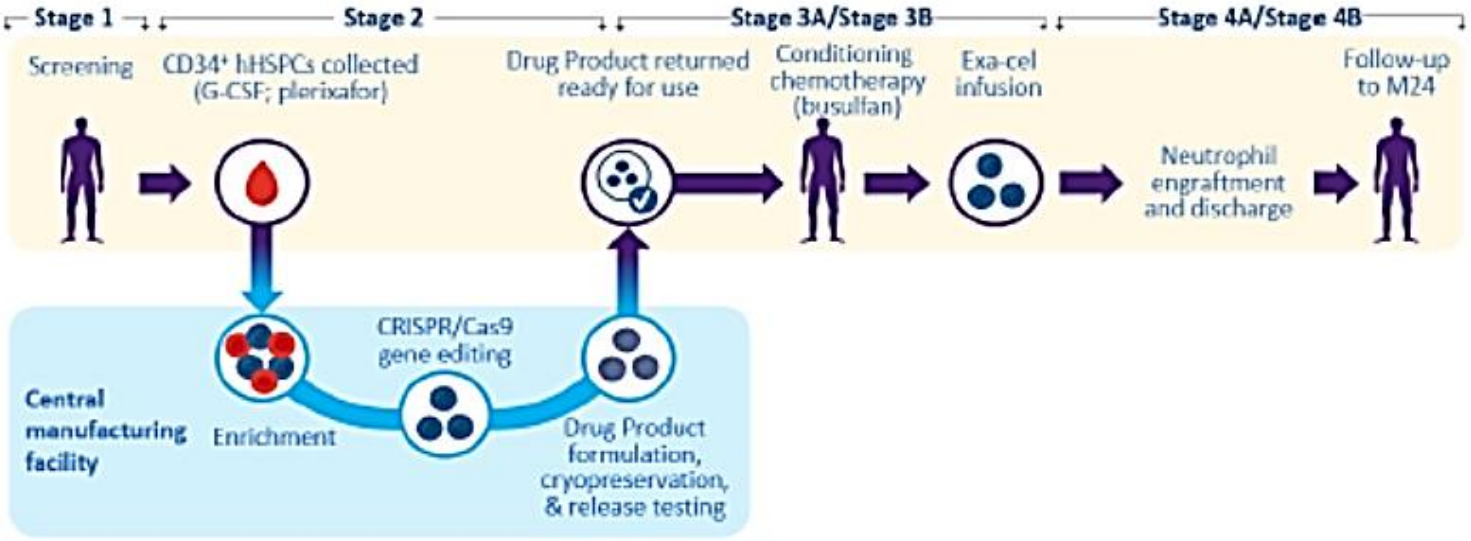
Transfusion-dependent β-Thalassemia - details of cell mobilisation, apheresis, and myeloablative conditioning used in the clinical studies for Casgevy.

Indication: Casgevy is indicated for the treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

Intervention

Each person enrolled into the study went through 'stages'; these stages are summarised in the following diagram:

Figure 9-1 Study 111 Study Design



Source: Adapted from Appendix 16.1.1/Protocol Version 6.7 EUR/Figure 6
CRISPR/Cas9: clustered regularly interspaced short palindromic repeats and CRISPR-associated 9 nuclease; exa-cel: exagamglogene autotemcel; G-CSF: granulocyte-colony stimulating factor; hHSPCs: human hematopoietic stem and progenitor cells; M24: Month 24
Note: Figure not drawn to scale.

Stage 1:
After eligibility was confirmed, prior to start of apheresis procedure and at least 60 days prior to planned initiation of busulfan conditioning, it was recommended that subjects be transfused to achieve a goal of pre-transfusion Hb ≥11 g/dL.

Subjects could undergo fertility preservation as per subject age and local practice.

Stage 2:
Before starting administration of plerixafor and G-CSF products, subjects were assessed by the study investigator to confirm whether they were eligible to proceed with apheresis, as per local guidelines.

Mobilisation consisted of a combination of G-CSF product and plerixafor.

On Day 1 of mobilization, subjects received granulocyte-colony stimulating factor (G-CSF) product (e.g. filgrastim). G-CSF was administered subcutaneously or intravenously at a dose of 5 μg/kg/dose approximately every 12 hours (q12h) for 5 to 6 days.

Plerixafor was administered after the subject had received G-CSF for 4 days. Plerixafor was administered via subcutaneous injection; the recommended dose was 0.24 mg/kg administered approximately 4 to 6 hours before planned apheresis.

The doses of G-CSF product and Plerixafor were based on the body weight taken within 5 days before the first day of mobilization. Doses were also adjusted for subjects with renal or hepatic impairment and obesity. The dose of G-CSF product was also adjusted for splenectomised subjects.

Splenectomised subjects received a lower dose of G-CSF of 5 μg/kg/dose once daily (qd) for 5 to 6 days to prevent leucocytosis. The dose could be increased to q12h if there was no significant increase in white blood cell or peripheral blood $CD34^+$ counts after discussion with the medical monitor.

Subjects underwent apheresis for up to 3 consecutive days to collect $CD34^+$ human haematopoietic stem and progenitor cells.

Day 2 and Day 3 (if required) were the same as Day 1. The targeted $CD34^+$ cell collection was at least 15 × 10^6 $CD34^+$ cells/kg.

An additional 2 × 10^6 $CD34^+$ cells/kg were collected as backup for rescue therapy in an event of non-neutrophil engraftment with exa-cel.

Collected cells intended for manufacturing were shipped same-day at 2°C to 8°C to the manufacturing facility. Backup $CD34^+$ stem cells did not undergo the editing / manufacturing process and were cryopreserved at the site.

Up to 2 additional mobilization and apheresis cycles were allowed to collect additional cells if sufficient numbers of cells for exa-cel manufacturing and backup were not obtained.

Comment: To note that described use of G-CSF and plerixafor is not fully consistent with their respective SmPCs.

The number of mobilisation cycles and cells collected for manufacturing are summarised in Table 10-5.

Table 10-5 Summary of Mobilization Overall (FAS)

Parameter	Total N = 54
Number of mobilization cycles	
n	54
Mean (SD)	1.26 (0.65)
Median	1.00
Min, max	1.00, 4.00
Cells collected for manufacturing (10^6 $CD34^+$ cells/kg)	
n	54
Mean (SD)	46.88 (32.27)
Median	37.58
Min, max	10.94, 202.36

Source: Table 14.1.7.1 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; N: total sample size; n: size of subsample
Note: Cells collected for manufacturing for a subject was calculated as a sum of all cells collected for manufacturing across all cycles for a subject/ the subject's most recent weight before the last mobilization cycle.

For the 54 subjects in the full analysis set, median (range) number of mobilization cycles was 1 (1 to 4).

The median (range) number of cells collected for drug product manufacturing was 37.58 (10.94 to 202.36) × 10^6 $CD34^+$ cells/kg.

Stage 3A:
After the exa-cel product was received at the clinical site and the backup $CD34^+$ stem cells were confirmed available and in acceptable condition to be administered if needed, the subject began busulfan conditioning.

Busulfan was administered intravenously through a central venous catheter once daily for 4 consecutive days with a starting dose of 3.2 mg/kg/day (based on body weight 3 to 7 days before the first day of busulfan administration).

Once-a-day dosing was the preferred schedule but the busulfan dose could be adjusted to be given every 6 hours (q6h) per site's standard practice.

A test dose of busulfan could be performed within 30 days before beginning myeloablation to pre-determine the busulfan dose.

For subjects <34 kg, weight-based starting dose recommendations for busulfan were as follows:

- For subjects weighing 16 to 23 kg, 1.1 mg/kg q6h or 4.4 mg/kg qd
- For subjects weighing >23 to 34 kg, 0.95 mg/kg q6h or 3.8 mg/kg qd

The target AUC was 74 mg-h/L (target range: 59 to 89) for the q6h regimen and 82 mg-h/L (target range: 74 to 90) for the once-a-day regimen. The target busulfan AUC or cumulative exposure for each dosing regimen was the same across all age groups.

During busulfan conditioning, anti-seizure prophylaxis (per institutional guidelines for medications, except phenytoin which was contraindicated) and other supportive measures were instituted as per hospital guidelines.

The conditioning regimen and total busulfan dose are summarised in Table 10-6.

Table 10-6 Summary of Conditioning Overall (FAS)

Parameter	Total N = 54
Busulfan dose regimen, n (%)	
q6h	23 (42.6)
qd	31 (57.4)
Total busulfan dose (mg/kg)	
n	54
Mean (SD)	14.91 (2.61)
Median	14.87
Min, max	10.62, 24.82

Source: Table 14.1.8 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; N: total sample size; n: size of subsample; q6h: every 6 hours; qd: once daily
Notes: Percentages were calculated relative to the number of subjects in the FAS. Total busulfan dose (mg/kg) for a subject was calculated as a sum of all busulfan doses for the subject/the subject's most recent weight before the start of conditioning.

Stage 3B:
The exa-cel infusion occurred at least 48 hours after completion of the busulfan infusion and no more than 7 days after completion of the busulfan infusion.

On Day 1, the entire dose (all vials) of exa-cel was infused IV through a central venous catheter.

Each vial containing exa-cel was infused within 20 minutes after thawing.

If exa-cel infusion did not occur within 7 days after the last dose of busulfan, subjects were to receive the backup $CD34^+$ stem cells.
Following exa-cel infusion, subjects underwent infection surveillance and prophylaxis (bacterial, viral, fungal) as per local guidelines for haematopoietic stem cell transplant and investigator judgment.

If engraftment did not occur by Day 21 after exa-cel infusion, G-CSF (e.g. filgrastim) could have been administered following discussion with the medical monitor.

Stage 4A:
Subjects were monitored for adverse events and neutrophil engraftment in the transplant unit and received supportive care (e.g. packed red blood cell and platelet transfusions according to standard practices for subjects undergoing haematopoietic stem cell transplant.

Subjects were discharged from the transplant unit upon neutrophil engraftment and stabilization of major medical issues as per local hospital guidelines and / or investigator judgment.

Subjects could have received G-CSF (e.g. filgrastim) if no neutrophil engraftment was apparent by Day 21. The use of G-CSF after exa-cel infusion was discussed with the study medical monitor before initiation.

Comment: granulocyte colony-stimulating factor (G-CSF) used after hematopoietic stem cell transplantation can enhance neutrophil recovery in patients rendered neutropenic by the preparative regimen.

If neutrophil engraftment was not achieved within 42 days after exa-cel infusion (after Study Day 43), the investigator determined whether and when the subject was to receive the backup $CD34^+$ stem cells according to his / her judgement based on all available clinical information (e.g. the subject's clinical status, presence of myeloid precursors on a bone marrow aspirate, presence of monocytes and neutrophils in the peripheral blood, whether engraftment had occurred by approximately Day 60).

Stage 4B:
After subjects achieved successful neutrophil engraftment and were clinically stable, they were discharged from the transplant unit and followed for approximately 2 years after the exa-cel infusion.

Subjects were recommended not to restart iron chelation (if needed) until at least 3 months after exa-cel infusion.

Following neutrophil engraftment, transfusions of packed RBCs were avoided for Hb ≥9 g/dL, unless medically indicated (e.g. symptomatic anaemia or as a requirement for surgery). It was recommended that subjects receive packed red blood cell transfusions for Hb <7.0 g/dL.

Comment: Management of subjects after receiving product appears in line with usual practice and so may be accepted.

Follow-up
All subjects who received exa-cel were offered enrolment into the long-term follow-up study (Study 131) after completion or withdrawal/discontinuation from Study 111.

Comment: long-term follow-up of subjects receiving a novel therapy is considered appropriate.

Comment: The MAH provided an "Apheresis and Infusion Specialist" and "Medical Monitor" to give oversight.
The MAH submits:

- an apheresis collection manual ver 9.0, dated 14 Oct 2022. The manual describes roles / responsibilities; equipment needed; chain of identity and chain of custody; labelling, packaging and shipping of material with GPS tracking.
- a product receipt, storage and infusion manual ver 9.0, dated 14 Oct 2022. The manual describes roles / responsibilities; equipment needed; chain of identity and chain of custody; product complaints procedure; shipment and receipt with GPS tracking; product storage; product administration.

Different versions of the web-based chain of identity / chain of custody system were used for the different CTX001 studies.

Exa-cel is held in cryo-storage; exa-cel must be infused within 20 minutes of completion of thawing; if exa-cel is in multiple vials then vials must be infused one at a time; 2 people must verify exa-cel labelling at the bedside prior to the infusion of each exa-cel vial; exa-cel is administered as an intravenous bolus.

Data cut-off
At the time of the interim data cut, a total of 54 subjects in the full analysis set had been infused with exa-cel. The median exa-cel dose was 8.0 (range: 3.0 to 19.7) × 10^6 $CD34^+$ cells/kg and the median follow-up duration after exa-cel infusion was 22.8 (range: 2.1 to 27.1) months.

The median (range) exa-cel dose for subjects ≥18 and ≤35 years of age was 6.5 (3.0 to 15.6) × 10^6 $CD34^+$ cells/kg. The median (range) exa-cel dose for subjects ≥12 and <18 years of age was 10.4 (3.2 to 19.7) × 10^6 $CD34^+$ cells/kg. There were no clinically relevant differences in the exa-cel dose and follow-up duration when analysed by genotype, sex, race, or region.

The median (range) follow-up was 23.9 (3.0 to 27.1) months for subjects ≥18 and ≤35 years of age. The median (range) follow-up was 19.6 (2.1 to 24.6) months for subjects ≥12 and <18 years of age (subjects ≥12 and <18 years of age have a shorter duration of follow-up compared to subjects ≥18 and ≤35 years of age because they were enrolled after efficacy and safety data from the first 2 adult subjects were reviewed).

The exa-cel dose data for the 42 subjects in the primary efficacy set are summarized in the tables below: The median dose was 7.5 (range: 3.0 to 19.7) × 10^6 $CD34^+$ cells/kg. The median (range) follow-up duration after exa-cel infusion was 23.9 (16.1 to 27.1) months.

Vertex Pharmaceuticals Incorporated
Protocol CTX001-111

Table 14.1.10.1
Summary of CTX001 Dose
Full Analysis Set and Primary Efficacy Set

	Full Analysis Set N = 54	Primary Efficacy Set N = 42
CTX001 Dose (10^6 CD34+ cells/kg)		
n	54	42
Mean (SD)	8.4 (4.26)	8.5 (4.30)
Median	8.0	7.5
Q1, Q3	4.8, 11.1	5.1, 11.3
Min, max	3.0, 19.7	3.0, 19.7

Table 14.1.11.2
Summary of Post-CTX001 Infusion Follow-up Duration
Full Analysis Set and Primary Efficacy Set

	Primary Efficacy Set N = 42
Post-CTX001 Infusion Exposure (patient-months)	946.0
Post-CTX001 Infusion Exposure (patient-years)	78.8
Post-CTX001 Infusion Follow-up Duration (months)	
n	42
Mean (SD)	22.5 (2.82)
Median	23.9
Q1, Q3	21.2, 24.2
Min, max	16.1, 27.1

Comparator
This is a single-arm study without concurrent comparator.

Outcomes

The main analyses of all efficacy endpoints were based on the primary efficacy set (N = 42), data cutoff date 16 Apr 2023.

Comments: Outcomes are assessed with the caveat of the fallacy of human reasoning referred to as: *post hoc ergo propter hoc* (Latin: 'after this, therefore because of this').

Primary Efficacy Outcome
The proportion of subjects who maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion is presented in Table 11-3:

Table 11-3 Proportion of Subjects Who Achieved TI12 (PES)

Category	Total N = 42
Subjects who achieved TI12	
n	39
%, 2-sided 95% CI	92.9 (80.5, 98.5)
1-sided *P* value against a 50% response rate	<0.0001

Source: Table 14.2.1.1 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; N: total sample size; n; size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion
Notes: The evaluation of TI12 started 60 days after the last RBC transfusion for post-transplant support or TDT disease management. Hb measurements used for the determination of the weighted average Hb were from central laboratory data. Only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included. The percentage of subjects who achieved TI12 was calculated relative to the number of subjects in PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method and the 1-sided *P* value was calculated using the exact binomial distribution.

Comment: 39/42 subjects maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion; this is considered to be notable in the context of subjects who were dependent upon red blood cell transfusions prior to the trial.

Subgroup analyses of the primary efficacy endpoint by age (≥12 and <18 years of age and ≥18 and ≤35 years of age), genotype (β0/β0-like and non-β0/β0-like), race (Asian, White and Other Races) and sex are presented in Table 11-4.

Table 11-4 Subgroup Analysis: Proportion of Subjects Who Achieved TI12 by Age at Screening, Genotype, Race, and Sex (PES)

Subgroup	Total N = 42
Age	
Subjects ≥12 and <18 years of age at screening, N1	13
Subjects ≥12 and <18 years of age at screening and achieved TI12	
n	12
%, 2-sided 95% CI	92.3 (64.0, 99.8)
Subjects ≥18 and ≤35 years of age at screening, N1	29
Subjects ≥18 and ≤35 years of age at screening and achieved TI12	
n	27
%, 2-sided 95% CI	93.1 (77.2, 99.2)
Genotype[a]	
Subjects with β^0/β^0-like genotypes, N1	25
Subjects with β^0/β^0-like genotypes and achieved TI12	
n	22
%, 2-sided 95% CI	88.0 (68.8, 97.5)
Subjects with non-β^0/β^0-like genotypes, N1	17
Subjects with non-β^0/β^0-like genotypes and achieved TI12	
n	17
%, 2-sided 95% CI	100.0 (80.5, 100.0)
Sex	
Male subjects, N1	21
Male subjects and achieved TI12	

n	19
%, 2-sided 95% CI	90.5 (69.6, 98.8)
Female subjects, N1	21
Female subjects and achieved TI12	
n	20
%, 2-sided 95% CI	95.2 (76.2, 99.9)
Race	
Subjects whose race is Asian, N1	16
Subjects whose race is Asian and achieved TI12	
n	14
%, 2-sided 95% CI	87.5 (61.7, 98.4)
Subjects whose race is White, N1	17
Subjects whose race is White and achieved TI12	
n	16
%, 2-sided 95% CI	94.1 (71.3, 99.9)
Subjects whose race is Other Races, N1	9
Subjects whose race is Other Races and achieved TI12	
n	9
%, 2-sided 95% CI	100.0 (66.4, 100.0)

Source: Table 14.2.1.2, Ad hoc Table 14.2.1.3 (data cutoff date of 16 April 2023)

EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; N: total sample size; n: size of subsample; N1: number of subjects in each subgroup; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained weighted average hemoglobin ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion

Notes: The evaluation of TI12 started 60 days after the last RBC transfusion for post-transplant support or TDT disease management. Hb measurements used for the determination of the weighted average Hb were from central laboratory data. Only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included. The percentage of subjects who achieved TI12 was calculated relative to the number of subjects in each subgroup, i.e., n/N1 × 100. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only a descriptive summary (n and percentage) was provided for subgroups with a sample size <5. Other Races included any races other than Asian and White. Multi-races were also included in Other Races.

[a] β^0/β^0-like genotypes included β^0/β^0, IVS-I-110/β^0, and IVS-I-110/IVS-I-110. All other genotypes were considered non-β^0/β^0-like.

The results of the subgroup analyses were generally consistent with the results from the primary analysis.

Comment: 12/13 (92%) subjects ≥12 and <18 years of age and 27/29 (93%) subjects ≥18 and ≤35 years of age achieved the primary outcome; results between the age groups are considered comparable.

A comparison of outcomes of sub-group by sex, race and genotype, as described, are also considered comparable.

Yet numbers are small and so final opinion is reserved at present. At present: such data would not give concern.

Secondary efficacy outcomes

1. Proportion of subjects who maintained a weighted average Hb ≥9 g/dL without red blood cell transfusions for at least 6 consecutive months any time after exa-cel infusion

This outcome is described by The MAH as 'key secondary'; data are presented in the following table:

Table 11-5 Proportion of Subjects Who Achieved TI6 (PES)

Category	Total N = 42
Subjects who achieved TI6	
n	39
%, 2-sided 95% CI	92.9 (80.5, 98.5)
1-sided *P* value against a 50% response rate	<0.0001

Source: Table 14.2.2.1 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI6: maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time after exa-cel infusion
Notes: The evaluation of TI6 started 60 days after the last RBC transfusion for post-transplant support or TDT disease management. Hb measurements used for the determination of the weighted average Hb were from central laboratory data. Only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included. The percentage of subjects who achieved TI6 was calculated relative to the number of subjects in the PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method.

Comment: 39/42 subjects maintained a weighted average Hb ≥9 g/dL without red blood cell transfusions for at least 6 consecutive months any time after exa-cel infusion. This outcome is considered notable for a population that was dependent upon transfusions.

Subgroup Analysis of Key Secondary Efficacy Outcome

Subgroup analyses of the key secondary efficacy endpoint by age (≥12 and <18 years of age and ≥18 and ≤35 years of age), genotype (β0/β0-like and non-β0/β0-like), race (Asian, White and Other Races) and sex are presented in Table 11-6.

Table 11-6 Subgroup Analysis: Proportion of Subjects Who Achieved TI6 by Age at Screening, Genotype, Race, and Sex (PES)

Subgroup	Total N = 42
Age	
Subjects ≥12 and <18 years of age at screening, N1	13
Subjects ≥12 and <18 years of age at screening and achieved TI6	
n	12
%, 2-sided 95% CI	92.3 (64.0, 99.8)
Subjects ≥18 and ≤35 years of age at screening, N1	29
Subjects ≥18 and ≤35 years of age at screening and achieved TI6	
n	27
%, 2-sided 95% CI	93.1 (77.2, 99.2)
Genotype[a]	
Subjects with β^0/β^0-like genotypes, N1	25
Subjects with β^0/β^0-like genotypes and achieved TI6	
n	22
%, 2-sided 95% CI	88.0 (68.8, 97.5)
Subjects with non-β^0/β^0-like genotypes, N1	17
Subjects with non-β^0/β^0-like genotypes and achieved TI6	
n	17
%, 2-sided 95% CI	100.0 (80.5, 100.0)
Sex	
Male subjects, N1	21
Male subjects and achieved TI6	
n	19
%, 2-sided 95% CI	90.5 (69.6, 98.8)
Female subjects, N1	21
Female subjects and achieved TI6	
n	20
%, 2-sided 95% CI	95.2 (76.2, 99.9)

Race	
Subjects whose race is Asian, N1	16
Subjects whose race is Asian and achieved TI6	
n	14
%, 2-sided 95% CI	87.5 (61.7, 98.4)
Subjects whose race is White, N1	17
Subjects whose race is White and achieved TI6	
n	16
%, 2-sided 95% CI	94.1 (71.3, 99.9)
Subjects whose race is Other Races, N1	9
Subjects whose race is Other Races and achieved TI6	
n	9
%, 2-sided 95% CI	100.0 (66.4, 100.0)

Source: Table 14.2.2.2, Ad hoc Table 14.2.2.6 (data cutoff date of 16 April 2023)

EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; N1: number of subjects in each subgroup; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI6: maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time after exa-cel infusion

Notes: The evaluation of TI6 started 60 days after last RBC transfusion for post-transplant support or TDT disease management. Hb measurements used for the determination of the weighted average Hb were from the central laboratory data. Only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included. The percentage of subjects who achieved TI6 was calculated relative to the number of subjects in each subgroup, i.e., n/N1 × 100. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only a descriptive summary (n and percentage) was provided for subgroups with a sample size <5. Other Races included any races other than Asian and White. Multi-races were also included in Other Races.

[a] β^0/β^0-like genotypes included β^0/β^0, IVS-I-110/β^0, and IVS-I-110/IVS-I-110. All other genotypes were considered non-β^0/β^0-like.

The results of the subgroup analyses were generally consistent with the results from the primary analysis.

Numbers in subgroups are small and so final opinion is reserved at present. At present: such data would not give concern.

2. Duration being transfusion-free for subjects who achieved the primary efficacy endpoint (where being transfusion-free is defined as maintaining a weighted average Hb ≥9 g/dL without red blood cell transfusions; evaluation started 60 days after last RBC transfusion for post-transplant support or transfusion-dependent β-thalassemia disease management).

Data are presented in the following tables:

Table 11-7 summarises time from exa-cel administration to last red blood cell transfusion for those who achieved the primary objective.

Table 11-7 Summary of Time From Exa-cel Infusion to the Last RBC Transfusion for Subjects Who Achieved TI12 (PES)

Category	Total N = 42 n (%)
Time from exa-cel infusion to the last RBC transfusion (days)	
n	39
Mean (SD)	32.5 (18.1)
Median	28.0
Min, max	11, 91

Source: Ad hoc Table 14.2.28 (data cutoff date of 16 April 2023)

EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion

Notes: Only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included. Time from exa-cel infusion to the last RBC transfusion for post-transplant support or TDT disease management (days) = Date of the last RBC transfusion for post-transplant support or TDT disease management – exa-cel infusion date + 1.

The mean (SD) time to the last red blood cell transfusion for subjects in this category was 32.5 (18.1) days from exa-cel infusion with the time to last red blood cell transfusion ranging from 11 to 91 days.

Comment: For the 39/42 subjects in this category, the median time to achieve 'free from transfusion' was (about) 1 month and the maximum time was (about) 3 months. Data are considered to be notable in a population previously dependent upon red blood cell transfusions.

Table 11-8 summarises time of being 'transfusion-free' from the last red blood cell transfusion for those who achieved the primary objective.

Table 11-8 Summary of Duration of RBC Transfusion Free While Maintaining Weighted Average Hb ≥9 g/dL for Subjects Who Achieved TI12 (PES)

Category	Total N = 42
Subjects who achieved TI12, N1	39
Duration of RBC transfusion free while maintaining weighted average Hb ≥9 g/dL for subjects who achieved TI12 (months)	
n	39
Mean (SD)	19.4 (2.8)
Median	20.4
Min, max	13.5, 24.3

Source: Table 14.2.4 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; N: total sample size; n: size of subsample; N1: subjects who achieved TI12; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion
Notes: The evaluation of duration of RBC transfusion free while maintaining a weighted average of Hb ≥9 g/dL in subjects who achieved TI12 started 60 days after the last RBC transfusion for post-transplant support or TDT disease management. Duration of RBC transfusion free while maintaining a weighted average of Hb ≥9 g/dL (months) = (the day before the start date of first RBC transfusion after achieving TI12 or the day of the last assessment before weighted average Hb <9 g/dL after achieving TI12 or data cut date or end of study date whichever was earlier - start date of TI12 + 1)/30. For post-baseline, only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included.

All subjects in the primary efficacy set who met the primary endpoint remained transfusion free for the duration of follow-up; the mean (SD) transfusion free duration while maintaining weighted average Hb ≥9 g/dL was 19.4 (2.8) months, starting 60 days after the last red blood cell transfusion.
The total duration of transfusion free ranged from 13.5 to 24.3 months.

Comment: for the 39/39 subjects in this category, the maximum time for being 'transfusion-free' is (about) 24 months. This is an on-going study with a story that is still evolving; there is potential for forthcoming data to support longer times for being 'transfusion-free'.

At the time of the interim data cut (16 April 2023), 54 subjects were in the full analysis set. 53 subjects have been transfusion-free for 0.3 to 24.3 months, starting 60 days after the last RBC transfusion.
Transfusion free duration data for the FAS are presented by subject in **Figure 11-5**:

Comment: the 3 subjects with extended need for red blood cell transfusion are described more fully under secondary outcome no. 3, below.

Transfusion data for the full analysis set are also presented by subject in **Figure 11-4** showing historical red blood cell transfusions and red blood cell transfusions after exa-cel infusion:

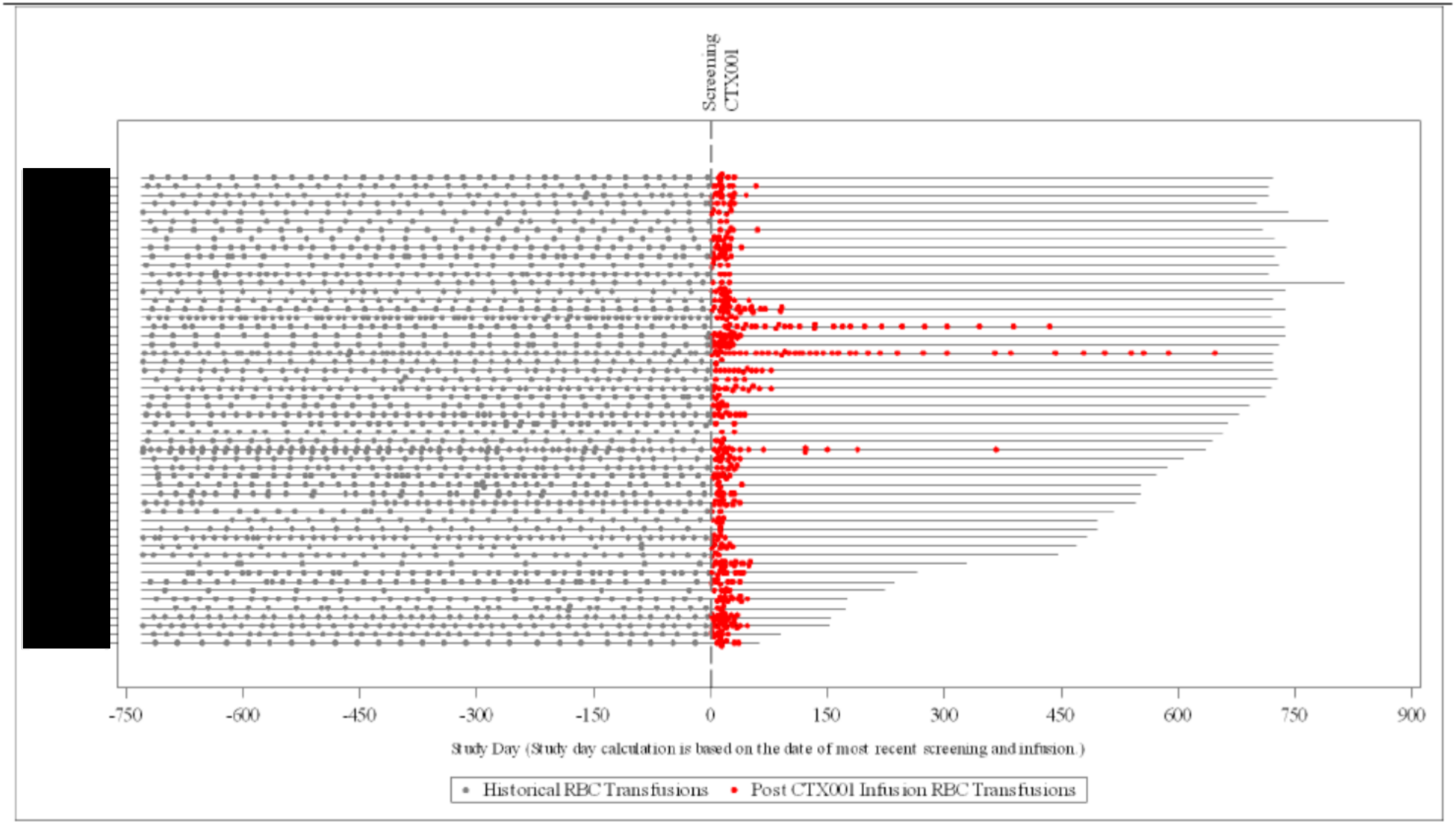
Comment: the pattern of red blood cell transfusions in the full analysis set (before and after exposure to exa-cel) is generally supportive towards the claims of The MAH based on the primary efficacy set.

Although such presentations (comparing historical data to current data) are prone to ascertainment bias, the difference between ‘before’ and ‘after’ is notable and would support the claim of the MAH for efficacy.

Three subjects continued to require blood transfusions after exposure to product.

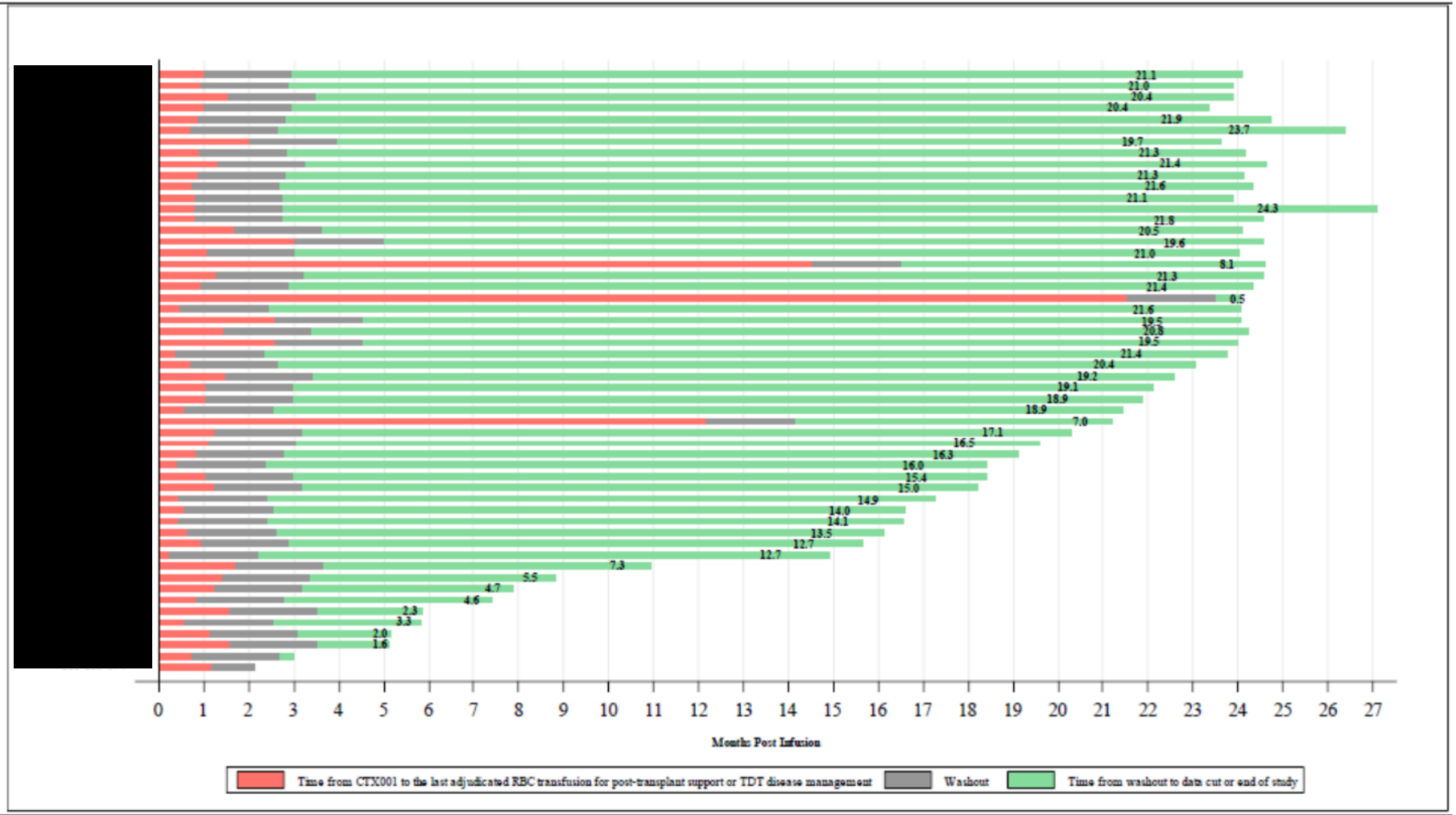
Further comment: Figures 11-4 and 11-5 are assessed with the caveat of the fallacy of human reasoning referred to as: *post hoc ergo propter hoc* (Latin: 'after this, therefore because of this')

Figure 11-4 Historical and After Exa-cel Infusion RBC Transfusions (FAS)



Source: Figure 14.2.1 (data cutoff date of 16 April 2023)
CTX001: exagamglogene autotemcel (exa-cel); FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia
Notes: Investigator-reported TDT-related historical RBC transfusions and all post-infusion RBC transfusions were included. * Indicates subjects in the PES.

Figure 11-5 Duration of Period Free From Transfusions (FAS)



Source: Figure 14.2.2 (data cutoff date of 16 April 2023)

EAC: Endpoint Adjudication Committee; CTX001: exagamglogene autotemcel (exa-cel); FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia

Notes: Only RBC transfusions adjudicated by the EAC for post-transplant support or TDT disease management were included. The number on the right end is the duration of total follow-up.
* Indicates subjects in the PES. Transfusion free duration starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management. The washout period refers to the duration between the last RBC transfusion for post-transplant support or TDT management to the start of transfusion free duration

3. For subjects who did not achieve the primary efficacy endpoint: relative reduction from baseline in annualised volume of red blood cell transfusions.

Of the 42 subjects in the primary efficacy set, 3 subjects had not achieved the primary objective at the time of the interim analysis data cut.

Relative reduction from baseline in annualised volume of red blood cell transfusions up to 24 months after exa-cel infusion for those 3 subjects is summarised in Table 11-9:

Table 11-9 Summary of Relative Reduction From Baseline in Annualized Volume of RBC Transfusions for Subjects Who Did Not Achieve TI12 (PES)

Category	Total N = 42
Subjects who did not achieve TI12, N1	3
Baseline annualized volume of RBC transfusions for subjects who did not achieve TI12 (mL/kg)	
n	3
Mean (SD)	233.7 (91.1)
Median	263.9
Min, max	131.4, 306.0
Annualized volume of RBC transfusions after exa-cel infusion for subjects who did not achieve TI12 (mL/kg)	
n	3
Mean (SD)	25.3 (21.3)
Median	25.1
Min, max	4.0, 46.6
Relative reduction from baseline[a] in annualized volume of RBC transfusions for subjects who did not achieve TI12 (%)	
n	3
Mean (SD)	88.0 (9.2)
Median	84.8
Min, max	80.9, 98.5

Source: Table 14.2.3 (data cutoff date of 16 April 2023)

EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; ICF: informed consent form; N: total sample size; n: size of subsample; N1: number of subjects in each subgroup; PES: Primary Efficacy Set; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia; TI12: maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel infusion

Notes: Baseline volume of RBC transfusions was based on the 2 years before signing of the ICF or the latest rescreening for subjects who rescreened. The evaluation of annualized volume of RBC transfusions after exa-cel infusion started following Month 10 after exa-cel infusion. For baseline, RBC transfusions were excluded if they were not for TDT disease management. Post-baseline, only RBC transfusions adjudicated by an EAC as meeting the purpose of post-transplant support or TDT disease management were included. The percentages of categories of relative reduction from baseline in annualized volume of RBC transfusions for subjects who did not achieve TI12 were calculated relative to the number of subjects who did not achieve TI12 (i.e., n/N1 × 100). Annualized volume = Total volume/number of years, with 1 year = 365.25 days.

[a] Relative reduction from baseline = 100% × (Baseline value – post-baseline value)/Baseline value.

All 3 subjects had a decrease in annualised red blood cell transfusion volume after administration of exa-cel compared to baseline: 81%, 85%, and 98%.

Comment: the marked reduction in need for red blood cell transfusion is noted for the 3 subjects who did not achieve the primary objective; at least 80% reduction in need for red blood cell transfusion is considered to be notable.

Three subjects did not achieve the primary objective. Summaries of the subjects' clinical statuses were provided.

4. Absolute and relative monthly reduction from baseline in volume / units / episodes of red blood cell transfusions

Primary efficacy set

- Of the 39 subjects in the primary efficacy set who achieved the primary objective, most (38 subjects) stopped receiving red blood cell transfusions by Month 3 (1 subject by Month 4).
- The mean (SD) monthly relative reduction from baseline in red blood cell transfusions at Month 12 was 98.3% (10.8%) by volume, 98.2% (11.4%) by units and 98.2% (11.4%) by episodes.
- For the subjects in the primary efficacy set at Month 24 (N = 27), the mean monthly relative reduction from baseline in red blood cell transfusion volume, units and episodes was 100%.

Full analysis set

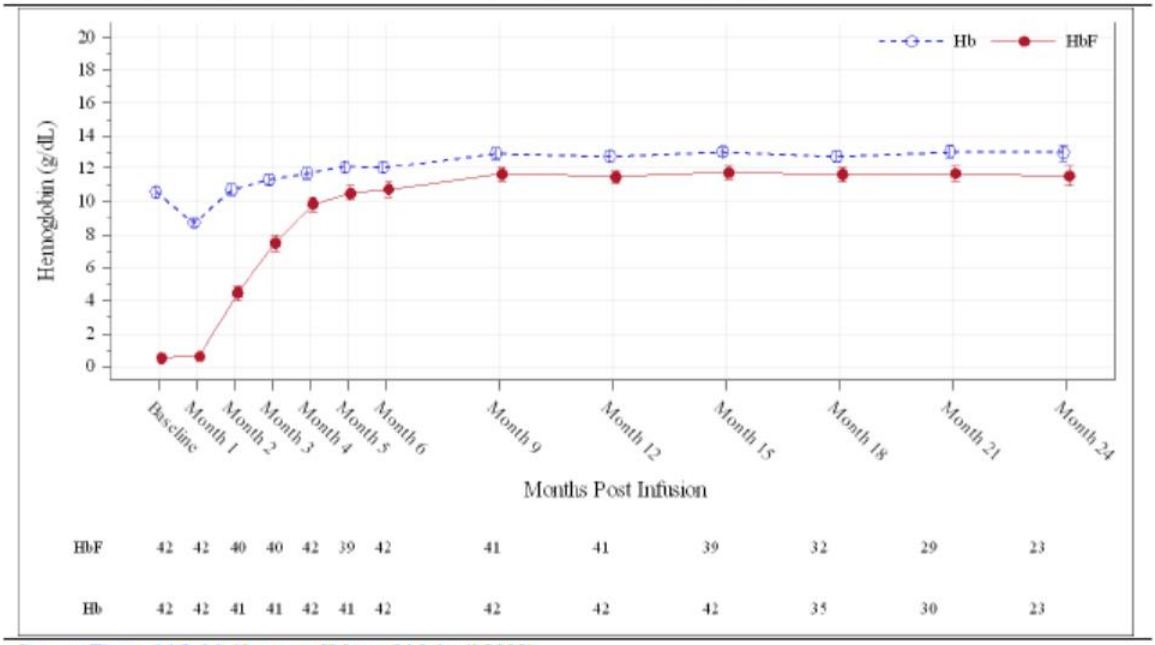
- For the subjects in the full analysis set who were past the washout period (N = 53), the mean (SD) time from exa-cel infusion to last red blood cell transfusion was 58.0 (110.2) days
- For the subjects in the full analysis set at Month 12 (N = 44), the mean (SD) monthly relative reduction from baseline in red blood cell transfusions was 98.4% (10.5%) by volume, 98.3% (11.1%) by units, and 98.3% (11.1%) by episodes.

Comment: The reductions in need for red blood cell transfusions, described above, are considered to be notable and supportive towards the claims of The MAH.

5. Total Hb and HbF in the primary efficacy set

Data are summarised in the figure on the following page.

Figure 11-6 Summary of Total Hb (g/dL) and HbF (g/dL) Over Time (PES)



Source: Figure 14.2.6.1 (data cutoff date of 16 April 2023)
Hb: hemoglobin; HbF: fetal hemoglobin; PES: Primary Efficacy Set
Notes: Mean values are plotted in the line; mean + SE and mean - SE values are plotted as bars at each visit. The numbers of subjects with total Hb and HbF values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

Mean (SD) total Hb concentration was 11.4 (2.3) g/dL at Month 3, increased to 12.1 (2.0) g/dL by Month 6 and was maintained ≥12 g/dL over the duration of follow-up.

Mean (SD) HbF concentration was 7.5 (3.0) g/dL at Month 3, increased to 10.8 (2.8) g/dL at Month 6 and were thereafter maintained ≥11 g/dL over the duration of follow-up.

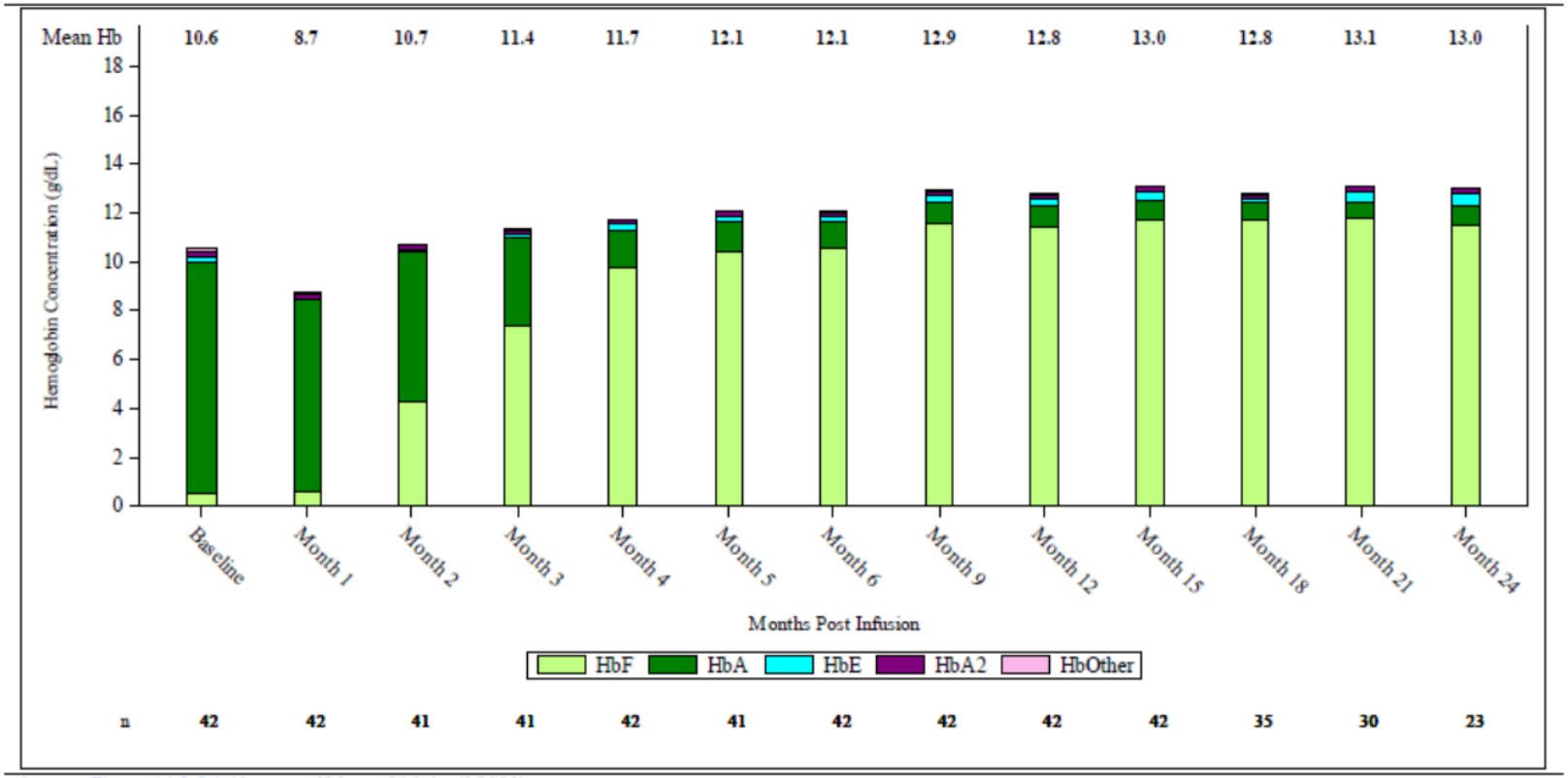
Comment: the marked increase in HbF concentration from baseline up to month 9 (from where HbF concentration is maintained) is in accord with the claimed mechanism of action of the CRISPR process.

By month 9: HbF was a mean of about 90% total haemoglobin.

Data from month 18 onwards are obtained in a reduced set of subjects; it may be expected that the numbers in this set will increase as the MAH submits further information.

Different Hb fractions over time after exa-cel infusion for the primary efficacy set is shown in Figure 11-7

Figure 11-7 Hb Fraction Summary Over Time (PES)



Source: Figure 14.2.5.1 (data cutoff date of 16 April 2023)

Hb: hemoglobin; HbA: hemoglobin A; HbA2: hemoglobin A2; HbE: hemoglobin E; HbF: fetal hemoglobin; Hb Other: Total Hb – HbA- HbA2 - HbE - HbF; n: size of subsample; PES: Primary Efficacy Set

Notes: Mean Hb fractions are plotted at each visit. The numbers of subjects with total Hb values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit is shown in the figure.

HbF was the dominant contributor to the total Hb value from Month 3 onward, with a relatively low contribution from other endogenous Hb forms.

Comment: HbF increased from trace concentrations at baseline to a mean (SD) of (about) 11.7 (2.7) g/dL by 9 months after exposure to exa-cel.

6. Proportion of alleles with intended genetic modification present in (i) the drug product, (ii) peripheral blood and (iii) $CD34^+$ cells of the bone marrow

Data for the drug product are presented for the PES and FAS in Table 11-12:

Table 11-12 Summary of the Proportion of Alleles With the Intended Genetic Modification in the Exa-cel Drug Product (PES and FAS)

Category	PES N = 42	FAS N = 54
Exa-cel product editing (%)		
n	42	54
Mean (SD)	87.15 (9.23)	88.04 (8.36)
Median	90.93	91.08
Min, max	58.43, 95.44	58.43, 95.44

Source: Table 14.1.9.1 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total sample size; n: size of subsample; PES: Primary Efficacy Set
Note: Proportion of alleles with intended genetic modification in exa-cel was from central laboratories. The proportion of alleles with intended genetic modification in exa-cel drug product is calculated as a weighted average based on lots with available data

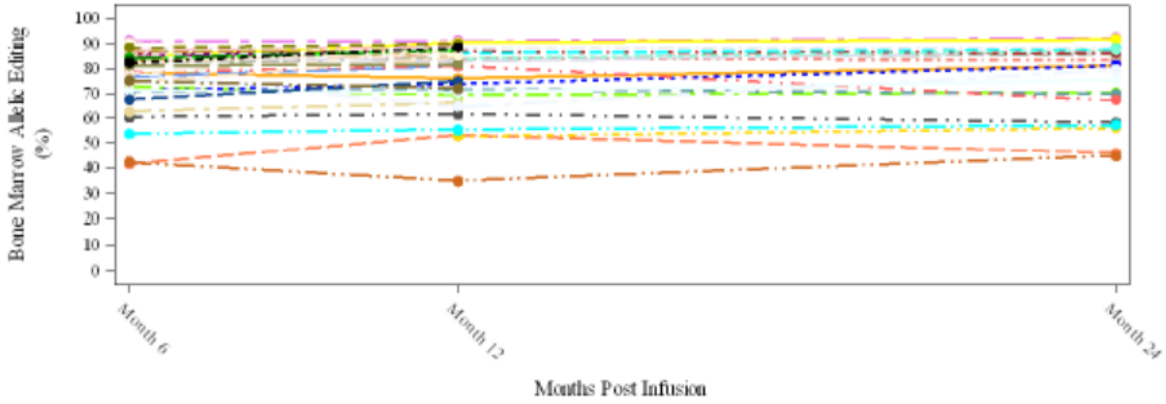
For subjects in the primary efficacy set, the mean (SD) proportion of alleles with the intended genetic modification in the drug product was 87.15% (9.23%).

Bone Marrow:

In the primary efficacy set, at Month 6 (first timepoint of evaluation), the mean (SD) proportion of alleles with the intended genetic modification in the $CD34^+$ cells of the bone marrow was 77.37% (11.83%), consistent with allelic editing in the drug product.

The mean proportion of alleles with the intended genetic modification in the $CD34^+$ cells of the bone marrow remained stable at Month 12 (≥75%) onward (Figure 11-10):

Figure 11-10 Individual Bone Marrow Allelic Editing (%) Over Time (PES)

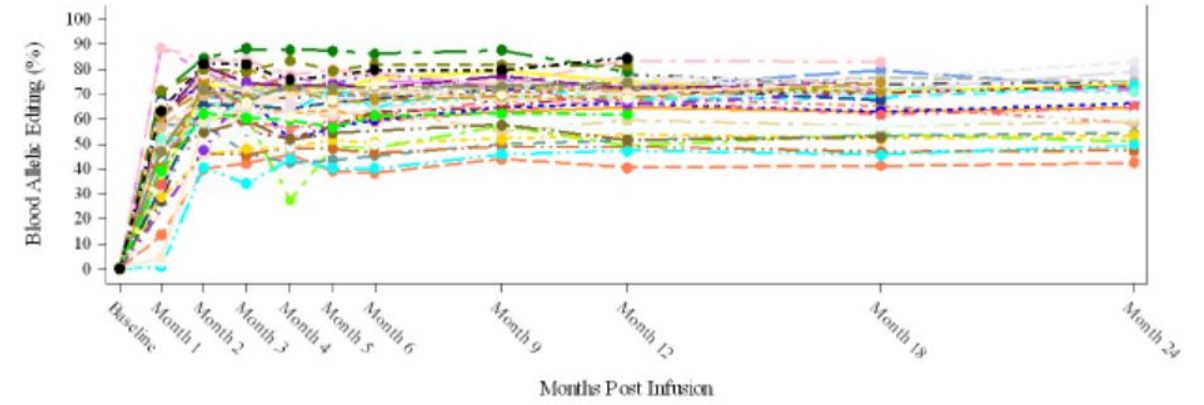


Source: Figure 14.2.9.1 (data cutoff date of 16 April 2023)
PES: Primary Efficacy Set
Note: Analysis visit was used in the figure.

Comment: the pattern of alleles in the bone marrow appears to reflect that of the drug product; there is a broad range of edits from (about) 30% to 90%.

Peripheral Blood:
Allelic editing in the peripheral blood was detectable within 1 month after exa-cel infusion. The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was 47.69% (20.22%) at Month 1 and the mean remained ≥60% from Month 2 onward. [The non-zero value at baseline (≤0.57%) is consistent with the background signal in the assay].

Figure 11-11 Individual Peripheral Blood Allelic Editing (%) Over Time (PES)



Source: Figure 14.2.7.1 (data cutoff date of 16 April 2023)
PES: Primary Efficacy Set
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

Allelic editing in the peripheral blood is lower than allelic editing in the $CD34^+$ cells of the bone marrow because the peripheral blood includes lymphocytes that are not derived from the edited $CD34^+$ haematopoietic stem cells.
Lymphocytes are not depleted following single agent busulfan conditioning; this results in a proportion of peripheral blood lymphocytes having been derived prior to therapy from haematopoietic stem cells that were not edited and led to the observed decreased allelic editing in the peripheral blood compared to the bone marrow $CD34^+$ cells.

Comment: The percentage of alleles with the intended change rises over the first 3 months and then reaches a plateau; there is a broad range from (about) 40% to 85%.
The half-life of a lymphocyte is known to be highly variable: most have a life span of a few weeks yet some may be present for years; there would not be any particular expectation that the percentages of cells in the peripheral circulation would match exactly those of the bone marrow with regards to nature of allele present.

7. Change from baseline in iron overload (primary efficacy set)

- Mean (SD) serum ferritin concentration at baseline was 3785.4 (2908.2) pmol/L.
- After exa-cel infusion, mean (SD) serum ferritin concentration increased to 19223.3 (36533.5) pmol/L at Month 1 and subsequently decreased over the duration of follow-up.
- At Month 18 (N = 36), the mean (SD) serum ferritin concentration was 2994.6 (2234.1) pmol/L.

- At Month 24 (N = 23), the mean (SD) serum ferritin concentration was 2295.1 (1813.9) pmol/L.

Comment: ferritin data are noted and would not give rise to particular concern; it is considered that the story will evolve as more data are acquired over a longer timeline after exposure to exa-cel.

8. Proportion of subjects receiving iron chelation therapy
Use of iron chelation was recommended to be started as soon as possible >3 months (or >6 months for deferiprone) following exa-cel infusion if hematopoietic recovery was stable.

All 42 (100%) subjects in the primary efficacy set were undergoing iron chelation therapy before exa-cel infusion.

After exa-cel infusion, individual subject iron removal was managed at the investigator's discretion.

24/42 subjects received chelation at any time after exa-cel infusion

- 17/42 of subjects received chelation >Month 12 to Month 15
- 11/32 of subjects received chelation >Month 21 to Month 24.

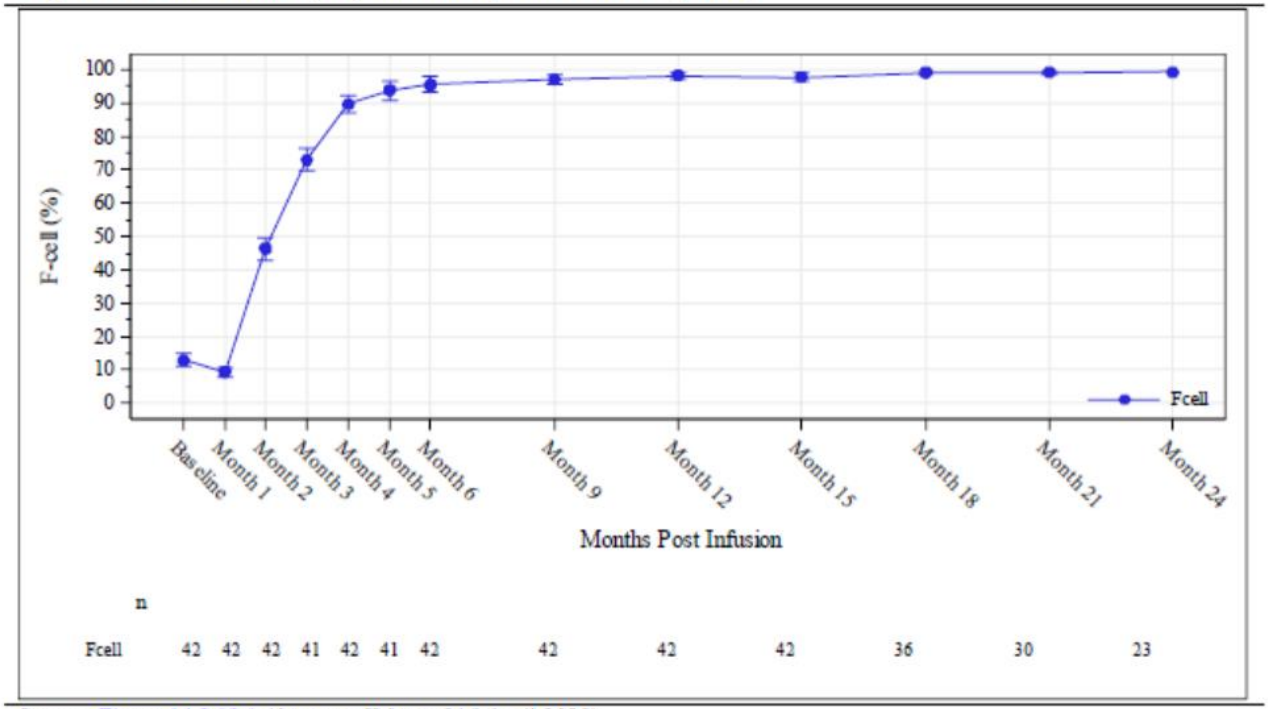
20 subjects received phlebotomy alone or in combination with chelation at any time after exa-cel infusion.

Comment: it is understood that there will be a timeline after exposure to exa-cel during which subjects will continue to require intervention to reduce iron load; it is considered that the story will evolve as more data are acquired over a longer timeline after exposure to exa-cel.

Exploratory endpoints

1. Hb fractions and change from baseline in proportion of circulating erythrocytes expressing γ-globin (HbF). Data are presented in the following figure:

Figure 11-14 F-cells (%) Summary Over Time (PES)



Source: Figure 14.2.12.1 (data cutoff date of 16 April 2023)
F-cells: erythrocytes expressing γ-globin (fetal hemoglobin); n: size of subsample; PES: Primary Efficacy Set
Notes: Mean values are plotted in the line, mean + SE and mean - SE values are plotted as bars at each visit. The number of subjects with F-cell values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

The mean (SD) proportion of F-cells was 73.08% (20.93%) at Month 3, increased to 95.63% (15.71%) at Month 6 and thereafter remained ≥95% for the duration of follow-up. The proportion of F-cells increased in a similar manner over time compared to HbF concentration after exa-cel infusion, indicating pan-cellular expression of HbF.

2. α-globin and non-α-globin mRNA

The mean (SD) ratio for α-globin to non-α-globin mRNA expression in circulating reticulocytes at baseline was 2.7 (1.4), decreased to 1.8 (0.4) at Month 3, and was maintained through Month 12 (1.8 [0.3]) and Month 24 (1.7 [0.3]).

3. Assessment of Ineffective Erythropoiesis

For the subjects in the primary efficacy set who had been followed to Month 24 (N = 23), the mean (SD) myeloid:erythroid ratio was 0.75 (0.64) at Month 6, 0.67 (0.36) at Month 12, and 0.83 (0.38) at Month 24.

Patient reported outcomes

The MAH reports on change in the following patient-reported outcomes over time; the MAH reports on the for the primary efficacy set:

- FACT-BMT - The Functional Assessment of Cancer Therapy-Bone Marrow Transplant
- EQ-5D-5L - Descriptive system for health-related quality of life states in adults
- PedsQL – The Paediatric Quality of Life Inventory

The agency position on patient-reported outcomes will be deferred until submission of reports of the finished trials.

Summary of clinical efficacy

Design

The MAH submits a single-arm, open-label, multi-site, single dose study in subjects 12 to 35 years of age who have transfusion-dependent β-thalassemia

Comment: It is noted that the study participants with transfusion-dependent β-thalassemia are able to carry on normal activities, despite their condition.

Genotyping was used to confirm a diagnosis of homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia / haemoglobin E.

Transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed red blood cell transfusions in the 2 years before signing the informed consent form.

The study evaluated the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified human haematopoietic stem and progenitor cells (exa-cel).

Conduct

There are 29 adults (age ≥18 to ≤35yrs) and 13 paediatric subjects (ages ≥12 to <18yrs) in the primary efficacy set; the median age was 20yrs; 25/42 subjects had a β0/β0-like genotype and 30/42 subjects had an intact spleen.

For the 2 years before screening: the baseline median (range) annualised units of thalassaemia-related red blood cell transfusions per year was 35.0 (20.5 to 71.0) units and the

baseline median (range) annualized volume of thalassaemia-related red blood cell transfusions was 201 (115.2, 330.9) mL/kg per year.

It is concurred that characteristics of the enrolled population describe people with transfusion-dependent β-thalassaemia.

Subjects were transfused red blood cells prior to the apheresis procedure (and at least 60 days before conditioning) in order to achieve a pre-transfusion goal of Hb ≥11 g/dL.

Mobilisation of cells from marrow was promoted with a granulocyte-colony stimulating factor and plerixafor.

$CD34^+$ haematopoietic stem and progenitor cells were harvested by apheresis using peripheral or central venous access and sent to the MAH site for modification with the CRISPR system to produce exa-cel

Subjects then underwent conditioning of the bone marrow with busulfan.
Intravenous infusion of exa-cel occurred between 2 to 7 days after completion of the busulfan conditioning regimen.

Subjects were then monitored in a transplant unit and given supportive care until there was evidence of engraftment of neutrophils and subjects were clinically stable.

Iron chelation and additional supportive therapies were administered at the discretion of the attending physician. Subjects were recommended not to restart iron chelation (if needed) until at least 3 months after exa-cel infusion. Subjects have been enrolled into a long-term follow-up study.

Outcomes and analysis

The MAH describes the study as a phase 1/2/3 study; the study is open-label and uncontrolled; the MAH does not describe aims of the study; objectives are described yet 'endpoints' of the MAH do not match exactly to the stated objectives; the MAH tends a null hypothesis of 50% response rate yet without sufficient justification. It would have been much preferred for the MAH to have used descriptive boundaries (as opposed to a probabilistic boundary) in order to demarcate small, medium or big effect sizes, as described: .Feinstein AR: Critical descriptive boundaries – J Clin Epidemiol 1998;51:527-530.

The assessor is unable to concur with the description or statistical analysis of the study by the MAH; the assessor considers that the study is a demonstration study i.e. demonstration of (i) method and (ii) outcome. In order to analyse the study, the assessor refers to the method of Bradford-Hill as updated by Aronson and colleagues: Howick J, Glasziou P & Aronson JK. The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? J R Soc Med. 2009;102:186-94.

Outcomes

For the primary efficacy set:

- 39/42 subjects achieved the primary outcome by maintaining a weighted average Hb ≥ 9g/dL without red blood cell transfusions for at least 12 consecutive months any time after exa-cel infusion.

12/13 (92%) subjects ≥12 and <18 years of age and 27/29 (93%) subjects ≥18 and ≤35 years of age achieved the primary outcome; results between the age groups are considered comparable.

A comparison of outcomes of sub-group by sex, race and genotype, as described, are also considered comparable. Yet numbers are small and so final opinion is reserved at present. At present: such data would not give concern.
For those who achieved the primary outcome:

- the median time to achieve 'free from transfusion' was (about) 1 month and the maximum time was (about) 3 months.
- the total duration of being transfusion-free ranged from (about) 13 to 24 months
- Mean HbF increased from trace concentrations at baseline to 10.8 g/dL by month 6 and remained so for the duration of follow-up.

For the 3/42 subjects who did not achieve the primary outcome: there was a reduction in annualised RBC transfusion volume by at least 80%.

The proportion of alleles with the intended genetic modification in bone marrow was between (about) 30 and 90%. Allelic editing in the peripheral blood was detectable within 1 month after exa-cel infusion and reached a plateau by about 3 months of between (about) 40 and 85%.

The main outcomes of no longer requiring RBC transfusion or marked reduction in need for RBC transfusion are considered to be notable.

Analysis
Aronson and colleagues (2009) have updated Bradford-Hill criteria and recommend that 7 lines of evidence (classified as direct, mechanistic and parallel) be met. Thus:
Direct evidence

1. Appropriate temporal spatial proximity the time interval between exposure and increase in HbF and subsequent reduction in clinical events is consistent with the proposed mechanism of action; appropriate temporal proximity is considered met; line 1 is considered met.
2. Effect not attributable to plausible confounding: plausible confounders not identified by the assessor; line 2 is considered met.
3. Dose responsiveness and reversibility: line 3 not tested.

Comment on direct evidence: 2/3 lines of direct evidence support the claims of the MAH.

Mechanistic evidence

4. Proposed mechanism of action

Exagamglogene autotemcel (exa-cel, formerly CTX001) consists of autologous $CD34^+$ human haematopoietic stem and progenitor cells modified by ex vivo CRISPR-Cas9-mediated gene editing. Haematopoietic stem and progenitor cells are harvested from the patient, modified using CRISPR technology and then returned to the patient; the product is intended as a one-off treatment.

The CRISPR system targets a critical binding site of the transcription factor GATA1 in the non-coding erythroid lineage-specific enhancer region of the BCL11A gene on chromosome 2.

Repair of these breaks by non-homologous end-joining produces insertions and deletions (indels) in the DNA that disrupt GATA1 binding thereby lowering BCL11A transcription. BCL11A codes for a transcriptional repressor of γ-globin. The reduction of BCL11A gene transcription and subsequent decrease in BCL11A protein concentration leads to increases in γ-globin mRNA transcription, γ-globin expression and, upon erythroid differentiation, an increase in production of HbF.

The mechanism of action is considered plausible; line 4 support is considered met.

5. Coherence: the causal hypothesis is considered to cohere with current knowledge of the genetics of globin production; line 5 support is considered met.

Comment on mechanistic evidence: 2/2 lines of mechanistic evidence support the claims of the MAH.

Parallel evidence

6. The MAH is conducting replicate-style trials i.e. studies 141 & 151; results awaited.
7. Studies 111 and 121 provide parallel evidence i.e. similar intervention / similar outcome; line 7 is considered met.

Comment on parallel evidence: 1/2 lines of parallel evidence support the claims of the MAH; line 6 may prove positive once outcomes are obtained.

Overall comment on outcomes and analysis: 5/7 lines of evidence are considered satisfied; line 6 support may be satisfied when the MAH reports on studies 141 and 151 whilst line 3 support on dose and reversibility is unlikely to be addressed by the MAH. Overall, evidence submitted by the MAH is consistent with administration of exa-cel being causative towards outcomes described.

Overall conclusion on clinical efficacy

efficacy (much reduced need for red blood cell transfusion) has been demonstrated in the target population of transfusion-dependent beta-thalassaemia.

Long-term efficacy will only be established by prolonged follow-up.

Data of the study 111 are consistent with administration of Casgevy being necessary for recipients to produce circulating red blood cells containing fetal haemoglobin.

The MAH did not undertake a dose-finding exercise; the MAH relied on published data of bone marrow transplant to decide upon a dosage. Although data of the study 111 are consistent with administration of Casgevy being necessary for recipients to produce fetal haemoglobin with a view to abolish / reduce the need for blood transfusions, 3 subjects continued to require blood transfusions apparently as a primary failure. The choice of posology has been based on published data in other haematological conditions; the MAH has agreed to submit data at annual reviews that will aid in the further assessment of sufficiency of number of cells administered to subjects; this is acceptable. Details of the data to be submitted is as below:

For subjects with transfusion-dependent beta-thalassaemia, the company has agreed to provide the following information at annual reviews:

Point 1: In order to provide clarity on those who were unable to gain freedom from red blood cell transfusion, the company will supply information for the full analysis set on numbers of cells administered to patients by means of bar charts:

(a) One bar chart with number of patients on the y-axis versus total number of cells/kg body weight administered, and

(b) One bar chart with number of patients on the y-axis versus total number of cells administered

In the above depictions: the company will highlight those subjects who did not achieve freedom from red blood cell transfusion and discuss the findings.

Point 2: For the full analysis set: the company will provide:

(a) a plot of bone marrow allele edit percentage at month 12 versus number of cells administered/kg body weight and discuss the findings.

(b) a plot of bone marrow allele edit percentage at month 12 versus total number of cells administered and discuss the findings.

The company will highlight those subjects who did not achieve freedom from red blood cell transfusion and discuss the findings.

Point 3: For the full analysis set: the company will provide a plot of bone marrow allele edit percentage versus peripheral blood allele edit percentage at month 12 versus and discuss the findings.
The company will highlight those subjects who did not achieve freedom from red blood cell transfusion in these depictions and discuss the findings.

Point 4: The company will submit a plot of HbF (g/dL) over time for each subject and discuss the findings in relation to bone marrow allele edit percentage and peripheral blood allele edit percentage.

I.V.2 Clinical Efficacy *Sickle cell disease – Study CTX001-121*

This section of the report discusses the clinical data and information to support the indication of sickle cell disease :

Casgevy is indicated for the treatment of sickle cell disease in patients 12 years of age and older with recurrent vasoocclusive crises who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype, for whom haematopoeitic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

Title: A Phase 1/2/3 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified $CD34^+$ Human Hematopoietic Stem and Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease

Dates of Study:
Study initiation: 27 Nov 2018 (date first eligible subject signed the informed consent form)
Interim Analysis cut-off date: 16 Apr 2023
Version of Report: 1.0, addendum 1
Date of Report: 06 Nov 2023

Study objectives

Primary Objective

- Evaluate the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified CD34+ human haematopoietic stem and progenitor cells (exa-cel) in subjects with severe sickle cell disease

Secondary Objectives

- Assess the effects of infusion of exa-cel on disease-specific events and clinical status
- Quantify gene editing efficiency

Exploratory Objective

- Assess the ability of biomarkers to characterize exa-cel effect and predict treatment outcomes

Study outcomes

Primary Efficacy Outcome

1. The primary efficacy outcome was the proportion of subjects who had not experienced any severe vaso-occlusive crisis for at least 12 consecutive months after exa-cel infusion.

The MAH states:

> The evaluation of the primary efficacy outcome started 60 days after the last RBC transfusion for post-transplant support or sickle cell disease management.
> The start of observation 60 days following the last RBC transfusion was consistent with sufficient time to allow for the known lifespan of transfused RBCs as well as the resolution of transient increases in HbF associated with the transplant procedure.
> A minimum of 12 months duration of absence of severe vaso-occlusive crises was considered to be highly unlikely to be due to chance in subjects who had 2 or more severe vaso-occlusive crises per year in the 2 years before screening.

Secondary Efficacy Outcomes

1. Proportion of subjects who remained free from inpatient hospitalisation (sustained for at least 12 months after exa-cel infusion) for severe vaso-occlusive crises.

The evaluation of the secondary efficacy outcome started 60 days after the last RBC transfusion for post-transplant support or sickle cell disease management.

2. For subjects who achieved absence of any severe vaso-occlusive crisis for at least 12 consecutive months: severe vaso-occlusive crisis free duration

The evaluation of the secondary efficacy outcome started 60 days after the last RBC transfusion for post-transplant support or sickle cell disease management.

3. For subjects who did not achieve absence of any severe vaso-occlusive crisis for at least 12 consecutive months:
    - Relative reduction from baseline in annualised rate of severe vaso-occlusive crises
    - Achieved at least 90%, 80%, 75% and 50% reduction from baseline in annualised rate of severe vaso-occlusive crises (severe vaso-occlusive crises were adjudicated by the efficacy analysis committee)

4. For subjects who did not achieve absence of any severe vaso-occlusive crisis for at least 12 consecutive months:
    - Relative reduction from baseline in annualised rate of inpatient hospitalisations for severe vaso-occlusive crises
    - Relative reduction in annualised duration of inpatient hospitalisations for severe vaso-occlusive crises

5. Proportion of subjects with sustained HbF ≥20% for at least 3 months, 6 months or 12 months. The evaluation of the outcome started 60 days after the last RBC transfusion for post-transplant support or sickle cell disease management.

6. Hb concentrations: total Hb (in absolute value) and HbF (in absolute value and %)

7. Proportion of alleles with intended genetic modification present in peripheral blood and $CD34^+$ cells of the bone marrow

8. Change from baseline in:
    - Reticulocyte count (in absolute reticulocyte count and %)
    - Indirect bilirubin
    - Lactate dehydrogenase
    - Haptoglobin

9. Relative reduction from baseline in number of RBC units transfused for sickle cell disease-related indications

10. Change from baseline in PRO

Exploratory outcomes

1. Hb fractions and change from baseline in proportion of circulating F-cells

Aspects of study design
A single-arm, open-label, multi-site, single-dose, Phase 1/2/3 study in subjects 12 to 35 years of age (inclusive) who have severe sickle cell disease.
A single-arm study design was used because of a lack of equipoise with existing standard of care treatments and because of the need for a transplant procedure to deliver exa-cel. The overall process was consistent with procedures used for autologous haematopoietic stem cell transplant in patients with malignant diseases including mobilization / apheresis and myeloablation. Therefore, the risk associated with the procedures in this study was not expected to be significantly different from the standard risks of these procedures.

Comment: a single-arm demonstration study may be understood in the context of subjects with a rare disease who are to be administered a novel therapy; it is acknowledged that the MAH has conducted the autologous haematopoietic stem cell transplant procedure in accord with current clinical practice and so risks are known.

Expansion of enrolment to increase the total number of subjects was based on data monitoring committee review of safety and efficacy data.

Adolescent-aged children were included once efficacy and safety had been shown in adults. The rationale for inclusion of adolescent-aged children was that the aetiology and pathophysiology of sickle cell disease are similar across age groups.

Comment: the MAH approach (with referral to the safety committee) to start with adults and then to take the study forward into an adolescent population is considered understood.

Further comment on study conduct
Recruitment - the population enrolled is considered representative for the claimed indication.

Allocation was not conducted - this is a single arm trial - likely to introduce bias.

Maintenance on product - the product is delivered in a single step and so maintenance is not considered to be an issue.

Blinding was not done - this is an open-label trial - likely to introduce bias.

For outcome in sickle cell subjects - a decision on the occurrence of a vaso-occlusive crisis is considered to be subjective (even with adjudication, as described) and likely associated with bias.
The use of 'before and after' to assess outcome is considered to introduce bias.

It is not possible to concur with the statistics analysis of the MAH because randomisation was not done; the assessor applies the technique of Bradford Hill and refers to "outcomes" rather than "endpoints".

There were 4 global amendments and 14 country-specific amendments (updates and clarifications in the main) between Apr 2018 and Sept 2022; the MAH provides information on these; the amendments are noted without further comment.
The MAH provides information on important protocol deviations that were, in the main, administrative. The MAH states that "there was no impact of these important protocol deviations to subject safety, data integrity or data interpretation". This is acceptable.

Dose

The study evaluated the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified human haematopoietic stem and progenitor cells (exa-cel).

Autologous transplantation for various indications typically uses at least 2×10^6 to 2.5×10^6 $CD34^+$ cells/kg to support engraftment.
To ensure engraftment in all subjects, a conservative minimum dose of 3×10^6 $CD34^+$ cells/kg (which is 20% to 50% higher than the typical minimum dose for autologous transplantation) was assessed (the MAH submits references to support).

The maximum cell dose of 20×10^6 $CD34^+$ cells/kg was selected based on manufacturing capabilities and projected cell yields at the time of protocol writing.

All subjects were infused per protocol; (to note that 3 subjects received lower than the selected minimum dose). Subjects were monitored for any potential dose related toxicities.

Comment: the MAH has based its dosing strategy on published information; this may be understood in the context of a study conducted on subjects with a rare condition yet the approach is considered to be a notable deficiency in a study that uses novel technology.

References submitted by the MAH suggest best outcome is achieved with >5 x 10^6 CD34 cells/kg administered.

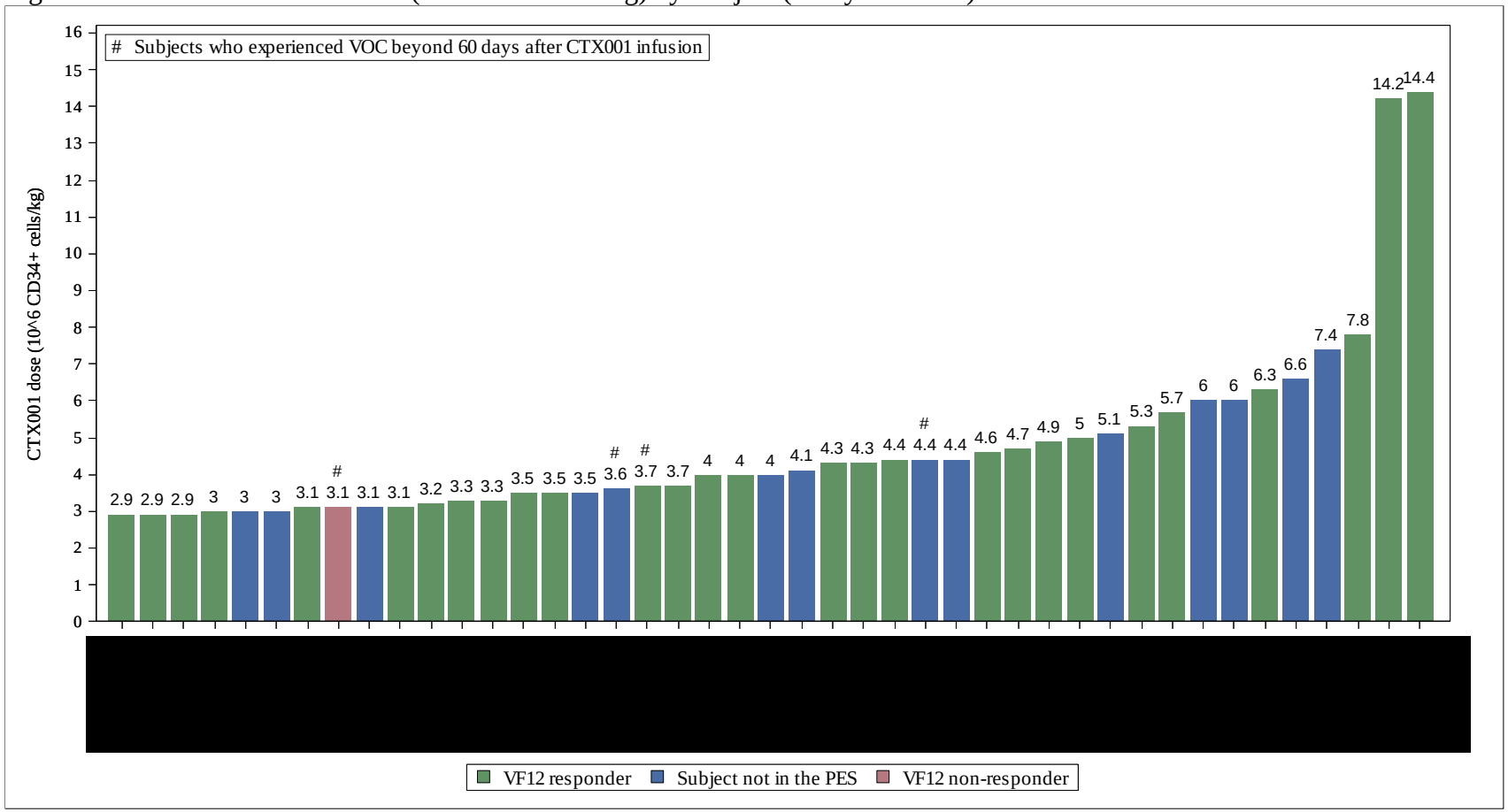
In response to request: the MAH has submitted a bar chart with number of patients on the x-axis versus number of cells / kg body weight administered as shown in the following page:

28 subjects were administered ≤4.4 x 10^6 CD34 cells/kg body weight; 4/28 experienced a vaso-occlusive crisis beyond 60 days after infusion of exa-cel i.e. 14% subjects.

15 subjects were administered >4.4 x 10^6 CD34 cells/kg body weight; 0/15 experienced a vaso-occlusive crisis beyond 60 days after infusion of exa-cel i.e. none.

It is recognised that number of subjects is small and so opinion is guarded at present; the issue of minimum number of cells administered needed to be sufficient is considered an on-going issue that may be revisited at annual review or at an intervening time point.

Figure 12. Individual Exa-cel Dose (10^6 $CD34^+$ cells/kg) by Subject (Study 121 FAS)



Source: Study 121/Ad hoc Figure 1.2 (data cutoff date of 16 April 2023)

CTX001: exagamglogene autotemcel; exa-cel: exagamglogene autotemcel; PES: Primary Efficacy Set; VF12: not experienced any (i.e., absence of) severe VOC for at least 12 consecutive months after exa-cel infusion; VOCs: vaso-occlusive crises

Notes: Only severe VOCs adjudicated by an Endpoint Adjudication Committee as meeting the protocol definition of severe VOCs were included. Subjects who had a VOC beyond 60 days after exa-cel infusion were marked.

Population

Inclusion Criteria

Subjects 12 to 35 years of age, inclusive.

- Documented βS/βS, βS/β0 or βS/β+. β0 genotypes were defined using the HbVar Database.

- Subjects with severe sickle cell disease as defined by the occurrence of at least 2 of the following events per year during the 2-year period before screening while receiving appropriate supportive care (e.g. pain management plan, hydroxyurea):
    - Acute pain event that required a visit to a medical facility and administration of pain medications (opioids or IV nonsteroidal anti-inflammatory drugs) or RBC transfusions
    - acute chest syndrome as indicated by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms, pain or fever
    - Priapism lasting >2 hours and requiring a visit to a medical facility
    - Splenic sequestration as defined by: an enlarged spleen, left upper quadrant pain and an acute decrease in Hb concentration of ≥2 g/dL.

- Karnofsky performance status of ≥80% for subjects ≥16 years of age or Lansky performance status of ≥80% for subjects <16 years of age

- Normal transcranial Doppler velocity (i.e. ultrasound analysis) in the middle cerebral artery and the internal carotid artery for subjects 12 to 16 years of age

Comment: enrolled subjects had genotype evidence to confirm the diagnosis of sickle cell disease and a clinical history of needing medical intervention consistent with a severe disease state. No additional comment on the above inclusion criteria.

See next page for exclusion criteria.

Exclusion Criteria

- An available 10/10 human leukocyte antigen (HLA)-matched related donor.
- Prior haematopoietic stem cell transplant
- Prior treatment with gene therapy / editing product
- Clinically significant infection
- White blood cell count $<3 \times 10^9$/L or platelet count $<50 \times 10^9$/L not related to hypersplenism.
- Treatment with regular RBC transfusions that could not be interrupted after engraftment.
- Subjects with history of allo-immunisation to RBC antigens and for whom there would be insufficient RBC units available for the duration of the study.
- More than 10 un-planned hospitalisations or emergency department visits related to sickle cell disease in the 1 year before screening that were consistent with significant chronic pain rather than acute pain crises
- History of abnormal TCD (TAMMV ≥200 cm/sec for non-imaging TCD and ≥185 cm/sec for imaging TCD) for subjects 12 to 18 years of age.
- History or presence of Moyamoya disease
- History of significant bleeding disorder
- Any prior or current malignancy / familial cancer or significant immunodeficiency disorder.
- Significant disease of the heart / central nervous system / mental well-being
- Advanced liver, renal, cardiac or lung disease based on laboratory testing
- Intolerance, contraindication or known sensitivity to plerixafor or busulfan
- Positive tests for human immunodeficiency virus, hepatitis B virus, hepatitis C virus and syphilis. Additional infectious disease markers were obtained and tested as required by local guidance.

Comment : Moyamoya disease is a rare blood vessel disorder whereby the carotid artery becomes blocked or narrowed thus reducing blood flow; the condition may cause a stroke. Moyamoya disease is a disease of young adults, most commonly from East Asian countries. Moyamoya syndrome (as opposed to disease) is known to be associated with sickle cell anaemia. Exclusion of subjects with the Moyamoya condition is acceptable. No additional comment on other aspects of the exclusion criteria.

Table 2-1 provides the number of subjects in each analysis set.

Table 2-1 Study 121 Analysis Populations

Analysis Set	Total
Enrolled Set[a]	63
Safety Analysis Set[b]	58
FAS[c]	43
PES[d]	29

Source: Table 14.1.1 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease
[a] Enrolled Set included all enrolled subjects who signed informed consent and met the eligibility criteria.
[b] Safety Analysis Set included all subjects who started the mobilization regimen.
[c] FAS included all subjects who received exa-cel infusion.
[d] PES included all subjects who were followed for at least 16 months after exa-cel infusion and for at least 14 months after completion of RBC transfusions for post-transplant support or SCD management. Completion of the (initial) RBC transfusions was determined when all those transfusions for post-transplant support or SCD management had finished followed by 60 days without transfusion. Subjects who completed the 24 months of follow-up in the study after exa-cel infusion were also included, with the exception of those who received RBC transfusions between Month 10 and Month 12 and had less than 14 months (including up to 2 months in Study 131) additional follow-up time. This set also included subjects who died or discontinued the study due to AEs considered related to exa-cel and had less than 16 months of follow-up after exa-cel infusion, or continuously received RBC transfusions for more than 12 months after exa-cel infusion.

Subjects were enrolled at 16 sites in the United States, Canada, United Kingdom, France, Belgium, Germany and Italy. Subject disposition is summarized in Table 10-1:

Table 10-1 Subject Disposition (Enrolled Set)

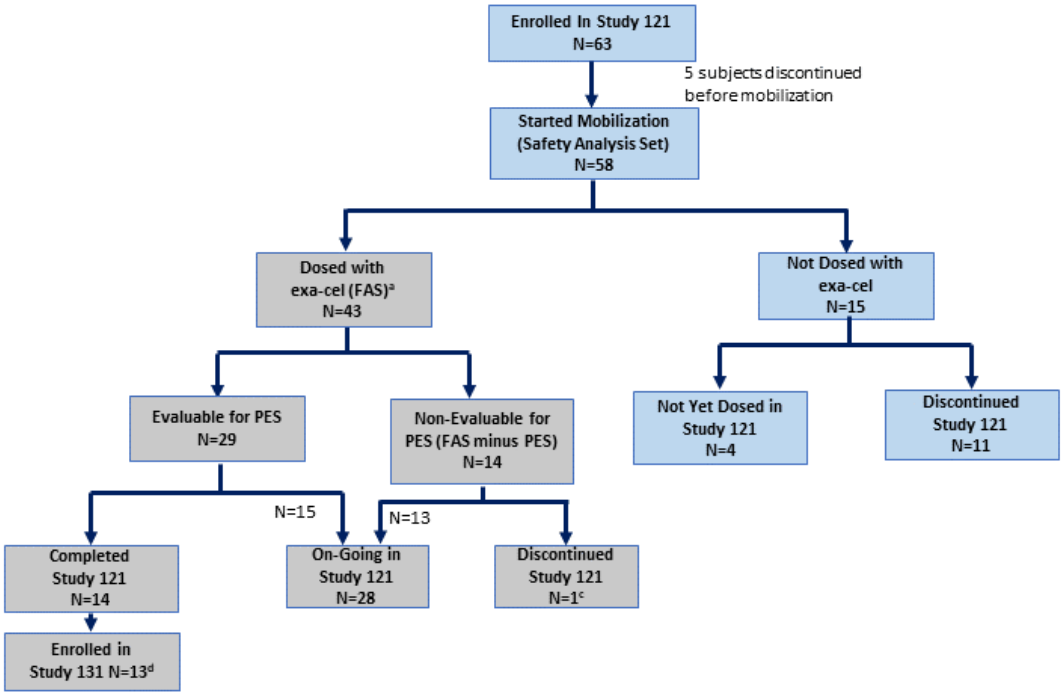
Disposition/Reason	Total n (%)
Enrolled Set[a]	63
Safety Analysis Set[b]	58
Started the conditioning regimen	43
FAS[c]	43
PES[d]	29
Never dosed with any study drug[e]	5
Never dosed with exa-cel[f]	16
Started exa-cel infusion	43 (68.3)
Completed exa-cel infusion	43 (100.0)
Not completed exa-cel infusion	0
On study and not yet dosed with exa-cel	4 (6.3)
On study and dosed with exa-cel	28 (44.4)
Completed study[g]	14 (22.2)
Discontinued study after exa-cel infusion	1 (1.6)
Discontinued study after exa-cel infusion and enrolled in long term follow-up study	0
Reason for discontinuing study after exa-cel infusion	
Death	1 (2.3)

Source: Study 121/Table 14.1.1 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease
Notes: Percentages were calculated relative to the number of subjects in the Enrolled Set, unless otherwise specified. Percentages of subjects who completed or did not complete the exa-cel infusion (and percentages of reasons for not completing exa-cel infusion) were calculated relative to the number of subjects who started the exa-cel infusion. Percentages of subjects who discontinued the study after exa-cel infusion and enrolled in the long-term follow-up study were calculated relative to the number of subjects who discontinued study after exa-cel infusion. Percentages of reasons for discontinuing study after exa-cel infusion were calculated relative to the number of subjects who received exa-cel infusion.
[a] Enrolled Set included all enrolled subjects who signed informed consent and met the eligibility criteria.
[b] Safety Analysis Set included all subjects who started the mobilization regimen.
[c] FAS included all subjects who received exa-cel infusion.
[d] PES included all subjects were followed for at least 16 months after exa-cel infusion and for at least 14 months after completion of the RBC transfusions for post-transplant support or SCD management. Completion of the (initial) RBC transfusions was determined when all those transfusions for post-transplant support or SCD management had finished followed by 60 days without transfusion. Subjects who completed the 24 months of follow-up in the study after exa-cel infusion were also included, with the exception of those who received RBC transfusions between Month 10 and Month 12 and had less than 14 months (including up to 2 months in Study 131) additional follow-up time. This set also included subjects who died or discontinued the study due to AEs considered related to exa-cel and had less than 16 months of follow-up after exa-cel infusion, or continuously received RBC transfusions for more than 12 months after exa-cel infusion.
[e] Never dosed with any drug included all subjects who discontinued the study and did not receive any study drugs for mobilization, conditioning, and exa-cel infusion.
[f] Never dosed with exa-cel included all subjects who discontinued the study and did not receive exa-cel infusion.
[g] Completed study included all subjects who completed the Month 24 Visit.

- 63 subjects were enrolled.
- 43 subjects had been infused with exa-cel at the time of the interim analysis.
- 29 subjects were evaluable for the primary efficacy set.
- 14 subjects completed Study 121 i.e. have reached & completed visit at month 24.

Subject disposition is also summarized in the following figure:

Figure 1. Disposition for Studies 121 and 131, Enrolled Set and [SCD]Enrolled Set



Sources: Study 121/Table 14.1.1 and Study 131/Table 14.1.1b (data cutoff date of 16 April 2023)

exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total number of subjects; PES: Primary Efficacy Set

Notes: Subjects listed as non-evaluable for PES are included in the FAS minus PES data set. For the 4 subjects not yet dosed in Study 121 as of the data cutoff date, 1 subject has since been dosed and 3 are planned to be dosed by Q4 2023.

[a] The FAS included all subjects who received exa-cel infusion.

[b] Reason for discontinuation after exa-cel: death due to COVID-19 infection that resulted in respiratory failure and was not related to exa-cel.

[c] Reason for discontinuation after starting mobilization: inadequate cell collections (6 subjects), no longer met eligibility criteria for renal function (1 subject), non-compliance (1 subject), withdrew consent (2 subjects), and [removed due to need to protect personal data] (1 subject).

[d] One subject enrolled in Study 131 after the data cutoff date.

Comment: It is noted that 6 subjects discontinued because of inadequate cell collection (compared to none in the thalassaemia study). Subject disposition is noted without additional comment.

Demographic data for the full analysis set and primary efficacy set are summarised in Table 10-2:

Table 10-2 Subject Demographics (FAS and PES)

Demographics	FAS N = 43	PES N = 29
Sex, n (%)		
Male	24 (55.8)	16 (55.2)
Female	19 (44.2)	13 (44.8)
Childbearing potential[a], n (%)		
Yes	[redacted]	
No		
Age at screening (year)		
n	43	29
Mean (SD)	21.2 (6.1)	22.2 (6.1)
Median	20.0	21.0
Min, max	12, 34	12, 34
Age category at screening, n (%)		
≥12 and <18 years	12 (27.9)	6 (20.7)
≥18 and ≤35 years	31 (72.1)	23 (79.3)
Race, n (%)		
White	3 (7.0)	1 (3.4)
Black or African American	37 (86.0)	26 (89.7)
Asian	0	0
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Not collected per local regulations	0	0
Other	3 (7.0)	2 (6.9)
Multiracial	0	0
Ethnicity, n (%)		
Hispanic or Latino	[redacted]	
Not Hispanic or Latino		
Not Collected per Local Regulations		

Sources: Table 14.1.3.1 and Ad hoc Table 14.1.3.3 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; N: total sample size; n: size of subsample; PES: Primary Efficacy Set
Notes: Percentages were calculated relative to the number of subjects in the FAS and PES, respectively, unless otherwise specified.
[a] Percentages for childbearing potential were calculated relative to the number of females in the FAS and PES, respectively.

Comment: there are 29 subjects in the primary efficacy set; 55% male; median age 21yrs (min 12yrs, max 34yrs); 6 subjects were ≥12yrs and <18yrs, 23 subjects were ≥18yrs to ≤35 years ; 26/29 declared as Black or of African heritage.
The demographics appear typical for a population with sickle cell disease.
Baseline demographics for the primary efficacy set appear similar to the full analysis set.

At the time of the data cutoff date of 16 Apr 2023, there were 12 adolescent subjects in the full analysis set in Study 121.Ages at screening for the 12 adolescent subjects with sickle cell disease in the full analysis set; ages of these subjects span the full age range of 12 through 17 years.

Baseline characteristics data are summarised in Table 10-3:

Table 10-3 Baseline Characteristics (FAS and PES)

Baseline Characteristics	FAS N = 43	PES N = 29
Genotype, n (%)		
β^S/β^S	39 (90.7)	28 (96.6)
β^S/β^0	3 (7.0)	1 (3.4)
β^S/β^+	1 (2.3)	0
Total Hb (g/dL)		
n	42	28
Mean (SD)	9.1 (1.6)	9.1 (1.6)
Median	9.4	9.5
Min, max	5.7, 12.6	5.7, 12.6
HbF (%)		
n	43	29
Mean (SD)	5.3 (3.8)	5.1 (3.8)
Median	5.0	5.2
Min, max	0.0, 14.7	0.0, 14.7
HbF (g/dL)		
n	42	28
Mean (SD)	0.5 (0.4)	0.5 (0.4)
Median	0.4	0.4
Min, max	0.0, 1.5	0.0, 1.5
Annualized rate of severe VOCs		
n	43	29

Mean (SD)	4.2 (3.0)	3.9 (2.2)
Median	3.5	3.0
Min, max	2.0, 18.5	2.0, 9.5
Annualized rate of inpatient hospitalizations for severe VOCs		
n	43	29
Mean (SD)	2.7 (2.1)	2.7 (2.1)
Median	2.5	2.0
Min, max	0.5, 9.5	0.5, 8.5
Annualized duration of inpatient hospitalizations for severe VOCs (days)		
n	43	29
Mean (SD)	19.6 (22.2)	17.4 (14.4)
Median	13.5	12.5
Min, max	2.0, 136.5	2.0, 64.6
Annualized units of RBCs transfused for SCD-related indication		
n	43	29
Mean (SD)	11.6 (18.5)	8.7 (15.1)
Median	5.0	3.5
Min, max	0.0, 86.1	0.0, 75.5
Reticulocytes (10^9/L)		
n	43	29
Mean (SD)	271.8 (112.9)	265.5 (113.9)
Median	251.7	251.5
Min, max	104.7, 679.6	116.3, 679.6

Indirect bilirubin (µmol/L)		
n	43	29
Mean (SD)	48.4 (43.5)	55.4 (48.4)
Median	29.1	32.5
Min, max	6.8, 210.3	12.0, 210.3
Lactate dehydrogenase (U/L)		
n	42	28
Mean (SD)	485.5 (223.4)	463.0 (194.4)
Median	427.5	430.0
Min, max	168.0, 1228.0	168.0, 913.0
Haptoglobin (g/L)		
n	42	28
Mean (SD)	0.1 (0.2)	0.1 (0.1)
Median	0.0	0.0
Min, max	0.0, 0.9	0.0, 0.3
Weight (kg)		
n	43	29
Mean (SD)	66.0 (17.4)	64.9 (14.8)
Median	[redacted]	
Min, max		

Sources: Table 14.1.4.1 and Table 14.1.4.2 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; Hb: hemoglobin; HbF: fetal hemoglobin; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VOCs: vaso-occlusive crises
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Baseline severe VOCs, inpatient hospitalizations for severe VOCs, and RBC transfusions were based on the 2 years before the most recent screening. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included. Hb measurements were from central laboratories. Annualized rate = total number of events/number of years. Annualized duration = total duration of events/number of years. Annualized units = total units/number of years. One year = 365.25 days. For hemolysis markers, values with "below detectable limit" were considered as 0.

Comment:
28/29 subjects in the primary efficacy set are homozygous for the βS/βS genotype;
Most subjects in the primary efficacy set received red blood cell transfusions (simple and/or exchange) for a sickle cell disease-related indication in the 2 years before enrolment.
The following data are annualised for the 2 years before enrolment:

- the median annualised rate of severe vaso-occlusive crises was 3 (min 2, max 9.5)
- the median annualised rate for in-patient management of severe vaso-occlusive crises was 2.0 (min 0.5, max 8.5)
- the median annualised duration of stay for in-patient management of severe vaso-occlusive crises was 12.5 days (max 65 days)
- the annualised median number of units of red blood cells transfused for sickle cell disease was 3.5 (min 0, max 75.5).

The 29 subjects in the primary efficacy set display much interaction with health services for management of sickle cell disease.

The median weight of subjects and min & max weights removed to protect personal information).
Baseline characteristic data for the primary efficacy set appear similar to the full analysis set.

The MAH submits a list of prior medications; the most common sickle cell disease-related prior medication used was hydroxyurea; in the Safety Analysis Set, 36 (62.1%; N = 58) subjects were receiving HU/hydroxycarbamide. In addition, 56 (96.6%; N = 58) subjects were receiving opioids.

All subjects used concomitant medications; the most common concomitant medications were typical of those used for the management of patients during peri- and post-haematopoietic stem cell transplant period and sickle cell disease-related chronic pain. In addition, 42 (97.7%; N = 43) subjects in the FAS received opioids.

Concomitant medications used by the primary efficacy set were consistent with those used by the full analysis set.

comment: the MAH provides detailed lists of medications, described.

The prior and concomitant medications are understood in the context of subjects with sickle cell disease undergoing an haematopoietic stem cell transplant procedure.

Use of G-CSF was allowed if engraftment did not occur by Day 21 after exa-cel infusion.

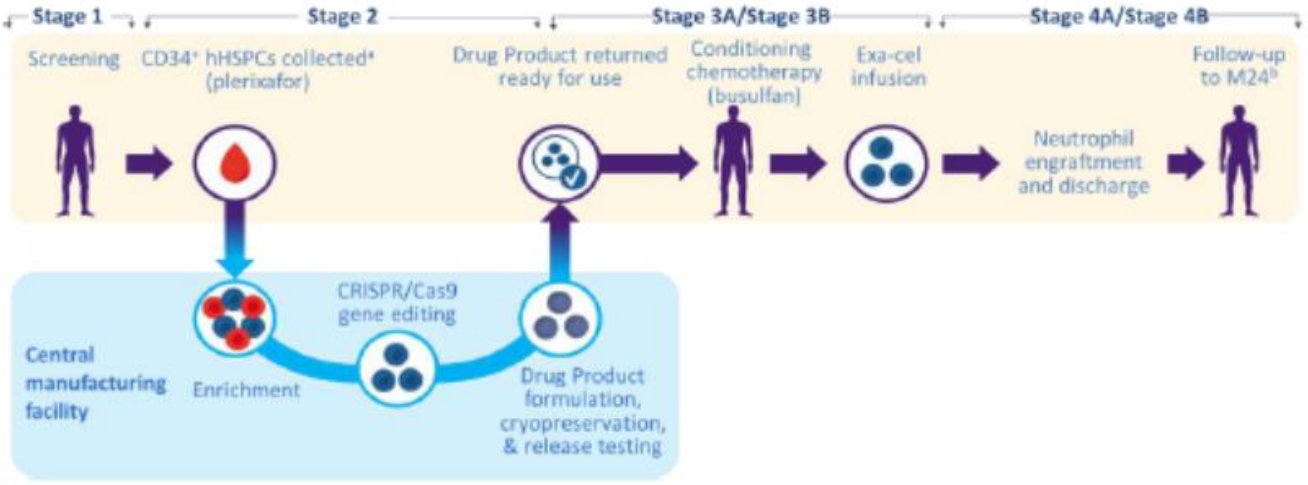
Sickle cell disease - details of cell mobilisation, apheresis, and myeloablative conditioning used in the clinical studies for Casgevy.

Indication: Casgevy is indicated for the treatment of sickle cell disease in patients 12 years of age and older with recurrent vasoocclusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom haematopoeitic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

Intervention

Each person enrolled into the study went through 'stages'; these stages are summarised in the following diagram:

Figure 9-1 Study 121 Study Design



Source: Adapted from Appendix 16.1.1/Protocol Version 6.4 EUR/Figure 9-1

CRISPR/Cas9: Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR associated 9 nuclease; exa-cel: exagamglogene autotemcel; Hb: hemoglobin; HbS: hemoglobin S; hHSPCs: human hematopoietic stem and progenitor cells; M24: month 24

Note: Figure is not drawn to scale. Starting at least 8 weeks before first day of mobilization in Stage 2, subjects received RBC transfusions to maintain HbS level of <30% of total Hb while keeping total Hb concentrations ≤11 g/dL from Stage 1 through the start of busulfan conditioning in Stage 3A.

[a] Including collection of CD34+ cells as back-up for rescue therapy in the event of non-neutrophil engraftment with exa-cel.

[b] Subjects were followed for approximately 2 years after the exa-cel infusion. All subjects who received exa-cel were asked to enroll into the long-term follow-up study.

Stage 1:

Subjects began red blood cell exchange or simple transfusions for a minimum of 8 weeks before the planned start of mobilization and continued receiving these transfusions until they began busulfan conditioning. The goal of these red blood cell transfusions was to maintain an HbS level of <30% of total haemoglobin while keeping total Hb concentration ≤11 g/dL.

Subjects could undergo fertility preservation as per subject age and local practice.

comment: stage 1 is consistent with usual clinical practice; no additional comment on stage 1.

Stage 2:
On Day 1 of mobilisation, subjects received plerixafor 2 to 3 hours before the start of apheresis. Subjects underwent apheresis for up to 3 consecutive days to collect $CD34^+$ human haematopoietic stem and progenitor cells. Day 2 and Day 3 (if required) were the same as Day 1.

Comment
Granulocyte colony-stimulating factor was not used to mobilise cells; because life-threatening complications can ensue in the presence of sickle vasculopathy.

Subjects received plerixafor at a dose of 0.24 mg/kg via subcutaneous injection 2 to 3 hours before the start of each apheresis. The dose was based on body weight taken within 5 days before the first day of mobilisation.

To note that described use of plerixafor is not fully consistent with their respective SPCs.

The targeted CD34+ cell collection was at least 15 × 10^6 $CD34^+$ cells/kg for manufacturing of exa-cel in order to achieve a minimum target dose of 3 × 10^6 $CD34^+$ cells/kg. The number of mobilisation cycles and cells collected for manufacturing are summarized in Table 10-5:

Table 10-5 Summary of Mobilization Overall (FAS)

Parameter	Total N = 43
Number of mobilization cycles	
n	43
Mean (SD)	2.21 (1.30)
Median	2.00
Min, max	1.00, 6.00
Cells collected for manufacturing (10^6 $CD34^+$ cells/kg)	
n	43
Mean (SD)	24.77 (11.67)

Median	22.30
Min, max	10.43, 76.18

Source: Table 14.1.7.1 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; N: total sample size; n: size of subsample
Note: Cells collected for manufacturing for a subject was calculated as sum of all cells collected for manufacturing across all cycles for a subject/the subject's most-recent weight before the last mobilization cycle.

An additional 2 × 10^6 $CD34^+$ cells/kg were collected as backup for rescue therapy in an event of non-neutrophil engraftment with exa-cel. These cells did not undergo the editing/manufacturing process and were cryopreserved at the clinical site.

Comment: the median (range) number of mobilisation cycles was 2 (1 to 6); the median (range) number of cells collected for drug product manufacturing was 22.3 (10.43 to 76.18) × 10^6 $CD34^+$ cells/kg.
The cell collection procedure appears in line with usual practice and so is concurred; the decision to obtain back-up cells is supported.

Stage 3A:
After the exa-cel product was received at the site and the backup $CD34^+$ stem cells were confirmed available and in acceptable condition to be administered if needed, the subject began busulfan conditioning. Busulfan was administered intravenously through a central venous catheter once daily for 4 consecutive days (based on body weight collected within 7 days before the first day of busulfan administration). Once-daily (qd) dosing was the preferred schedule, but the busulfan dose regimen could be adjusted to be given every 6 hours (q6h) per site's standard practice.

For subjects <34 kg, weight-based starting dose recommendations for busulfan were as follows:

- For subjects weighing 16 to 23 kg, 1.1 mg/kg q6h or 4.4 mg/kg qd
- For subjects weighing >23 to 34 kg, 0.95 mg/kg q6h or 3.8 mg/kg qd

Target busulfan AUC or cumulative exposure for each dosing regimen was the same across all age groups. If the planned start of busulfan conditioning was >4 months after the completion of mobilisation, the investigator could stop the RBC transfusion regimen and restart hydroxyurea, crizanlizumab or voxelotor for those subjects who had previously been treated with these agents.

The conditioning regimen and total busulfan dose are summarized in Table 10-6:

Table 10-6 Summary of Conditioning Overall (FAS)

Parameter	Total N = 43
Busulfan dose regimen, n (%)	
q6h	28 (65.1)
qd	15 (34.9)
Total busulfan dose (mg/kg)	
n	43
Mean (SD)	12.37 (2.31)
Median	12.63
Min, max	6.53, 17.64

Source: Table 14.1.8 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; N: total sample size; n: size of subsample; q6h: every 6 hours; qd: once daily
Notes: Percentages were calculated relative to the number of subjects in the FAS. Total busulfan dose (mg/kg) for a subject was calculated as the sum of all busulfan doses for the subject/the subject's most recent weight before conditioning.

Comment: **To note that described use of busulfan is not fully consistent with its SmPC.**

Stage 3B:
The exa-cel infusion occurred at least 48 hours after completion of the busulfan infusion and no more than 7 days after completion of the busulfan infusion.

On Day 1, the entire dose of exa-cel was infused IV through a central venous catheter.

Each vial containing exa-cel was infused within 20 minutes after thawing.

If exa-cel infusion did not occur within 7 days after the last dose of busulfan, subjects were to receive the backup $CD34^+$ stem cells.

Following exa-cel infusion, subjects underwent infection surveillance and prophylaxis (bacterial, viral, fungal) as per local guidelines for haematopoietic stem cell transplant and investigator judgment.

If engraftment did not occur by Day 21 after exa-cel infusion, G-CSF (e.g. filgrastim) could have been administered following discussion with the medical monitor.

Stage 4A:
Subjects were monitored in the transplant unit and received supportive care according to standard practices for subjects undergoing haematopoietic stem cell transplant.

Subjects received red blood cell transfusions to maintain Hb ≥7 g/dL and platelet transfusions to maintain platelets >50,000/uL or otherwise followed institutional practices.

Subjects were monitored for adverse events and engraftment. If engraftment did not occur by Day 21 after exa-cel infusion, G-CSF (e.g. filgrastim) could have been administered following discussion with the medical monitor.

Subjects were discharged from the transplant unit upon neutrophil engraftment (absolute neutrophil count ≥500/μL for 3 consecutive measurements on 3 different days) and stabilisation of major medical issues as per local hospital guidelines and investigator judgment.

Stage 4B:
After discharge from the transplant unit: subjects were followed for about 2 years after the exa-cel infusion with physical examinations, laboratory and imaging assessments and AE evaluations.

Comment: management of subjects after receiving product appears in line with usual practice and so may be accepted; no additional comment on stage 4.

Follow-up
All subjects who received exa-cel were offered enrolment into the long-term follow-up study (Study 131) after completion or withdrawal / discontinuation from Study 121.

Comment:
The MAH provided an "Apheresis and Infusion Specialist" and "Medical Monitor" to give oversight.

The MAH submits

- an apheresis collection manual ver 9.0, dated 14 Oct 2022. The manual describes roles / responsibilities; equipment needed; chain of identity and chain of custody; labelling, packaging and shipping of material with GPS tracking.
- a product receipt, storage and infusion manual ver 9.0, dated 14 Oct 2022. The manual describes roles / responsibilities; equipment needed; chain of identity and chain of custody; product complaints procedure; shipment and receipt with GPS tracking; product storage; product administration.

Different versions of the web-based chain of identity / chain of custody system were used for the different CTX001 studies

Exa-cel is held in cryo-storage; exa-cel must be infused within 20 minutes of completion of thawing; if exa-cel is in multiple vials then vials must be infused one at a time; 2 people must verify exa-cel labeling at the bedside prior to the infusion of each exa-cel vial; exa-cel is administered as an intravenous bolus.

Exa-cel exposure as of the data cutoff date of 16 April 2023:
Full analysis set: a total of 43 subjects had been infused with exa-cel. The median exa-cel dose was 4.0 (range: 2.9 to 14.4) × 10^6 $CD34^+$ cells/kg. The median duration of follow-up after exa-cel infusion was 17.5 (range: 1.2 to 25.6) months.

There are 29 subjects in the primary efficacy set. For this set, the median (range) dose was 4.0 (2.9 to 14.4) × 10^6 $CD34^+$ cells/kg. The median (range) follow-up duration after exa-cel infusion was 23.6 (16.1 to 25.6) months.

Comment: the median number of cells administered is notably lower than the median 7.5 (range: 3.0 to 19.7) × 10^6 $CD34^+$ cells/kg administered to subjects with thalassaemia in study 111 and presumably reflects differences in the underlying patho-physiologies of these diseases and that mobilisation in the sickle patients was done without use of G-CSF.

Comparator
This is a single-arm study without concurrent comparator.

Outcomes
Outcomes are assessed with the caveat of the fallacy of human reasoning referred to as: *post hoc ergo propter hoc* (Latin: 'after this, therefore because of this').

Primary efficacy outcome:
The proportion of subjects who had not experienced any severe vaso-occlusive crisis for at least 12 consecutive months after exa-cel infusion is presented in Table 11-3:

Table 11-3 Proportion of Subjects Who Achieved VF12 (PES)

Category	Total N = 29
Subjects who achieved VF12	
n	28
%, 2-sided 95% CI	96.6 (82.2, 99.9)
1-sided *P* value against a 50% response rate	<0.0001

Source: Table 14.2.1.1 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VF12: absence of any severe VOC for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crisis
Notes: The evaluation of VF12 started 60 days after the last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The percentage of subjects who achieved VF12 was calculated relative to the number of subjects in the PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.

28/29 (96.6%) subjects in the primary efficacy set achieved the primary outcome.

To note that 27 of the 28 subjects in the primary efficacy set who achieved the primary outcome remained vaso-occlusive crisis free until the end of study date or the interim data cut date, whichever was earlier.

1 subject was vaso-occlusive crisis free (60 days after the last RBC transfusion) , and had a vaso-occlusive crisis (~22.7 months after exa-cel infusion) and was subsequently vaso-occlusive crisis free to their completion of study 121.

Comment: for a population of subjects with severe sickle cell disease and a history of needing frequent medical interventions: 28/29 subjects achieving the primary outcome of not experiencing any severe vaso-occlusive crisis for at least 12 consecutive months after exa-cel infusion is considered to be notable.

Subgroup Analysis of Primary Efficacy Endpoint

Subgroup analyses of the primary endpoint were performed by age at screening (≥12 and <18 years of age and ≥18 and ≤35 years of age), genotype (βS/βS and non βS/βS), race (Black or African American and other races), sex, and the subset of subjects with ≥3 vaso-occlusive crises per year for the prior 2 years at baseline were performed and are summarized in Table 11-4:

Table 11-4 Subgroup Analysis: Proportion of Subjects Who Achieved VF12 by Age at Screening, Genotype, Sex, Race, and ≥3 VOCs/year for the Prior 2 Years at Baseline (PES)

Subgroup	Total N = 29
Age	
Subjects ≥12 and <18 years of age at screening, N1	6
Subjects ≥12 and <18 years of age at screening and achieved VF12	
n	6
%, 2-sided 95% CI	100.0 (54.1, 100.0)
Subjects ≥18 and ≤35 years of age at screening, N1	23
Subjects ≥18 and ≤35 years of age at screening and achieved VF12	
n	22
%, 2-sided 95% CI	95.7 (78.1, 99.9)
Genotype	
Subjects with the β^S/β^S genotype, N1	28
Subjects with β^S/β^S genotype and achieved VF12	
n	27
%, 2-sided 95% CI	96.4 (81.7, 99.9)
Subjects with the Non- β^S/β^S genotype, N1	1
Subjects with the Non- β^S/β^S genotype and achieved VF12	
n	1
%, 2-sided 95% CI	100.0 (--, --)
Sex	
Male subjects, N1	16
Male subjects who achieved VF12	
n	16
%, 2-sided 95% CI	100.0 (79.4, 100.0)
Female subjects, N1	13
Female subjects who achieved VF12	
n	12
%, 2-sided 95% CI	92.3 (64.0, 99.8)
VOCs	
Subjects with ≥3 VOCs per year for the prior 2 years at baseline, N1	16
Subjects with ≥3 VOCs per year for the prior 2 years at baseline and achieved VF12	
n	15
%, 2-sided 95% CI	93.8 (69.8, 99.8)
Race	
Subjects whose race is Black or African American, N1	26
Subjects whose race is Black or African American and achieved VF12	
n	25
%, 2-sided 95% CI	96.2 (80.4, 99.9)
Subjects whose race is Other Races, N1	3
Subjects whose race is Other Races and achieved VF12	
n	3
%, 2-sided 95% CI	100.0 (--, --)

Source: Table 14.2.1.3, Ad hoc Table 14.2.1.6 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; N1: number of subjects in each subgroup; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VF12: absence of any severe VOC for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crisis
Notes: The evaluation of VF12 started 60 days after the last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion referred to that in the period of the initial RBC transfusion for post-transplant support or SCD management. The percentage of subjects who achieved VF12 was calculated relative to the number of subjects in each subgroup (i.e., n/N1 × 100). The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only a descriptive summary (n and %) was provided for subgroups with a sample size <5 subjects. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis. Other Races include any races other than Black or African American. Multi-races are also included in Other Races.

The results of the subgroup analyses for age, sex, race, and subjects with ≥3 vaso-occlusive crises per year were consistent with the results from the primary analysis.

27 of 28 (96.4%) subjects in the primary efficacy set who achieved the primary outcome had the βS/βS genotype; the only subject in the primary efficacy set with a non- βS/βS genotype also achieved the primary outcome.

Comment: efficacy appears to be evident in all described subgroups.

Secondary efficacy outcomes

1. The proportion of subjects who remained free from in-patient hospitalisation (sustained for at least 12 months after exa-cel infusion) for severe vaso-occlusive crises is shown in table 11-5:

Table 11-5 Proportion of Subjects Who Achieved HF12 (PES)

Category	Total N = 29
Subjects who achieved HF12	
n	29
%, 2-sided 95% CI	100.0 (88.1, 100.0)
1-sided *P* value against a 50% response rate	<0.0001

Source: Table 14.2.2.1 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; HF12: free from inpatient hospitalization for severe VOCs and sustained for at least 12 months after exa-cel infusion; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VOC: vaso-occlusive crisis
Notes: The evaluation of HF12 started 60 days after the last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of initial RBC transfusions for post-transplant support or SCD management. The percentage of subjects who achieved HF12 was calculated relative to the number of subjects in the PES. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.

Following infusion with exa-cel, all 29 subjects in the primary efficacy set achieved this secondary outcome.

Comment: for a population of subjects with severe sickle cell disease and a history of needing frequent medical interventions: 29/29 subjects not requiring in-hospital care for at least 12 consecutive months after exa-cel infusion is considered to be notable.

This secondary outcome was found in all subgroups of age (≥12 and <18 years of age and ≥18 and ≤35 years of age), genotype, race, sex, and the subset of subjects with ≥3 vaso-occlusive crises per year for the prior 2 years at baseline.

This outcome is / these outcomes are considered to support the primary outcome data.

2. The vaso-occlusive crisis free duration in subjects who achieved the primary outcome is summarized in Table 11-7.

Table 11-7 Summary of Duration of Severe VOC Free for Subjects Who Achieved VF12 (PES)

Category	Total N = 29
Subjects who achieved VF12, N1	28
Duration of severe VOC free for subjects who achieved VF12 (months)	
n	28
Mean (SD)	18.3 (3.4)
Median	20.5
Min, max	13.5, 22.4

Source: Table 14.2.4 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; N1: number of subjects in each subgroup; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VF12: absence of any severe VOC for at least 12 consecutive months after exa-cel infusion; VOC: vaso-occlusive crisis
Notes: The evaluation of the severe VOC free duration in subjects who achieved VF12 started 60 days after the last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of the initial RBC transfusions for post-transplant support or SCD management. Duration of severe VOC free (months) = (the day before the start date of the first severe VOC after achieving VF12 or the data cutoff date or the end of study date whichever was earlier - the start date of VF12 + 1)/30. Only severe VOCs adjudicated by an EAC as meeting the protocol definition of severe VOCs were included in the analysis.

For the 28/29 subjects in the primary efficacy set who achieved the primary outcome, the mean (SD) vaso-occlusive crisis free duration was 18.3 (3.4) months.

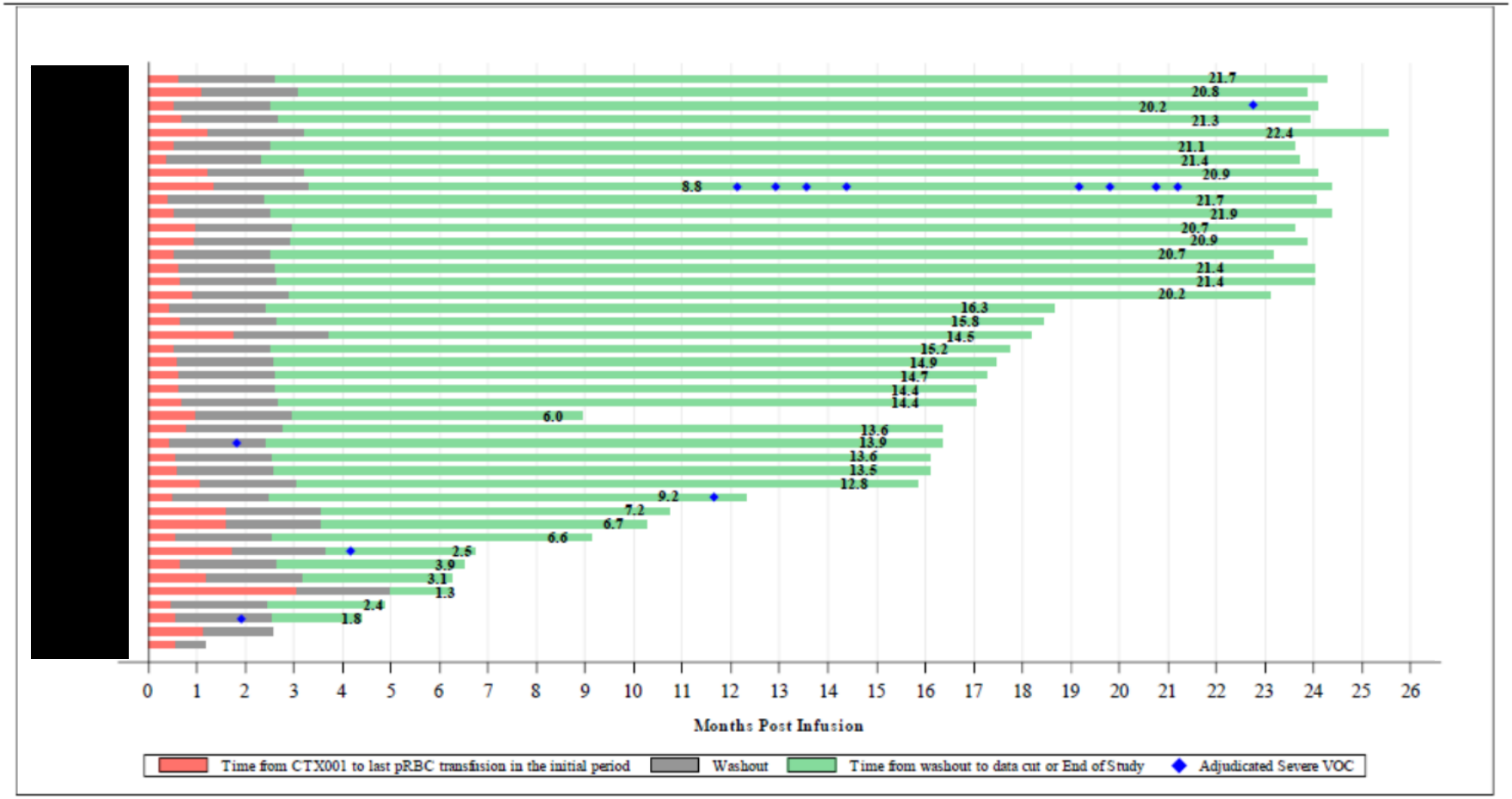
Comment: the achievement of (about) 18 months being free of a vaso-occlusive crisis is considered to be notable in a population of subjects with severe sickle cell disease.

For the full analysis set population: 2/43 subjects had less than 60 days of follow-up after the last RBC transfusion for post-transplant support or sickle cell disease management.

41 of 43 subjects had at least 60 days of follow-up after the last RBC transfusion for post-transplant support or SCD management and have been VOC free for 1.3 to 22.4 months, starting 60 days after the last RBC transfusion

Information is summarised in figure 11-4: figure 11-4 is assessed with the caveat of the fallacy of human reasoning referred to as: *post hoc ergo propter hoc* (Latin: 'after this, therefore because of this').

Figure 11-4 Duration of Severe VOC Free Period (FAS)



Source: Figure 14.2.2.1 (data cutoff date of 16 April 2023)

EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VOC: vaso-occlusive crisis

Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria were included. The number at the right end of the figure is the duration of total follow-up. Completion of the initial RBC transfusion is determined when all those transfusions for post-transplant support or SCD management have finished followed by 60 days without transfusion. * indicates subjects in the PES.

For the full analysis set: 41 subjects had at least 60 days follow-up after last clinical intervention; these include:

- 37/41 subjects who did not experience any vaso-occlusive crisis
- 4/41 subjects had events adjudicated as a vaso-occlusive crisis, starting 60 days after the last red blood cell transfusion; these include:
    - ❖ Subject [subject no. removed to protect personal information], included in the primary efficacy set, who had small number of acute pain events adjudicated as vaso-occlusive crises between 12.1 and 21.2 months after exa-cel infusion; the subject did not achieve the primary outcome.
    - ❖ Subject [subject no. removed to protect personal information], included in the primary efficacy set, achieved the primary outcome and was vaso-occlusive crisis free for ~22.7 months after exa-cel infusion, then had a single event adjudicated as a vaso-occlusive crisis by the external adjudication committee in the setting of a viral infection and has subsequently remained vaso-occlusive crisis free through their completion of Study 121.
    - ❖ Subject [subject no. removed to protect personal information], not yet included in the primary efficacy set, was vaso-occlusive crisis free for ~11.7 months after exa-cel infusion, then had an acute pain event adjudicated as a vaso-occlusive crisis; the subject has subsequently remained vaso-occlusive crisis free.
    - ❖ Subject [subject no. removed to protect personal information], not yet included in the primary efficacy set, had an event adjudicated as vaso-occlusive crisis on Day [removed to protect personal information] after exa-cel infusion; the subject has subsequently remained vaso-occlusive crisis free.

Comment: The 4 subjects who sustained a vaso-occlusive crisis after exposure to exa-cel are noted; 3 of the subjects had one event only (one appears to have been related to viral infection); 1 subject sustained a small number of pain related events.

In order to provide clarity on those who experienced one or more vaso-occlusive crises beyond 150 days after administration of Casgevy, the MAH has been requested to add to information (via annual updates to the conditional licence) on the relationship between total number of cells administered to each patient and increase in circulating fetal haemoglobin and duration of sustained efficacy.

3. Relative reduction from baseline in annualised rate of severe vaso-occlusive crises for subjects who did not achieve the primary outcome.

1/29 subjects in the primary efficacy set did not achieve the primary outcome.

This subject had a small number of events adjudicated as vaso-occlusive crises (between 12.1 and 21.2 months after exa-cel infusion) and 1 event that was sent for adjudication but was confirmed to be non-vaso-occlusive crisis.

At the time of the data cut date, there was no reduction in annualised vaso-occlusive crises for this subject

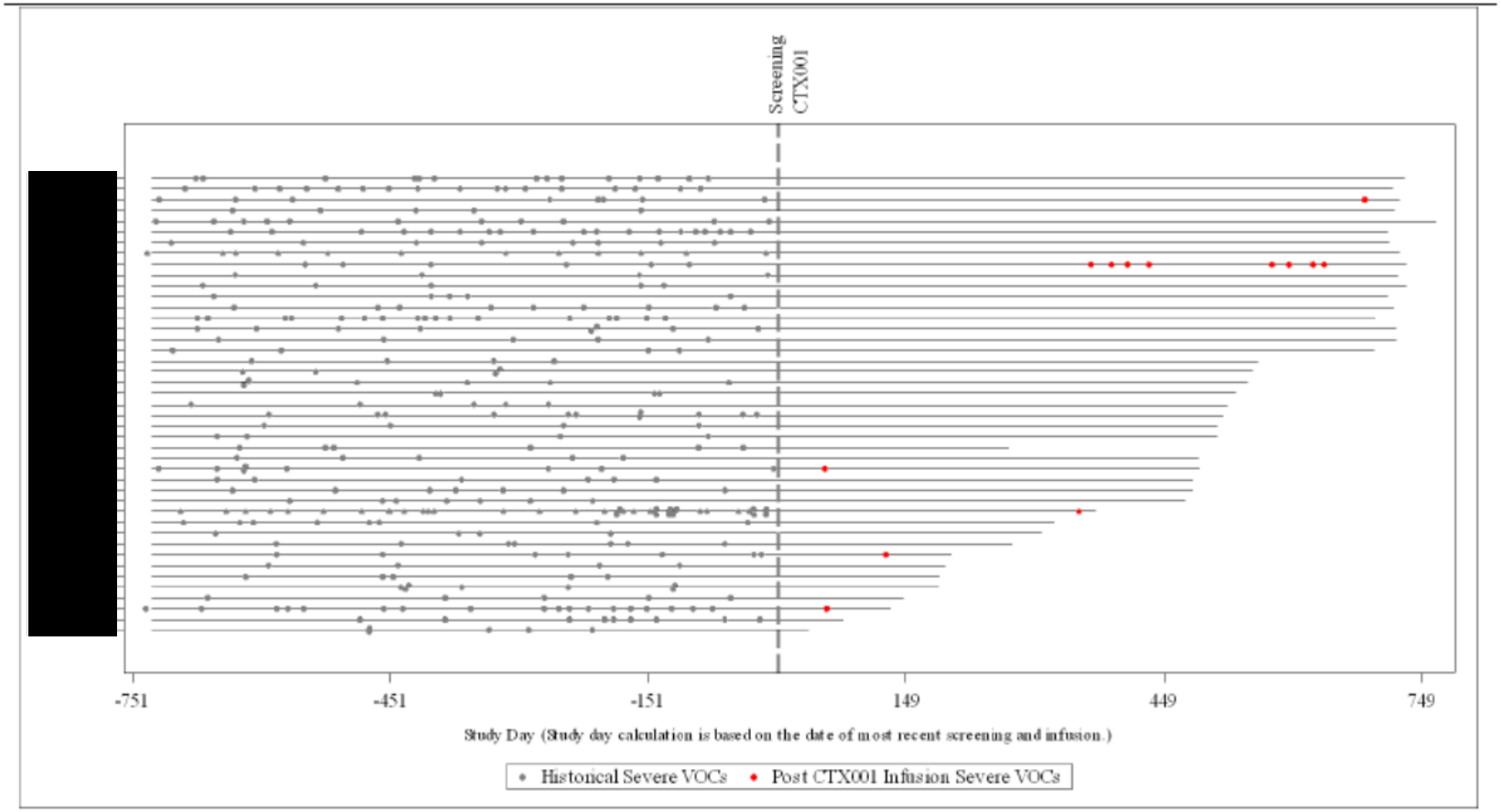
The occurrence of vaso-occlusive crises before and after exa-cel infusion for the 43 subjects in the full analysis set are shown in Figure 11-5, including subjects who achieved and did not achieve the primary outcome:

figure 11-5 is assessed with the caveat of the fallacy of human reasoning referred to as: *post hoc ergo propter hoc* (Latin: 'after this, therefore because of this')

Regarding the 3 subjects who experience one or more vaso-occlusive crises beyond 300 days after exposure to product: there would be concern that this represents loss of efficacy; further follow-up is considered needed to gain more understanding.

Irrespective, the comparison of ‘before’ and ‘after’ in figure 11-5 is consistent with the current product bearing efficacy (albeit with the caveat of the fallacy of reasoning described above).

Figure 11-5 Historical and After Exa-cel Infusion Severe VOCs (FAS)



Source: Figure 14.2.1 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; PES: Primary Efficacy Set; VOC: vaso-occlusive crisis
Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria are displayed. * indicates subjects in the PES.

4. Hospitalisation for subjects who did not remain free from inpatient hospitalisation (sustained for at least 12 months after exa-cel infusion) for severe vaso-occlusive crisis:

All (100%) subjects in the primary efficacy set were free from inpatient hospitalisation for severe vaso-occlusive crisis sustained for at least 12 months and so this outcome cannot be presented at this stage.

In the full analysis set:

41 of 43 subjects had at least 60 days of follow-up after the last red blood cell transfusion for post-transplant support or sickle cell disease management.

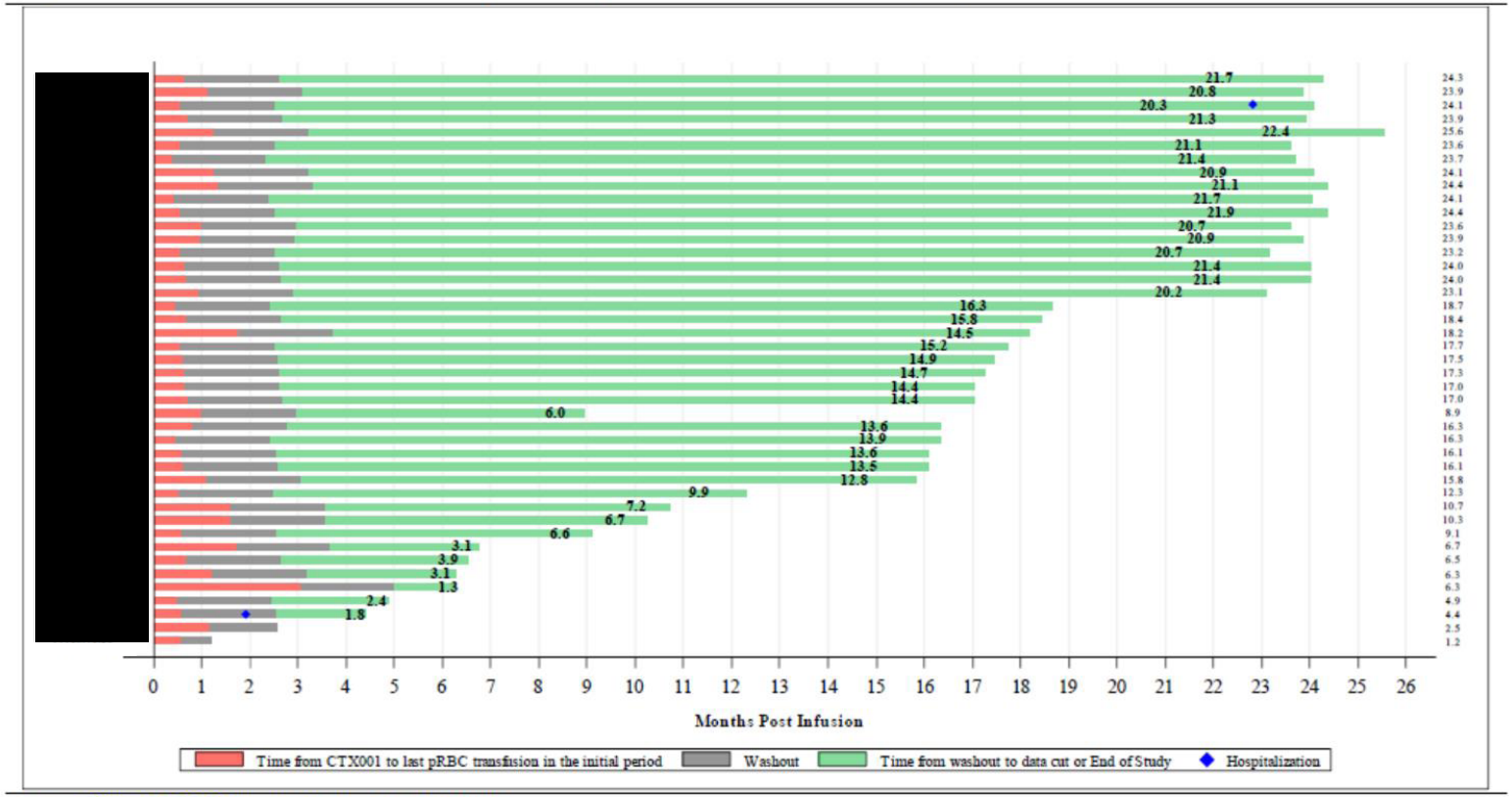
Of these 41 subjects, 40 subjects were free from inpatient hospitalization for vaso-occlusive crises starting 60 days after the last red blood cell transfusion, with a duration of 1.3 to 22.4 months as of the data cutoff date (16 April 2023).

Two subjects who were recently dosed had less than 60 days follow-up after the last red blood cell transfusion for post-transplant support or sickle cell disease management.

Comment: no additional comment / secondary outcome 4 is considered supportive towards the main claim of the MAH.

For the full analysis set: duration of period free of in-patient hospitalization for severe vaso-occlusive crisis is illustrated in Figure 11-6:

Figure 11-6 Duration of Period Free of Inpatient Hospitalization for Severe VOC (FAS)



Source: Figure 14.2.2.2 (data cutoff date of 16 April 2023)
EAC: Endpoint Adjudication Committee; FAS: Full Analysis Set; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease; VOC: vaso-occlusive crisis
Notes: Only severe VOCs that were adjudicated by an EAC as meeting the protocol criteria were included. The number at the right end of the figure is the duration of total follow-up. Completion of the initial RBC transfusion is determined when all those transfusions for post-transplant support or SCD management have finished followed by 60 days without transfusion. * indicates subjects in the PES.

5. Proportion of subjects with sustained HbF ≥20% for at least 3 months, 6 months or 12 months

All 29 (100%) subjects in the primary efficacy set sustained HbF ≥20% for at least 12 months; refer to table 11-10:

Table 11-10 Proportion of Subjects with Sustained HbF Concentration ≥20% (PES)

Category	Total N = 29
Subjects with sustained HbF ≥20% for at least 3 months	
n	29
%, 2-sided 95% CI	100.0 (88.1, 100.0)
Subjects with sustained HbF ≥20% for at least 6 months	
n	29
%, 2-sided 95% CI	100.0 (88.1, 100.0)
Subjects with sustained HbF ≥20% for at least 12 months	
n	29
%, 2-sided 95% CI	100.0 (88.1, 100.0)

Source: Table 14.2.7 (data cutoff date of 16 April 2023)
HbF: fetal hemoglobin; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease
Notes: The evaluation started 60 days after the last RBC transfusion for post-transplant support or SCD management. The last RBC transfusion refers to that in the period of the initial RBC transfusions for post-transplant support or SCD management. Hemoglobin measurements were from central laboratories. One month = 30 days. The 2-sided 95% CI was calculated using the exact Clopper-Pearson method.

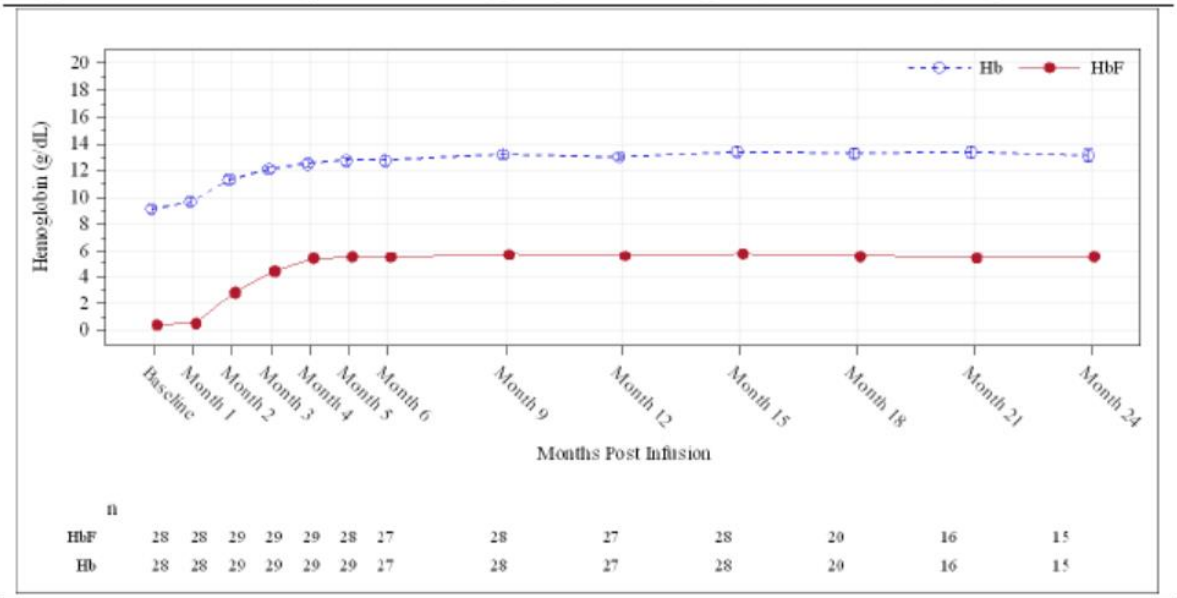
40/43 subjects in the full analysis set had a sustained HbF ≥20%; 2 subjects did not have sufficient follow-up (<60 days after last red blood cell transfusion) and 1 subject had HbF <20% after Month 3 due to frequent red blood cell transfusions for a serious adverse event.

Comment: refer to secondary outcome 6.

6. Total Hb and HbF concentration over time

Total Hb and HbF concentrations over time after exa-cel infusion are presented in Figure 11-8 (at each visit).

Figure 11-8 Summary of Total Hb (g/dL) and HbF (g/dL) Over Time (PES)



Source: Figure 14.2.6.1 (data cutoff date of 16 April 2023)
Hb: hemoglobin, HbF: fetal hemoglobin; n: size of subsample; PES: Primary Efficacy Set
Notes: Mean values are plotted in the line, mean + standard error and mean - standard error values are plotted as bars at each visit. The numbers of subjects with total Hb and HbF values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

There were increases in mean total Hb and HbF concentrations for subjects in the primary efficacy set, which occurred early (Month 3) and were maintained over time.

Mean (SD) total Hb levels were 12.1 (1.3) g/dL at Month 3, increased to 12.7 (1.7) g/dL at Month 6 and were maintained ≥12 g/dL over the duration of follow-up.

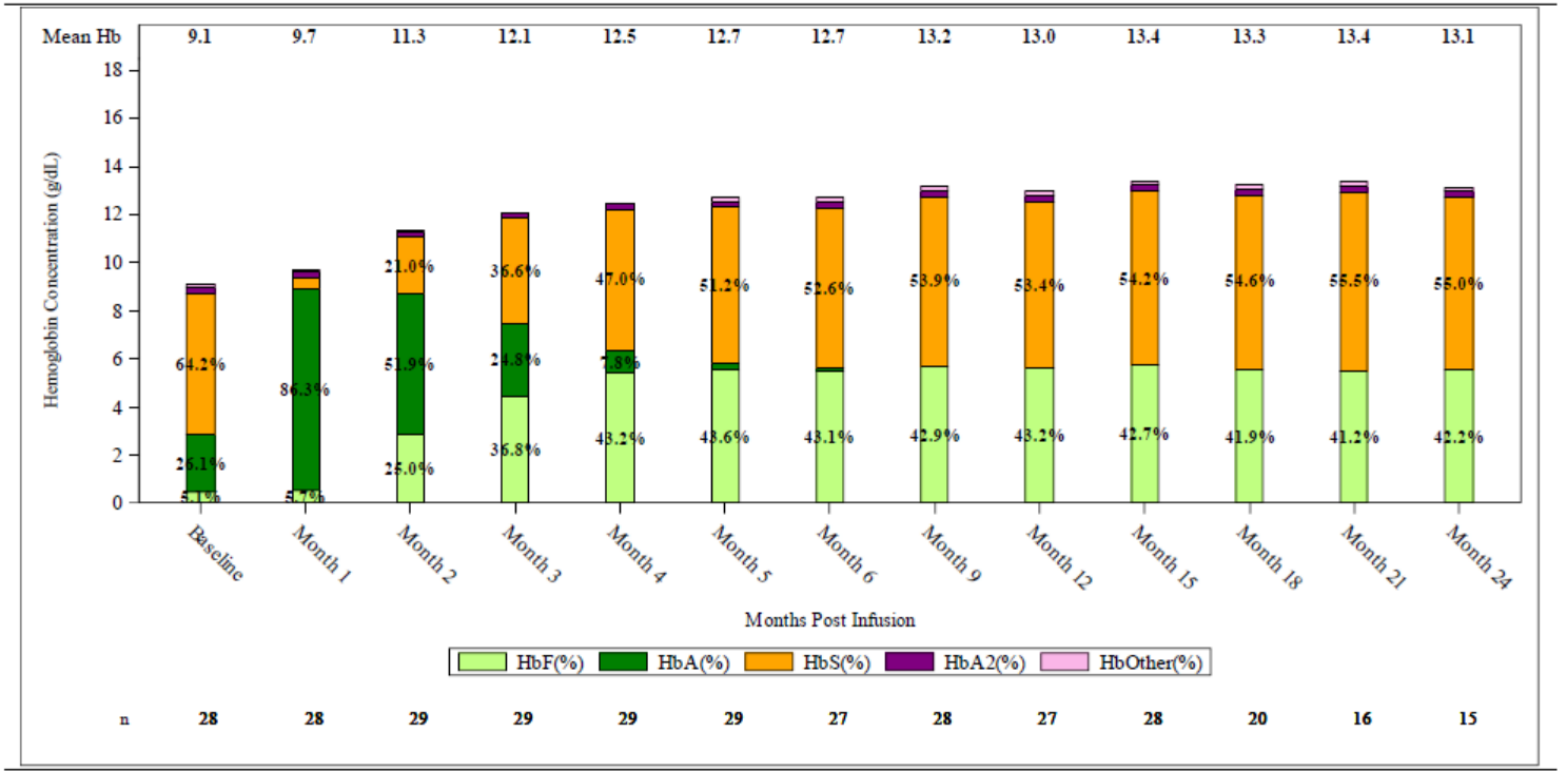
Mean (SD) proportion of total Hb comprised by HbF (HbF %) was 36.8% (7.9%) at Month 3, increased to 43.1% (6%) at Month 6, and was thereafter maintained ≥40% over the duration of follow-up.

All subjects in the primary efficacy set sustained HbF ≥20% for at least 12 months.

Comment: the increase in HbF concentration from trace amounts to (about) 4.5 g/dL from month 4 onwards is accompanied by an increase in total Hb to (about) 12 g/dL from month 4 onwards. Data support the claimed mode of action and the primary outcome now reported.

Total Hb and HbF concentrations over time after exa-cel infusion for the 29 subjects in the primary efficacy set are presented in figure 11-7 (each visit).

Figure 11-7 Hb Fraction Over Time (PES)



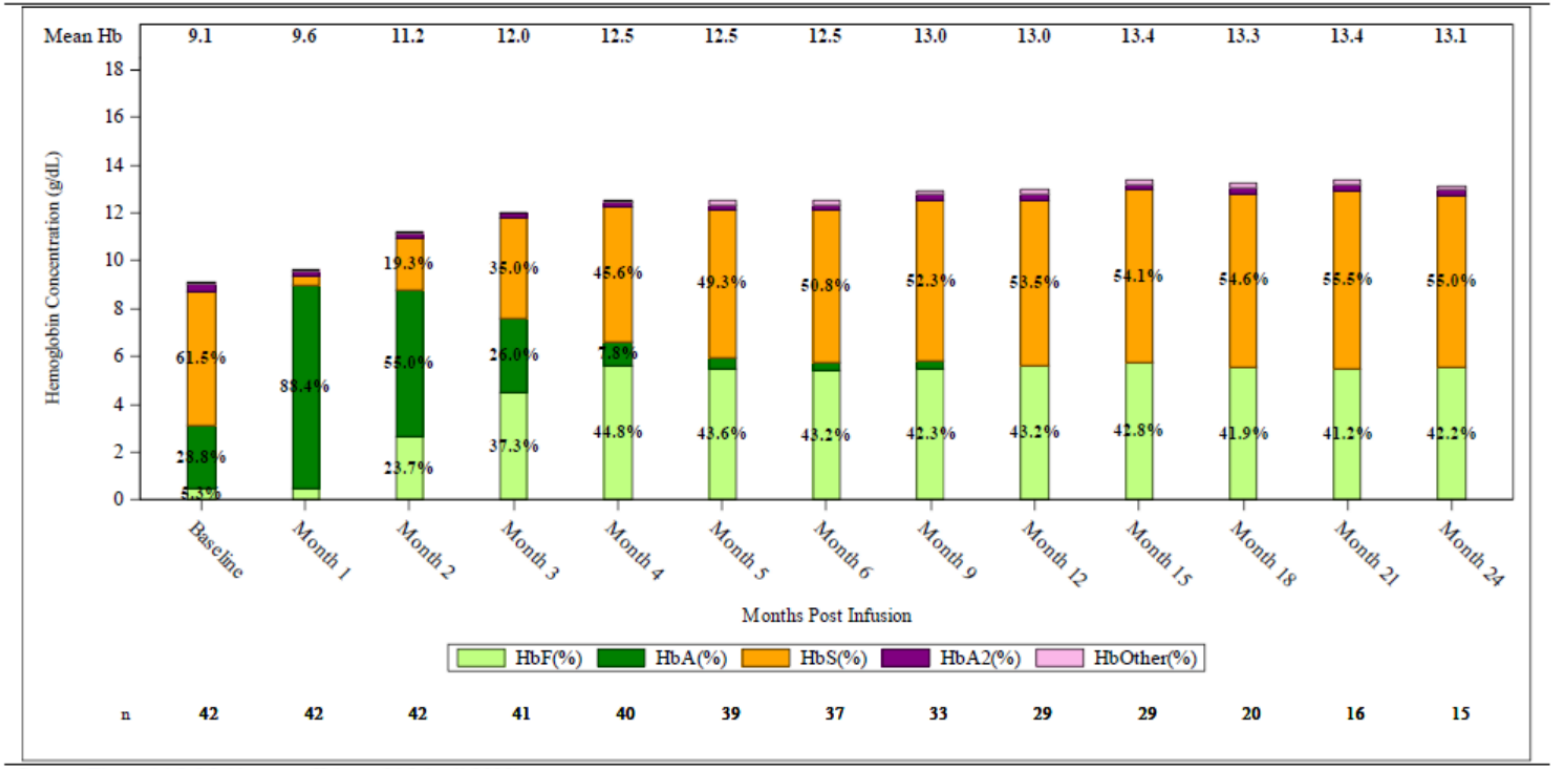
Source: Figure 14.2.5.1 (data cutoff date of 16 April 2023)

Hb: hemoglobin; HbA: hemoglobin A; HbA2: hemoglobin A2; HbF: fetal hemoglobin; Hb Other: Total Hb - HbA - HbA2 - HbF - HbS; HbS: hemoglobin S; n: size of subsample; PES: Primary Efficacy Set

Notes: Mean Hb fractions are plotted at each visit. The numbers of subjects with total Hb values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit is shown in the figure.

Total Hb and HbF concentrations over time after exa-cel infusion for the full analysis set are presented in figure 11-9 (each visit)

Figure 11-9 Hb Fraction Over Time (FAS)



Source: Figure 14.2.5.3 (data cutoff date of 16 April 2023)
FAS: Full Analysis Set; Hb: hemoglobin; HbA: hemoglobin A; HbA2: hemoglobin A2; HbF: fetal hemoglobin; Hb Other: Total Hb - HbA - HbA2 - HbF - HbS; HbS: hemoglobin S; n: size of subsample
Notes: Mean Hb fractions are plotted at each visit. The numbers of subjects with total Hb values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit is shown in the figure.

HbF appears to displace HbA with HbS remaining present at (about) 55% of total Hb. Data for the full analysis set suggests that the primary efficacy set is representative of a broader picture.

7. Proportion of alleles with intended genetic modification present in (i) drug product, (ii) peripheral blood and (iii) $CD34^+$ cells of the bone marrow

The proportion of alleles with the intended genetic modification in the exa-cel drug product is summarised for the primary efficacy set and full analysis set in Table 11-11

Table 11-11 Summary of the Proportion of Alleles with the Intended Genetic Modification in Exa-cel Drug Product (PES and FAS)

Category	PES N = 29	FAS N = 43
Exa-cel Product Editing (%)		
n	29	43
Mean (SD)	89.92 (6.34)	89.92 (6.01)
Median	92.55	92.09
Min, max	65.13, 95.11	65.13, 95.11

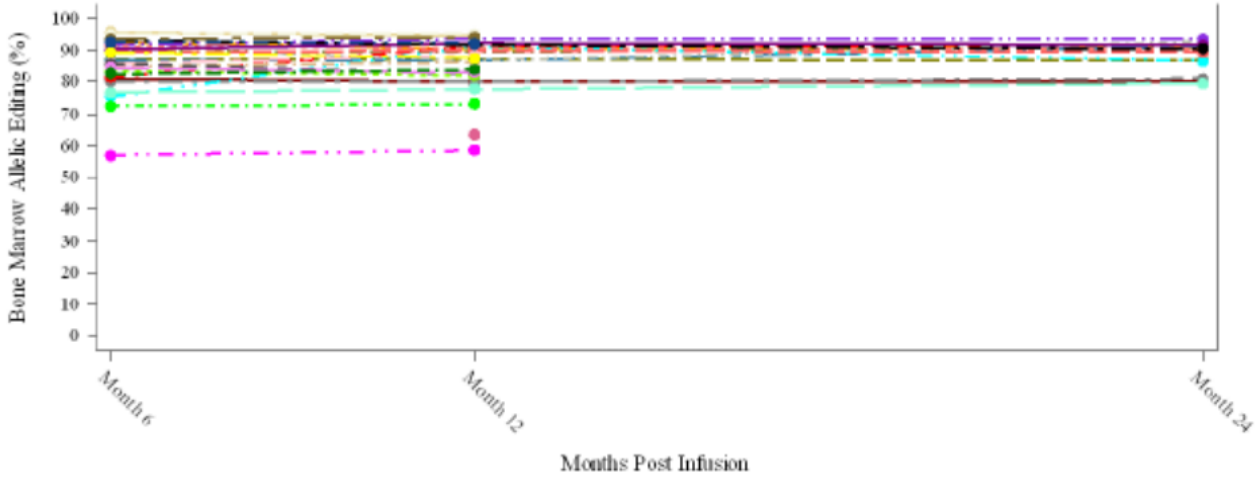
Source: Table 14.1.9.1 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total sample size; n: size of subsample; PES: Primary Efficacy Set
Note: Proportion of alleles with intended genetic modification in exa-cel is from central laboratories. The proportion of alleles with intended genetic modification in exa-cel drug product is calculated as a weighted average based on lots with available data. Only 1 subject did not have data available for all lots in their respective exa-cel drug products (data available for 3 of the 4 lots).

Comment: at least 65% drug product cells have evidence of a modified target.

In support of the application, the following was submitted:

The mean proportion of alleles with the intended genetic modification in the $CD34^+$ cells of the bone marrow remained stable (≥85%) from Month 6 onward (Figure 11-12).

Figure 11-12 Individual Bone Marrow Allelic Editing (%) Over Time (PES)



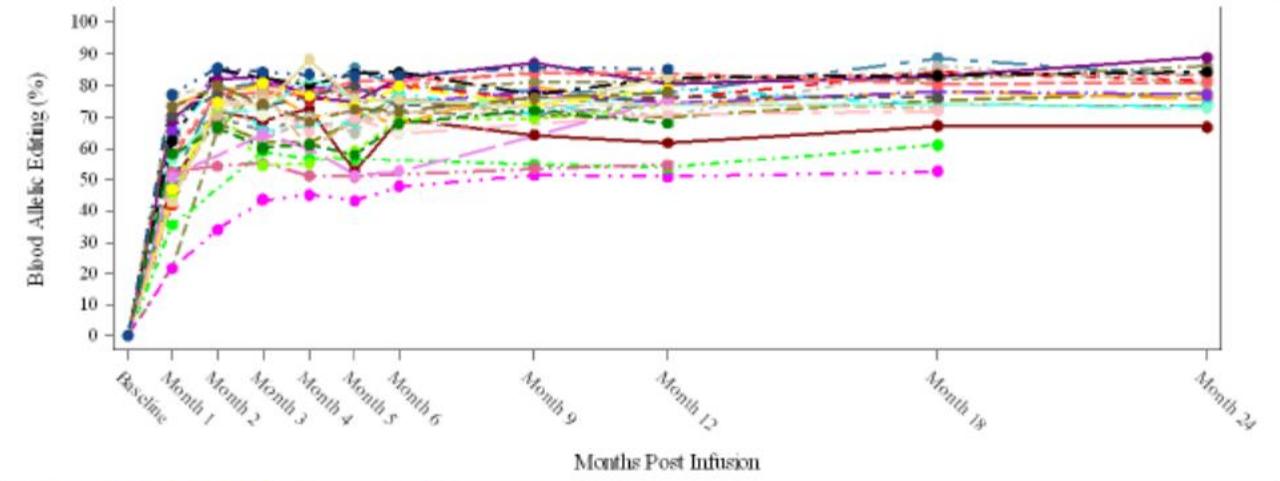
Source: Figure 14.2.9.1 (data cutoff date of 16 April 2023)
PES: Primary Efficacy Set
Notes: Analysis visit was used in the figure.

Comment: for any given individual, the percentage of bone marrow allele editing appears to be constant up to month 12 in all subjects displayed and up to 24 months in those with extended follow-up.

The MAH gives emphasis to the mean proportion of alleles; there are notably some subjects who achieve much lower percentages (to about 55%); the clinical significance of this is not known.

Allelic editing in the peripheral blood was detectable within 1 month after exa-cel infusion. The mean (SD) proportion of alleles with the intended genetic modification in peripheral blood was 56.53% (15.27%) at Month 1 and the mean generally remained ≥70% from Month 2 onward (figure 11-13):

Figure 11-13 Individual Peripheral Blood Allelic Editing (%) Over Time (PES)



Source: Figure 14.2.7.1 (data cutoff date of 16 April 2023)
PES: Primary Efficacy Set
Notes: Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

The small, non-zero value at baseline (<0.5%) was consistent with the expected background signal in the assay.

Allelic editing in the peripheral blood is lower than allelic editing in the $CD34^+$ cells of the bone marrow because the peripheral blood includes lymphocytes that are not derived from the edited $CD34^+$ haematopoietic stem cells.

With single agent busulfan conditioning, lymphocytes are not depleted. This results in a proportion of peripheral blood lymphocytes having been derived prior to therapy from haematopoietic stem cells that were not edited and led to the observed decreased allelic editing in the peripheral blood compared to the bone marrow $CD34^+$ cells.

Comment: The MAH gives emphasis to the mean proportion of alleles; there are notably some subjects who achieve much lower percentages (to about 50%) and take up to 9 months to achieve this; the clinical significance of this is not known.

The MAH also presents data for the full analysis set that suggests that the data from the primary efficacy set is representative of a broader picture.

8. ‘Routine’ laboratory safety testing:

A summary of haemolysis assessments including the change from baseline in reticulocyte count and indirect bilirubin concentration over time for the 29 subjects in the primary efficacy set is presented in Table 11-14:

Table 11-14 Summary of Reticulocyte and Indirect Bilirubin Assessments Over Time (PES)

Visit	Statistic	Reticulocyte (10^9/L) N = 29	Indirect Bilirubin (µmol/L) N = 29
Baseline	n	29	29
	Mean (SD)	265.46 (113.85)	55.4 (48.4)
	Median	251.49	32.5
	Min, max	116.34, 679.60	12.0, 210.3
Month 3	n	29	27
	Mean (SD)	129.58 (57.90)	13.8 (6.5)
	Median	118.72	12.0
	Min, max	44.22, 336.00	4.3, 30.8
Month 6	n	28	27
	Mean (SD)	141.46 (60.01)	20.1 (15.0)
	Median	126.15	15.4
	Min, max	33.57, 293.90	5.1, 68.4
Month 9	n	28	26
	Mean (SD)	138.30 (76.05)	23.5 (20.1)
	Median	120.30	18.0
	Min, max	45.96, 411.68	1.7, 83.8
Month 12	n	28	28
	Mean (SD)	142.00 (67.64)	21.5 (21.1)
	Median	130.45	13.7
	Min, max	66.20, 413.28	4.3, 100.9
Month 18	n	20	18
	Mean (SD)	132.74 (41.07)	25.7 (21.6)
	Median	125.85	18.0
	Min, max	85.96, 234.30	3.4, 83.8
Month 24	n	14	14
	Mean (SD)	152.20 (47.93)	24.9 (21.0)
	Median	149.63	19.7
	Min, max	79.92, 273.10	3.4, 78.7

Source: Table 14.2.11.1 (data cutoff date of 16 April 2023)
LDH: lactate dehydrogenase; N: total sample size; n: size of subsample; PES: Primary Efficacy Set
Notes: If there is at least one measurement before mobilization, baseline is defined as the most recent one prior to start of exchange transfusions. Otherwise, the baseline is defined as the measurement that is most distant from last exchange transfusion prior to this measurement and still before start of mobilization. Laboratory values with "below detectable limit" were considered as 0. All measurements are from local laboratories. Subjects with a medical history of Gilbert's syndrome are excluded from the summary of indirect bilirubin.

Measurements were generally maintained over time.

Comment: with this interim report, the following data are submitted:

Indirect Bilirubin (the assessor works to a reference interval <20µmol/L)
at baseline: n = 29; min 12, max 210
at month 12: n = 28; min 4, max 101

reticulocyte count (the assessor usually works to a reticulocyte count expressed as a percentage of red cell count i.e. <2.5%; for total reticulocyte count, the assessor works to a reference interval <100x10^9/L)
at baseline: n = 29; min 116, max 680
at month 12: n = 28; min 66, max 413

Data now submitted by the MAH are consistent with on-going haemolysis in all / most subjects though seemingly with less activity by month 12 compared to baseline.

At the previous interim report, the MAH submitted the following data:

Serum Haptoglobin concentration (the assessor works to a reference interval >0.5G/L)
at baseline:n=17 min 0.0, max 0.3
at month 12: n=16 min 0.04, max 1.45

serum lactate dehydrogenase activity (the assessor works to a reference interval <250U/L)
at baseline: n = 16; min 195, max 913
at month 12: n = 17; min 138, max 917

indirect bilirubin
at baseline: n = 17; min 8.6, max 154
at month 12: n = 16; min 4.3, max 62

reticulocyte count
at baseline: n = 17; min 77, max 436
at month 12: n = 17; min 82, max 238

Data submitted by the MAH with the previous interim report are consistent with on-going haemolysis in all / most subjects (high LDH, bilirubin and reticulocyte count and low haptoglobin) though seemingly with less activity by month 12 compared to baseline. It is considered that individual progress would be more informative than mean data (especially since reference intervals are different for men / women / children).
It is understood that the MAH will continue to submit data on haemolysis via study 131; this is acceptable.

9. Relative reduction from baseline in number of red blood cell units transfused for sickle cell disease-related indications

None of the subjects in the primary efficacy set received red blood cell transfusions for sickle cell disease-related indications starting 12 months after exa-cel infusion; see table 11-15 on the following page.:

Table 11-15 Summary of Relative Reduction From Baseline in Number of Annualized RBC Units Transfused for SCD-related Indications (PES)

Category	Total N =29
Baseline number of annualized RBC units transfused	
n	29
Mean (SD)	8.7 (15.1)
Median	3.5
Min, max	0.0, 75.5
Number of annualized RBC units transfused after exa-cel infusion	
n	29
Mean (SD)	0.0 (0.0)
Median	0.0
Min, max	0.0, 0.0
Relative reduction from baseline in number of annualized RBC units transfused[a]	
n	26
Mean (SD)	100.0 (0.0)
Median	100.0
Min, max	100.0, 100.0
Baseline annualized number of units of Simple RBC transfused	
n	22
Mean (SD)	4.4 (4.9)
Median	2.8
Min, max	0.5, 19.5
Baseline annualized number of units of Exchange RBC transfused	
n	10
Mean (SD)	15.3 (23.3)
Median	5.8
Min, max	1.5, 75.5

Sources: Table 14.2.8 and Ad hoc Table 14.2.30 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; N: total sample size; n: size of subsample; PES: Primary Efficacy Set; RBC: red blood cell; SCD: sickle cell disease
Notes: Baseline number of annualized units of RBC transfused was based on the 2 years before the most recent screening. The evaluation of the number of annualized units of RBC transfused after exa-cel infusion started 12 months after exa-cel infusion.
[a] Relative reduction from baseline = 100% × (Baseline value – post-baseline value)/Baseline value.

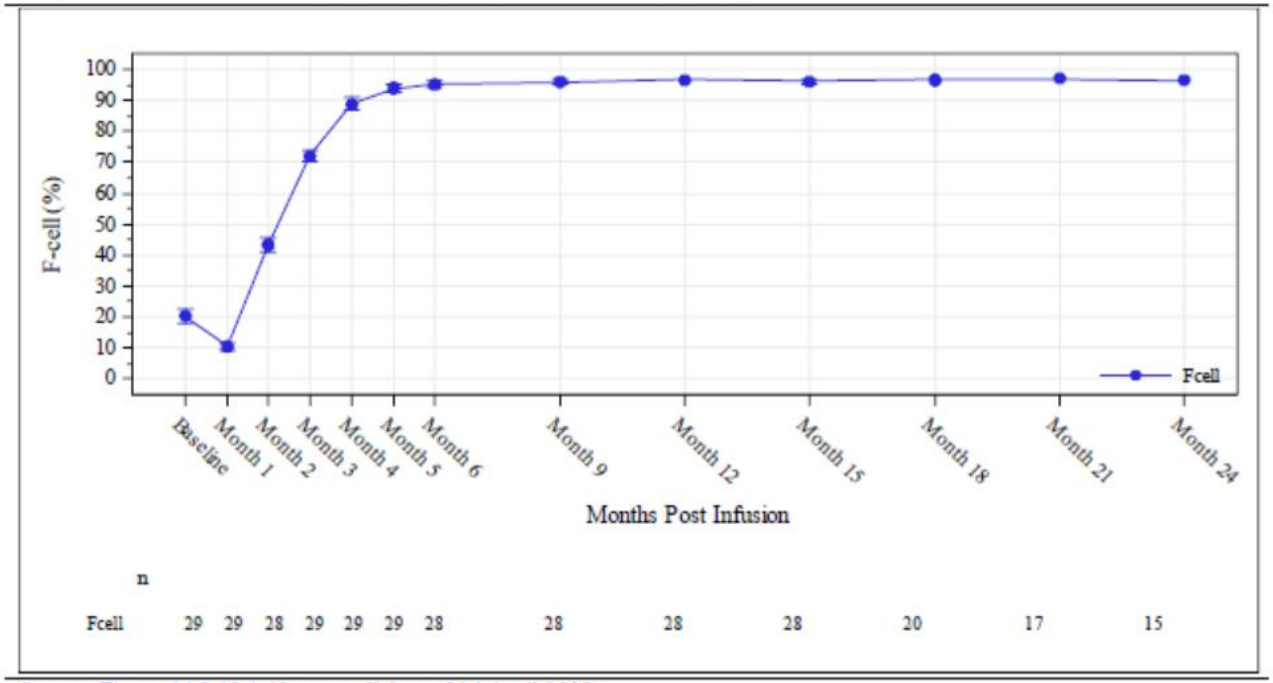
Of the 29 subjects in the PES, 26 subjects had a 100% reduction in annualized number of red blood cell units transfused for sickle cell-related indications starting 12 months after exa-cel infusion. 3 subjects did not receive red blood cell transfusions either in the 2 years prior to enrolment or after exa-cel infusion.

Exploratory outcomes

1. Hb fractions and change from baseline in proportion of circulating F-cells

The proportion of F-cells over time after exa-cel infusion is presented in Figure 11-20 (at each visit).

Figure 11-20 F-cells (%) Summary Over Time (PES)



Source: Figure 14.2.12.1 (data cutoff date of 16 April 2023)
F-cells: erythrocytes expressing γ-globin (fetal hemoglobin); n: size of subsample; PES: Primary Efficacy Set
Notes: Mean values are plotted in the line, mean + standard error and mean - standard error values are plotted as bars at each visit. The numbers of subjects with F-cells values available at the corresponding visits are shown at the bottom. Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the start of mobilization. Analysis visit was used in the figure.

The mean (SD) proportion of F-cells was 72.07% (10.88%) at Month 3, increased to ≥95% at Month 6, and was thereafter maintained ≥95% for the duration of follow-up. Consistent with the increases in HbF levels observed after exa-cel infusion, the proportion of F-cells increased in a similar manner over time, indicating pan-cellular production of HbF.

The MAH also presents data for the full analysis set that appears to be consistent with the primary efficacy set.

Patient reported outcomes

Comment: The MAH reports on change in patient-reported outcomes over time; the MAH reports on the FACT-BMT, EQ-5D-5L, PedsQL, Pain Scale (11-point NRS), and ASCQ-Me Adult Sickle Cell Quality of Life Measurement Information System for the primary efficacy set.

The agency position on patient-reported outcomes will be deferred until submission of reports of the finished trials.

Summary of clinical efficacy

Design

The MAH submits a single-arm, open-label, multi-site, single dose study in subjects 12 to 35 years of age who have severe sickle cell disease

Comment: It is noted that the study participants with sickle cell disease are able to carry on normal activities, despite their condition

Subjects had documented βS/βS, βS/β0 or βS/β^+ genotypes and a history of at least 2 events, described (acute chest syndrome, priapism, splenic sequestration or attending a medical facility for management of an acute pain event), in the 2 years before the study and whilst receiving appropriate supportive care.

The study evaluated the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified human haematopoietic stem and progenitor cells (exa-cel).

Conduct

Subjects began red blood cell exchange or simple transfusions for a minimum of 8 weeks before the planned start of mobilization and continued receiving these transfusions until they began busulfan conditioning. The goal of the red blood cell transfusions was to maintain an HbS level of <30% of total haemoglobin while keeping total Hb concentration ≤11 g/dL.

Mobilisation of cells from marrow was promoted with plerixafor.

$CD34^+$ haematopoietic stem and progenitor cells were harvested from the peripheral circulation and sent to the MAH site for modification with the CRISPR system to produce exa-cel

Subjects then underwent conditioning of the bone marrow with busulfan.

Intravenous infusion of exa-cel occurred between 2 to 7 days after completion of the busulfan conditioning regimen.

Subjects were then monitored in a transplant unit and given supportive care until there was evidence of engraftment of neutrophils and subjects were clinically stable.

Supportive therapies were administered thereafter at the discretion of the attending physician.

Subjects have been enrolled into a long-term follow-up study.

Outcomes and analysis

The MAH describes the study as a phase 1/2/3 study; the study is open-label and uncontrolled; the MAH does not describe aims of the study, objectives are described yet

'endpoints' of the MAH do not match exactly to the stated objectives; the MAH tends a null hypothesis of 50% response rate yet without sufficient justification. It would have been much preferred for the MAH to have used descriptive boundaries (as opposed to a probabilistic boundary) in order to demarcate small, medium or big effect sizes, as described: .Feinstein AR: Critical descriptive boundaries – J Clin Epidemiol 1998;51:527-530.

The assessor is unable to concur with the description or statistical analysis of the study by the MAH; the assessor considers that the study is a demonstration study i.e. demonstration of (i) method and (ii) outcome.
In order to analyse the study, the assessor refers to the method of Bradford-Hill as updated by Aronson and colleagues: Howick J, Glasziou P & Aronson JK. The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute? J R Soc Med. 2009;102:186-94.
Outcomes

For the primary efficacy set (29 subjects):

- 28/29 subjects achieved the primary outcome by not experiencing any severe vaso-occlusive crisis for at least 12 consecutive months after exa-cel infusion.
- 6 subjects were in the age range ≥12 and <18yrs; all 6 achieved the primary outcome.

For those who achieved the primary outcome:

- 27/28 subjects remained vaso-occlusive crisis free until the end of study date or the interim data cut date, whichever was earlier

All 29 subjects remained free from in-patient hospitalisation (sustained for at least 12 months after exa-cel infusion) for severe vaso-occlusive crises.

There were increases in mean total Hb and HbF concentrations for subjects in the primary efficacy set, which occurred early (Month 3) and were maintained over time.

Mean (SD) total Hb levels were 12.1 (1.3) g/dL at Month 3, increased to 12.7 (1.7) g/dL at Month 6 and were maintained ≥12 g/dL over the duration of follow-up.

Mean total HbF was present in trace amounts at baseline and rose over the first months after exposure to exa-cel. Mean (SD) proportion of total Hb comprised by HbF (HbF %) was 36.8% (7.9%) at Month 3, increased to 43.1% (6%) at Month 6, and was thereafter maintained ≥40% over the duration of follow-up. All 29 (100%) subjects in the primary efficacy set sustained HbF ≥20% for at least 12 months.

HbF appears to displace HbA with HbS remaining present at (about) 55% of total Hb.

Of the 29 subjects in the primary efficacy set, 26 subjects had a 100% reduction in annualized number of red blood cell units transfused for sickle cell-related indications starting 12 months after exa-cel infusion (to note that 3 of these subjects had not received red blood cell transfusions in the 2 years prior to enrolment).

From month 6 after exa-cel infusion: bone marrow allele editing in the $CD34^+$ cells of the bone marrow was present at range between (about) 55 to 90%.

Allelic editing in the peripheral blood was detectable within 1 month after exa-cel infusion and was present at range between (about) 50 to 85%.

By month 6: about 95% erythrocytes expressed fetal haemoglobin consistent with pan-cellular production of HbF.

For the full analysis set: 4/41 subjects have had events adjudicated as a vaso-occlusive crisis, starting 60 days after the last red blood cell transfusion.

Although subjects display a mean reduction in indices of haemolysis after exposure to exa-cel, there is a broad range of experience i.e. many subjects continue to demonstrate evidence of a chronic haemolytic state. Since the underlying pathophysiology of sickle cell disease is still a matter of academic enquiry, it may be anticipated that some subjects will continue to experience vaso-occlusive crises in spite of the increase in red cell content of HbF.

The increase in HbF content of red blood cells accompanied by 28/29 subjects in the primary efficacy set achieving the primary outcome with a reduction in the need for hospitalisation and a reduction in the need for red blood cell transfusions is considered to be notable.

Analysis

Aronson and colleagues (2009) have updated Bradford-Hill criteria and recommend that 7 lines of evidence (classified as direct, mechanistic and parallel) be met. Thus:

Direct evidence

1. Appropriate temporal spatial proximity the time interval between exposure and increase in HbF and subsequent reduction in clinical events is consistent with the proposed mechanism of action; appropriate temporal proximity is considered met; line 1 is considered met.

2. Effect not attributable to plausible confounding: plausible confounders not identified by the assessor; line 2 is considered met.

3. Dose responsiveness and reversibility: line 3 not tested.

Comment on direct evidence: 2/3 lines of direct evidence support the claims of the MAH.

Mechanistic evidence

4. Proposed mechanism of action

Exagamglogene autotemcel (exa-cel, formerly CTX001) consists of autologous $CD34^+$ human haematopoietic stem and progenitor cells modified by ex vivo CRISPR-Cas9-mediated gene editing.

Haematopoietic stem and progenitor cells are harvested from the patient, modified using CRISPR technology and then returned to the patient; the product is intended as a one-off treatment.

The CRISPR system targets a critical binding site of the transcription factor GATA1 in the non-coding erythroid lineage-specific enhancer region of the BCL11A gene on chromosome 2. Repair of these breaks by non-homologous end-joining produces insertions and deletions (indels) in the DNA that disrupt GATA1 binding thereby lowering BCL11A transcription.

BCL11A codes for a transcriptional repressor of γ-globin. The reduction of BCL11A gene transcription and subsequent decrease in BCL11A protein concentration leads to increases in γ-globin mRNA transcription, γ-globin expression and, upon erythroid differentiation, an increase in production of HbF.

The mechanism of action is considered plausible; line 4 support is considered met.

5. Coherence: the causal hypothesis is considered to cohere with current knowledge of the genetics of globin production; line 5 support is considered met.

Comment on mechanistic evidence: 2/2 lines of mechanistic evidence support the claims of the MAH.

Parallel evidence

6. The MAH is conducting replicate-style trials i.e. studies 141 & 151; results awaited.
7. Studies 111 and 121 provide parallel evidence i.e. similar intervention / similar outcome; line 7 is considered met.

Comment on parallel evidence: 1/2 lines of parallel evidence support the claims of the MAH; line 6 may prove positive once outcomes are obtained.

Overall: 5/7 lines of evidence are considered satisfied; line 6 support may be satisfied when the MAH reports on studies 141 and 151 whilst line 3 support on dose and reversibility is unlikely to be addressed by the MAH. Overall, evidence submitted by the MAH is consistent with administration of exa-cel being causative towards outcomes described.

Conclusions

Overall conclusion on clinical efficacy: efficacy (reduction in vaso-occlusive crises) has been demonstrated in the target population of severe sickle cell disease.

Long-term efficacy will only be established by prolonged follow-up.

Data of the study 121 are consistent with administration of Casgevy being necessary for recipients to produce circulating red blood cells containing fetal haemoglobin.

The MAH did not undertake a dose-finding exercise; the MAH relied on published data of bone marrow transplant to decide upon a dosage. Although data of the study 121 are consistent with administration of Casgevy being necessary for recipients to produce fetal haemoglobin with a view to abolish sickle cell crises, 4 subjects in the full analysis set have experienced vaso-occlusive crises after exposure to exa-cel; these crises may represent either primary or secondary failure of exa-cel; prolonged follow-up of subjects in study 131 may add to understanding on this issue.. The choice of posology has been based on published data in other haematological conditions; the MAH has agreed to submit data at annual reviews that will aid in the further assessment of sufficiency of number of cells administered to subjects; this is acceptable. Details of the data to be submitted is as below:

For subjects with sickle cell disease, the company has agreed to provide the following information at annual reviews:

Point 1: In order to provide clarity on those who experienced one of more vaso-occlusive crises beyond 60 days after administration of Casgevy, the company will supply information for the full analysis set on numbers of cells administered to patients by means of bar charts:
(a) One bar chart with number of patients on the y-axis versus total number of cells/kg body weight administered, and
(b) One bar chart with number of patients on the y-axis versus total number of cells administered
In the above depictions: the company will highlight those subjects who experienced one or more vaso-occlusive crises beyond 60 days after administration of Casgevy and discuss the findings.

Point 2: For the full analysis set: the company will provide:
(a) a plot of bone marrow allele edit percentage at month 12 versus number of cells administered/kg body weight and discuss the findings.

(b) a plot of bone marrow allele edit percentage at month 12 versus total number of cells administered and discuss the findings.
The company will highlight those subjects who experienced one of more vaso-occlusive crises beyond 60 days after administration of Casgevy and discuss the findings.

Point 3: For the full analysis set: the company will provide a plot of bone marrow allele edit percentage versus peripheral blood allele edit percentage at month 12 versus and discuss the findings.
The company will highlight those subjects who experienced one of more vaso-occlusive crises beyond 60 days after administration of Casgevy and discuss the findings.

Point 4: The company will provide a plot of HbF (g/dL) over time for each subject and discuss the findings in relation to bone marrow allele edit percentage and peripheral blood allele edit percentage.

IV.5 Clinical safety

Introduction

Safety data are summarized from 2 main studies (both submitted at an interim stage); the studies were conducted in subjects aged ≥12 to 35 years with up to 2 years of follow up after exa-cel infusion:

- Study CTX001-111 (Study 111; cut-off date: 16 Apr 2023): Phase 1/2/3 study in subjects with transfusion-dependent β-thalassemia.
- Study CTX001-121 (Study 121; cut-off date: 16 Apr 2023): Phase 1/2/3 study in subjects with sickle cell disease.

Data are also submitted from Study VX18-CTX001-131 (Study 131), a long-term follow-up study for both indications (data cut-off date: 16 Apr 2023 [subjects from Study 111] [subjects from Study 121]). The update of 16 Apr 2023 was performed in response to regulatory authority request and was not pre-specified in the statistical analysis plan.

Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment.

The following data will be documented for each AE:

- Description of the event
- Classification of “serious” or “nonserious”
- Date of first occurrence and date of resolution (if applicable)
- Severity or Toxicity grade
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

Table 9: Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record).

A serious AE is any AE occurring during any study phase from signing of the Informed Consent Form that meets any of the following outcomes: fatal, life-threatening, hospitalisation, significant disability, important medical event, new malignancy, and engraftment failure: failure to reach ANC ≥ 500 cells/μL on three consecutive measurements on three different days by Day 42 after CTX001 infusion and need to receive backup stem cells at any time during period of neutropenia.

Comment: there is not any particular objection to the MAH adding engraftment failure to the usual list of events considered as 'serious'.

Severity will be assessed per the Common Terminology Criteria for Adverse Events v5.0 scale.

Table 10: Grading Scale for Adverse Events

Classification	Definition
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization of prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Note: A semi-colon indicates 'or' within the description of the grade.

An AE will be followed until the investigator has determined and provided the final outcome.

Table 11: Classifications for Outcome of an AE

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

Comment: no additional comment on processes of safety analysis.

A Data Monitoring Committee (DMC) was charged with ensuring the safety of subjects, safeguarding their interests and ensuring the quality and integrity of the trials; as described in the Committee charter.

As the safety profile is well-characterized and understood for the drugs used during mobilization/apheresis (plerixafor in both studies and granulocyte colony-stimulating factor [G-CSF] in Study 111) and myeloablative conditioning (busulfan), the primary focus of the safety presentation is the study interval from the day of exa-cel infusion up to Month 24 (M24).

Safety in other study intervals, including mobilization/apheresis up to before myeloablative conditioning, is also presented.

Comment: it is confirmed that plerixafor (PLGB 04425/0769), granulocyte colony-stimulating factor (PLGB 00057/1593) and busulfan (PL 39699/ 0042) are all licensed medicinal products with known aspects of clinical safety.

The following safety endpoints were included in both main studies (Study 111 & Study 121):

- Successful neutrophil engraftment
- Time to neutrophil engraftment
- Time to platelet engraftment
- Safety and tolerability assessments based on AEs, clinical laboratory values and vital signs
- Incidence of transplant-related mortality within 100 days and within 1 year after exa-cel infusion
- All-cause mortality

These endpoints are standard-evaluated following haematopoietic stem cell transplant. At least annual malignancy screening was performed.

All subjects who received exa-cel were asked to enrol into the long-term follow-up study (Study 131) after completion from the pivotal study. Study 131 included the following safety endpoints:

- New malignancies
- New or worsening haematologic disorders e.g. immune-mediated cytopenias, aplastic anaemia, primary immunodeficiencies
- All-cause mortality
- All serious adverse events (SAEs) occurring up to 15 years after exa-cel infusion
- Adverse events (AEs) and SAEs related to exa-cel

Analysis sets for integrated summary of safety were defined as follows:

- The Enrolled Set / integrated Enrolled Set included all enrolled subjects, defined as subjects who signed informed consent and met the eligibility criteria for the respective study.
- The Safety Analysis Set (SAS) / integrated Safety Analysis Set (iSAS) is a subset of the Enrolled Set that included all subjects who started the mobilization regimen.
- The Full Analysis Set (FAS) / integrated Full Analysis Set (iFAS) is a subset of the Enrolled Set that included all subjects who received exa-cel infusion.

Safety data from the pivotal Studies 111 (transfusion-dependent beta-thalassaemia) and 121 (sickle cell disease) are presented for the time interval after exa-cel infusion up to Month 24; safety data are also presented from the long-term follow-up study (Study 131).

Study 111 has 59 subjects in the safety analysis population; study 121 has 58 subjects in the safety analysis population.

Comment: analysis of safety and safety populations are noted without additional comment.

Exposure to product

Overall Exposure and Exa-cel Dose in Clinical Studies

In Study 111 and Study 121, the protocol-specified minimum dose of exa-cel was 3×10^6 $CD34^+$ cells/kg administered IV as a single infusion.

Data are presented for a total of 97 subjects have been dosed with exa-cel. Subjects have been enrolled into Study 131 after completing Study 111 or Study 121.

54 subjects with transfusion-dependent thalassaemia have been exposed to exa-cel at a median dose of 8.0 (range: 3.0 to 19.7) × 10^6 $CD34^+$ cells/kg: the median follow-up duration after exa-cel infusion was 22.8 (range: 2.1 to 51.1) months.

43 subjects with sickle cell disease have been exposed to exa-cel at a median dose of 4.0 (range: 2.9 to 14.4) × 10^6 $CD34^+$ cells/kg: the median follow-up duration after exa-cel infusion was 17.5 (range: 1.2 to 46.2) months.

Of these subjects: 19 (35%) subjects with transfusion-dependent thalassaemia and 12 (28%) subjects with sickle cell disease were adolescents.

Comment: the median number of cells administered are noticeably higher in those with transfusion-dependent β-thalassemia compared to sickle cell disease, presumably reflecting the different patho-physiologies of the disease and because cell mobilisation in sickle cell subjects was conducted without G-CSF.

There is a total of 167 patient-years of exposure after infusion of exa-cel (100.5 patient-years for transfusion-dependent thalassaemia and 66.5 patient-years for sickle cell disease).

Exposure is summarised in the following table 22:

Table 22 Follow-up Duration After Exa-cel Infusion through Study 131 (Long-term Follow-Up): FAS

	TDT (Studies 111 + 131) N = 54	SCD (Studies 121 + 131) N = 43
Follow-up duration after exa-cel infusion (month)		
n	54	43
Mean (SD)	22.3 (10.51)	18.6 (9.99)
Median	22.8	17.5
Min, max	2.1, 51.1	1.2, 46.2
Exposure after exa-cel infusion (patient-months)	1205.9	797.9
Exposure after exa-cel infusion (patient-years)	100.5	66.5
Follow-up duration after exa-cel infusion by interval[a], n (%)		
≤3 months	2 (3.7)	2 (4.7)
>3 months to ≤6 months	4 (7.4)	2 (4.7)
>6 months to ≤12 months	4 (7.4)	8 (18.6)
>12 months to ≤24 months	20 (37.0)	16 (37.2)
>24 months[a]	24 (44.4)	15 (34.9)

Sources: Study 131/Table 14.1.10.1a and Study 131/Table 14.1.10.1b (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total sample size; n: size of subsample; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia
Notes: Follow-up duration (months) after exa-cel infusion= (Data cutoff date or end date of Study 131 whichever is earlier – exa-cel infusion date + 1)/30. Exposure (patient-months/patient-years) after exa-cel infusion = Sum of the after exa-cel infusion follow-up duration (months/years) from subjects who have received exa-cel infusion in the FAS.
[a] Follow-up duration is not equivalent to study visit (see calculation above). Due to protocol-specified visit windows, a subject in this category may not have completed the Month 24 visit in Study 111 or Study 121, as applicable, thus had not enrolled in Study 131.

Comment: follow-up durations for those who were administered product are noted; most subjects have more than 12-month length of follow-up; the total amount of follow-up in patient-years is considered to be modest yet this may be understood in the context of rare diseases.

Overall: the company presents a limited data set for clinical safety in each population. Subject dispositions / demographics / other characteristics of the populations (including medical history & other medications) are described in the assessment report on efficacy for each study.

Overview of Adverse Events

The incidence of AEs and SAEs after exa-cel infusion was consistent with that expected from myeloablative conditioning with busulfan and autologous haematopoietic stem cell transplant.

An overview of AEs is presented for the interval from exa-cel infusion to Month 24 by study in Table 24.

Table 24 → Overview of AEs for the Exa-cel to M24 Interval (Studies 111 and 121): FAS

	TDT (Study 111) n (%)	SCD (Study 121) n (%)
Evaluable subjects, N1	54	43
Subjects who received exa-cel infusion, N2	54	43
Subjects who received busulfan, N3	54	43
Subjects with		
any AEs	54 (100.0)	43 (100.0)
any AEs related or possibly related to exa-cel	14 (25.9)	13 (30.2)
any AEs related or possibly related to busulfan	53 (98.1)	43 (100.0)
Grade 3 or above AEs	48 (88.9)	41 (95.3)
SAEs	19 (35.2)	16 (37.2)
SAEs related or possibly related to exa-cel	2 (3.7)	0
SAEs related or possibly related to busulfan	9 (16.7)	4 (9.3)
AEs leading to study discontinuation	0	0
AEs leading to death	0	1 (2.3)a

Source: Study 111/Table 14.3.1.1.1 and Study 121/Table 14.3.1.1.1 (data cutoff date of 16 April 2023)

AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; M24: Month 24 Visit; n: size of subsample; SAE: serious adverse event; SAS: Safety Analysis Set; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

Notes: MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of each study interval. N2/N3: The number of subjects in the SAS who were on or after the start date of each study interval and had received exa-cel infusion (i.e., FAS)/busulfan dosing. Percentages were calculated as n/N1*100 within each interval, unless otherwise specified. Percentages of subjects with AEs/SAEs related or possibly related to exa-cel/busulfan were calculated relative to the number of subjects with exa-cel infusion/busulfan dosing within each interval, as n/N2*100 or n/N3*100. Percentages of subjects with AEs by strongest relationship to exa-cel/busulfan were calculated relative to the number of subjects with exa-cel infusion/busulfan dosing within each interval, as n/N2*100 or n/N3*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. An AE with relationship missing to busulfan/exa-cel was counted as related to busulfan/exa-cel in this table. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.

[a] → As reported in the initial MAA, 1 subject died due to COVID-19 infection that resulted in respiratory failure, not related to exa-cel (Section 4.4); this resulted in study discontinuation.

Overall, most AEs were non-serious and Grade 1 or Grade 2 in severity.

Deaths

There were no deaths in the transfusion-dependent β-thalassemia study (Study 111).

There was 1 death that occurred in the sickle cell disease study (Study 121).

The underlying SAEs were determined by the investigator as not related to exa-cel and related to COVID-19 and busulfan. Lung injury and serious infections, including fatal outcome, are known risks of busulfan treatment.

Comment: based on the narrative provided, it may be acknowledged that the death reported was related to a combination of acute covid disease and exposure to busulfan.

Other Serious Adverse Events

In total, 2 (3.7%) subjects with transfusion-dependent beta-thalassaemia and no subjects with sickle cell disease had an SAE considered related or possibly related to exa-cel; these events were characterized as complications in the context of myeloablation and autologous haematopoietic stem cell transplant.

Among the subjects who completed busulfan conditioning and received exa-cel, 19 (35.2%) subjects with transfusion-dependent beta-thalassaemia and 16 (37.2%) subjects with sickle cell disease had at least 1 SAE (Table 24).

The majority of SAEs occurred within the first 6 months after exa-cel infusion (Table 27).

SAEs that occurred in ≥2 subjects are presented by study in Table 28 (transfusion-dependent beta-thalassaemia) and Table 29 (sickle cell disease).

Table 28 → SAEs Occurring in ≥2 Subjects With TDT by PT for the Exa-cel to M24 Interval (Study 111): FAS

Preferred Term[a]	TDT (Study 111) n (%)
Evaluable subjects, N1	54
Subjects with any SAEs	19 (35.2)
Venoocclusive liver disease	5 (9.3)
Pneumonia	3 (5.6)
COVID-19	2 (3.7)
Hypoxia	2 (3.7)
Thrombocytopenia	2 (3.7)
Upper respiratory tract infection	2 (3.7)

Source: Study 111/Table 14.3.2.2.1 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; M24: Month 24 Visit; n: size of subsample; PT: preferred term; SAE: serious adverse event; SAS: Safety Analysis Set; TDT: transfusion-dependent β-thalassemia
Notes: MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the day of exa-cel infusion (i.e., FAS). Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.
[a] → All PTs are described in busulfan product information by matching PT or similar medical concept.[8]

Table 29 → SAEs Occurring in ≥2 Subjects With SCD by PT for the Exa-cel to M24 Interval (Study 121): FAS

Preferred Term[a]	n (%)
Evaluable subjects, N1	43
Subjects with any SAEs	16 (38.1)
Cholelithiasis	4 (9.3)
Pneumonia	4 (9.3)
Abdominal pain	3 (7.0)
Constipation	3 (7.0)
Pyrexia	3 (7.0)
Abdominal pain upper	2 (4.7)
Non-cardiac chest pain	2 (4.7)
Oropharyngeal pain	2 (4.7)
Pain	2 (4.7)
Sepsis	2 (4.7)
Sickle cell anaemia with crisis	2 (4.7)[b]

Source: Study 121/Table 14.3.2.2.1 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; M24: Month 24 Visit; n: size of subsample; PT: preferred term; SAE: serious adverse event; SAS: Safety Analysis Set; VOC: vaso-occlusive crisis
Notes: MedDRA version 26.0. Evaluable subjects, N1: the number of subjects in the SAS who were on or after the day of exa-cel infusion (i.e., FAS). Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.
[a] → All PTs are either described in the busulfan product information by matching PT or similar medical concept or are associated with underlying disease (cholelithiasis, sickle cell anemia with crisis).[8, 81]
[b] → Corresponds to hospitalizations for VOCs [redacted]

The incidence and nature of SAEs from exa-cel administration to Month 24 were generally consistent with myeloablative busulfan conditioning, autologous haematopoietic stem cell transplant and underlying disease. There were not additional exa-cel specific safety concerns identified.

Serious Adverse Events by Relationship

transfusion-dependent β-thalassemia: 9 (16.7%) subjects had at least 1 SAE considered related or possibly related to busulfan and 2 (3.7%) subjects had at least 1 SAE considered related or possibly related to exa-cel (table 24). Most SAEs were assessed by the investigator as not related to any study drug or related to busulfan only and were generally consistent with anticipated events due to myeloablative conditioning with busulfan and autologous haematopoietic stem cell transplant.

A description of events is provided for the 2 subjects with SAEs reported related or possibly related to exa-cel:

sickle cell disease: 4 (9.3%) subjects had at least 1 SAE considered related or possibly related to busulfan. All SAEs were assessed by the investigator as not related to any study drug or related to busulfan only and were generally consistent with anticipated events due to myeloablative conditioning with busulfan, autologous haematopoietic stem cell transplant and the underlying disease. No subject with sickle cell disease had an SAE considered related to or possibly related to exa-cel (Table 24).

Comment: it may be concurred that most reported serious adverse events are in relation to exposure to busulfan or the overall procedure, as described. There is no additional comment on this issue.

Common Adverse Events

AEs occurring in ≥25% of subjects are presented by study in Table 25 (transfusion-dependent beta-thalassaemia) and Table 26 (sickle cell disease).

Table 25 → AEs Occurring in ≥25% of Subjects With TDT After Exa-cel Infusion by PT for the Exa-cel to M24 Interval (Study 111): FAS

Preferred Term[a]	TDT (Study 111) n (%)
Evaluable subjects, N1	54
Subjects with any AEs	54 (100.0)
Febrile neutropenia	33 (61.1)
Headache	30 (55.6)
Stomatitis	28 (51.9)
Thrombocytopenia	25 (46.3)
Anaemia	24 (44.4)
Mucosal inflammation	23 (42.6)
Nausea	23 (42.6)
Vomiting	22 (40.7)
Hypokalaemia	21 (38.9)
Platelet count decreased	21 (38.9)
Abdominal pain	20 (37.0)
Epistaxis	20 (37.0)
Arthralgia	19 (35.2)
Constipation	18 (33.3)
Neutrophil count decreased	16 (29.6)
Diarrhoea	15 (27.8)
Pruritus	15 (27.8)
Pyrexia	15 (27.8)
COVID-19	14 (25.9)
Decreased appetite	14 (25.9)

Source: Study 111/Table 14.3.1.3.1 (data cutoff date of 16 April 2023)

AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; M24: Month 24 Visit; n: size of subsample; PT: preferred term; SAS: Safety Analysis Set; TDT: transfusion-dependent β-thalassemia

Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the day of exa-cel infusion (i.e., FAS). Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table is sorted in descending order of frequency by PT. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.

[a] → All PTs are described in busulfan product information by matching PT or similar medical concept.[8]

Table 26 → AEs Occurring in ≥25% of Subjects With SCD After Exa-cel Infusion by PT for the Exa-cel to M24 Interval (Study 121): FAS

Preferred Term[a]	n (%)
Evaluable subjects, N1	43
Subjects with any AEs	43 (100.0)
Nausea	30 (69.8)
Stomatitis	27 (62.8)
Vomiting	25 (58.1)
Febrile neutropenia	23 (53.5)
Abdominal pain	22 (51.2)
Headache	22 (51.2)
Pruritus	21 (48.8)
Decreased appetite	20 (46.5)
Pain in extremity	20 (46.5)
Platelet count decreased	20 (46.5)
Arthralgia	19 (44.2)
Constipation	18 (41.9)
Diarrhoea	17 (39.5)
Neutrophil count decreased	17 (39.5)
Pyrexia	17 (39.5)
Anaemia	16 (37.2)
Mucosal inflammation	16 (37.2)
Back pain	15 (34.9)
Fatigue	15 (34.9)
Hypokalaemia	15 (34.9)
Skin hyperpigmentation	14 (32.6)
Neutropenia	13 (30.2)
Oedema peripheral	12 (27.9)
Thrombocytopenia	12 (27.9)
Abdominal pain upper	11 (25.6)
Alanine aminotransferase increased	11 (25.6)
COVID-19	11 (25.6)
Gastritis	11 (25.6)
Pain	11 (25.6)

Source: Study 121/Table 14.3.1.3.1 (data cutoff date of 16 April 2023)

AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; M24: Month 24 Visit; n: size of subsample; PT: preferred term; SAS: Safety Analysis Set

Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the day of exa-cel infusion (i.e., FAS). Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table is sorted in descending order of frequency by PT. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.

[a] → All PTs are described in busulfan product information by matching PT or similar medical concept.[8]

Overall, the incidence and nature of AEs, including the most common AEs (≥25% of subjects in each study), from exa-cel administration to Month 24, were generally consistent with myeloablative busulfan conditioning, autologous haematopoietic stem cell transplant and underlying disease. No additional exa-cel specific safety concerns were identified.

Adverse Events by Relationship
In both Studies 111 and 121, the majority of subjects had at least 1 AE that was considered related or possibly related to busulfan (transfusion-dependent beta-thalassaemia: 53 of 54 [98.1%]; sickle cell disease: 43 of 43 [100.0%]) (Table 24); fewer subjects had at least 1 AE that was considered related or possibly related to exa-cel, as outlined below:

14 (25.9%) subjects with transfusion-dependent beta-thalassaemia had at least 1 AE that was considered related or possibly related to exa-cel.
AEs occurring in ≥2 subjects with transfusion-dependent beta-thalassaemia were headache and laboratory related events (CD4 lymphocytes decreased, neutrophil count decreased, lymphopenia, platelet count decreased, thrombocytopenia and white blood cell count decreased).

Most AEs considered related or possibly related to exa-cel were also considered related or possibly related to busulfan; 5 (9.3%) subjects had at least 1 AE that was considered related or possibly related to exa-cel only.

13 (30.2%) subjects with sickle cell disease had at least 1 AE that was considered related or possibly related to exa-cel.

AEs occurring in ≥2 subjects with sickle cell disease were laboratory related events (CD4 lymphocyte decreased, lymphopenia, and neutropenia).

Most AEs considered related or possibly related to exa-cel were also considered related or possibly related to busulfan; only 1 non-serious AE of neutropenia was considered related or possibly related to exa-cel only.

The events occurring in ≥2 subjects, including cytopenia events, were consistent with myeloablative busulfan conditioning. No additional exa-cel specific safety concerns were identified.

Time to Onset of Adverse Events
Intervals of 6 months were selected to assess trends in events over time and to compare the first 6 months, during which the majority of myeloablation and haematopoietic stem cell transplant -related events would be anticipated to occur, with later time-periods and facilitate identification of any new, clinically relevant events, patterns or trends.
AEs by onset interval after exa-cel infusion are summarised in Table 27 on the following page:

Table 27 → Time-Adjusted Rates, Number of Events, Incidence of AEs by Onset Time Intervals After Exa-cel Infusion for TDT (Study 111) and SCD (Study 121): FAS

Category	TDT (Study 111)				SCD (Study 121)			
	Exa-cel Infusion to <6 Months	6 Months to <12 Months	12 Months to <18 Months	≥18 Months	Exa-cel Infusion to <6 Months	6 Months to <12 Months	12 Months to <18 Months	≥18 Months
Evaluable subjects, N1	54	48	44	38	43	39	31	20
Exposure (patient-months)	313.4	275.2	253.2	196.8	245.6	203.1	167.9	103.8
Subjects with any AEs, n (%)	54 (100.0)	30 (62.5)	22 (50.0)	11 (28.9)	43 (100.0)	26 (66.7)	20 (64.5)	15 (75.0)
Total Number of AEs	1694	98	59	37	1515	200	112	57
Subjects with any Grade 3/4 AEs, n (%)	48 (88.9)	5 (10.4)	5 (11.4)	1 (2.6)	41 (95.3)	9 (23.1)	6 (19.4)	3 (15.0)
Total Number of Grade 3/4 AEs	437	7	6	1	356	31	10	8
Subjects with any SAEs, n (%)	18 (33.3)	4 (8.3)	3 (6.8)	1 (2.6)	14 (32.6)	6 (15.4)	2 (6.5)	3 (15.0)
Total Number of SAEs	44	5	3	1	44	11	2	4
Time-Adjusted AE Rates (Events/patient-months)								
All AEs	5.406	0.356	0.233	0.188	6.168	0.985	0.667	0.549
AEs related to exa-cel	0.124	0.007	0.004	0.005	0.090	0.010	0.006	0
Grade 3/4 AEs	1.395	0.025	0.024	0.005	1.449	0.153	0.060	0.077
SAEs	0.140	0.018	0.012	0.005	0.179	0.054	0.012	0.039
SAEs related to exa-cel	0.019	0	0	0	0	0	0	0

Sources: Study 111/Table 14.3.1.1.3 and Study 121/Table 14.3.1.1.3 (data cutoff date of 16 April 2023)

AEs: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; n: size of subsample; SAE: serious adverse event; SAS: Safety Analysis Set; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

Notes: MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of each study interval (i.e., FAS). Percentages were calculated as n/N1*100. When summarizing number of events for each study interval, a subject with multiple events within a category and study interval was counted multiple times in that category. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. An AE with relationship missing to exa-cel was counted as related to exa-cel in this table.
AE onset Month = (AE start date − exa-cel infusion date + 1)/30. Study Day 1 is the day of exa-cel infusion. One month is 30 days. Exposure (patient-months) within each interval = Sum of the follow-up duration (months) within each interval from subjects who are in each interval. The follow-up duration (months) within each interval = (Data cutoff date or end date of each interval whichever is earlier - start date of each interval + 1)/30. The follow-up duration within each interval is only calculated for subjects who are in each interval. Events/patient-months within each interval = Total number of events within each interval / Exposure (patient-months) within each interval. Study interval ≥18 months includes any assessments from 18 months to Month 24 visit or end of study visit.

Across all 6-month intervals, most AEs were non serious and Grade 1 or Grade 2 in severity. The majority (>80% for Study 111; >70% for Study 121) of AEs, SAEs, and Grade 3 or above AEs, occurred in the first 6 months after exa-cel infusion. None of the SAEs that occurred ≥6 months after exa-cel infusion were considered related or possibly related to busulfan or exa-cel.

The number and time-adjusted rate (events/patient-months) of AEs, Grade 3 or above AEs, and SAEs was highest within the first 6 months following myeloablative conditioning with busulfan and exa-cel infusion, as compared to all the following 6 months intervals (6 to <12, 12 to <18, and 18 to 24 months).

After the first 6 months following exa-cel infusion, the time-adjusted AE rates (events/patient-months) decreased markedly in successive 6-month intervals through Month 24, including an approximately 6 to 29-fold reduction between the 0 to 6 months and each of the subsequent 6-month intervals. Furthermore, evaluation of the first 6 months by 3-month intervals showed that the time adjusted rates for AEs, Grade 3 or higher AEs and SAEs during the first 3 months were overall the highest of any subsequent time interval.

Overall, the type of AEs and timing of onset, which were generally as anticipated due to busulfan myeloablative conditioning and were findings to be expected in the peri-transplant period.

No new trends or patterns associated with exa-cel were observed.

Adverse Events Leading to Discontinuation
No subject had an AE that led to study discontinuation after exa-cel infusion (Table 24).

Adverse Events Leading to Interruption of Study Drug
No subject had an AE that led to exa-cel infusion interruption in Study 111 or Study 121

Infusion-related reactions
Infusion reactions, which may range from mild to severe reactions including anaphylaxis, are a known risk of dimethylsulfoxide (DMSO) and Dextran which are excipients present in the exa-cel formulation. The protocol specified that subjects should be pre-medicated with an antihistamine (e.g., diphenhydramine hydrochloride) and an antipyretic (e.g. acetaminophen, paracetamol) per institutional guidelines for infusion during haematopoietic stem cell transplant.

An analysis of AEs considered related to exa cel with onset on Study Day 1 (day of exa-cel infusion) was performed to identify infusion reactions. After exa-cel infusion, 2 (3.7%) subjects with transfusion-dependent beta-thalassaemia and no subjects with sickle cell disease had infusion-related AEs on Study Day 1 that were considered related to exa-cel and consistent with common infusion reaction signs and symptoms.

All infusion-related AEs (sinus tachycardia and chills in 1 subject and tachycardia in 1 subject) were considered by the investigator to be related to exa-cel, were Grade 1 in severity, did not require treatment and resolved on the same day.

No infusion-related AEs were serious. No anaphylactic reactions due to exa-cel occurred at any time point. In addition, no infusion-related AEs resulted in interruption or discontinuation of exa cel infusion. Overall, no clinically significant infusion-related reactions were observed and the exa-cel infusion was tolerated.

The sponsor considers that adverse events reported in relation to the infusions such as nausea, pruritus, vomiting, abdominal pain and tachycardia may be attributed to myeloablative conditioning with busulfan or other factors not related to exa-cel.

Comment: whilst it is appreciated that there would be difficulty in assigning cause of an adverse event, it is preferred for adverse events considered related to Casgevy be given prominence in the SmPC section 4.8. The company has been requested to ensure that infusion-related reactions are adequately described in the SmPC.

Haematopoietic stem cell transplant -associated complications
Data were reviewed for: transplant-related mortality; primary or secondary graft failure; graft rejection and acute or chronic graft-versus-host-disease; febrile neutropenia; infections; bleeding; veno-occlusive liver disease; engraftment syndrome; and haemophagocytic lymphohistiocytosis.

No subject had primary or secondary graft failure and (given the autologous nature of exa-cel) no subjects had graft rejection or graft-versus-host-disease.

Transplant-Related Mortality

From the literature: Transplant-related mortality was defined as a death caused by AEs considered related or possibly related to busulfan, exa-cel or both that occurred within 100 days or within 12 months after exa-cel infusion.

1 subject with sickle cell disease died, see description above. The death met criteria for Transplant-Related Mortality based on timing relative to exa-cel infusion (i.e. within 1 year) and the attribution of possible relationship to busulfan.

Comment: the case of transplant-related mortality is described in sec 4.8 of the SmPC; this is acceptable.

Febrile Neutropenia

From the literature: Febrile neutropenia is a common complication following haematopoietic stem cell transplant for any indication (reported in up to 90% cases). Febrile neutropenia typically occurs in the early recovery / pre-neutrophil engraftment (2 to 6 weeks) phase. Febrile neutropenia is treated empirically.

In subjects with transfusion-dependent β-thalassemia, (N=54) 33 (61.1%) subjects had an AE of febrile neutropenia, 29 (53.7%) had a Grade 3 or 4 AE and 1 subject had an SAE of febrile neutropenia. Most events of febrile neutropenia had an onset within 21 days following exa-cel infusion; all events had an onset within the first 3 months after exa-cel infusion. All events resolved within 1 to 18 days of onset.

In subjects with sickle cell disease, (N=43) 23 (53.5%) subjects had an AE of febrile neutropenia, 20 (46.5%) had a Grade 3 or 4 AE and 1 subject had an SAE of febrile neutropenia. All events had an onset within the first 21 days after exa-cel infusion and resolved within 1 to 12 days of onset.

None of the AEs or SAEs of febrile neutropenia were considered related to exa-cel. 25 (46.3%) subjects with transfusion-dependent beta-thalassaemia and 22 (51.2%) subjects with sickle cell disease had at least 1 AE of febrile neutropenia that was considered related or possibly related to busulfan.

Infection

From the literature: Neutropenia is associated with increased risk of serious infection following myeloablative conditioning and haematopoietic stem cell transplant, particularly during the period before neutrophil engraftment. In both studies, prophylactic anti-infective agents were used according to individual site practices for haematopoietic stem cell transplant.

In subjects with transfusion-dependent β-thalassemia:

- Infection AEs occurred in 35 (64.8%) subjects; the most common AEs of infection (occurring in ≥10% of subjects) were covid-19 (14 [25.9%]).
- Grade 3 or 4 infection AEs occurred in 15 (27.8%) subjects and infection SAEs occurred in 11 (20.4%) subjects.
- SAEs of pneumonia (3 [5.6%] subjects), covid-19 (2 [3.7%] subjects) and upper respiratory tract infection (2 [3.7%] subjects) were the only SAEs that occurred in ≥2 subjects.
- 10 (18.5%) subjects with transfusion-dependent beta-thalassaemia had at least 1 infection AE that was considered related or possibly related to busulfan. No infection AEs were considered related or possibly related to exa-cel.

In subjects with sickle cell disease:

- Infection AEs occurred in 28 (65.1%) subjects; the most common AEs of infection (occurring in ≥10% of subjects) were oral candidiasis (8 [18.6%]), covid-19 (11 [25.6%]), upper respiratory tract infection (6 [14.0%]) and pneumonia (5 [11.6%]).
- Grade 3 or 4 infection AEs occurred in 10 (23.3%) subjects and SAEs of infection occurred in 9 (20.9%) subjects.
- SAEs of pneumonia (4 [9.3%]) and sepsis (2 [4.7%]) were the only SAEs that occurred ≥2 subjects.
- 12 (27.9%) subjects with sickle cell disease had at least 1 infection AE that was considered related or possibly related to busulfan. No infection AEs were considered related or possibly related to exa-cel.

There was no association between infection AEs or SAEs and neutrophil engraftment times in subjects with transfusion-dependent β-thalassemia or sickle cell disease.

Post-transplant infections may be under-reported in the literature. For autologous haematopoietic stem cell transplant: bloodstream infections of bacterial origin occur in up to 10% and invasive fungal infections occur in about 2%.

The incidence of infection was consistent with that observed after haematopoietic stem cell transplant.

No events of infection were considered related to exa-cel.

Bleeding

From the literature: There is an increased risk of bleeding events following myeloablative conditioning, with the highest risk of bleeding after haematopoietic stem cell transplant occurring before platelet engraftment. Clinically significant bleeding events occurring within 180 days of transplant and leading to specific clinical intervention have been reported in about 15% subjects after haematopoietic stem cell transplant. In a study of (about) 450 patients, there were (about) 1200 bleeding events following bone marrow transplant; the peak incidence was the second week after transplant.

In subjects with transfusion-dependent β-thalassemia:

Bleeding events occurred in 37 (68.5%) subjects.

The majority of bleeding events were Grade 1 or Grade 2 in severity.

Grade 3 or 4 bleeding AEs occurred in 11 (20.4%) subjects.

The most common bleeding events (occurring ≥10% subjects) after exa-cel infusion were epistaxis (20 [37.0%]), petechiae (12 [22.2%]), haematuria (7 [13.0%] subjects), and gingival bleeding (6 [11.1%] subjects). The majority of epistaxis and gingival bleeding events were Grade 1 or Grade 2 and all events of petechiae were Grade 1 or Grade 2 in severity; 3 out of 7 events of haematuria were Grade 1 or Grade 2 in severity.

The median duration of bleeding events was 3.5 (range: 1 to 48) days.

26 (48.1%) subjects with transfusion-dependent beta-thalassaemia had at least 1 bleeding AE that was considered related or possibly related to busulfan.

2 (3.7%) subjects with transfusion-dependent beta-thalassaemia had non-serious bleeding AEs (petechiae [1 subject] and epistaxis [1 subject]) assessed by the investigator as related or possibly related to exa-cel and busulfan; both events had an onset of Study Day 17, were non serious and resolved. None of the bleeding AEs were considered related to exa-cel only.

One (1.9%) subject with transfusion-dependent β-thalassemia had bleeding SAEs, which occurred in the early period after myeloablative conditioning and before platelet engraftment. The investigator assessed one SAE as related to busulfan and the other SAE as the result of surgical treatment. Both SAEs resolved and the subject achieved platelet engraftment.

In subjects with sickle cell disease:

Bleeding events occurred in 18 (41.9%) subjects.

The majority of bleeding events were Grade 1 or Grade 2 in severity. Grade 3 or 4 bleeding AEs occurred in 3 (7.0%) subjects. The most common bleeding event (occurring ≥10% subjects) after exa-cel infusion was epistaxis (8 [18.6%]).

The majority of epistaxis events were Grade 1 or Grade 2 in severity.

The median duration of bleeding events was 3.0 (range: 1 to 126) days.

11 (25.6%) subjects with sickle cell disease had at least 1 bleeding AE that was considered related or possibly related to busulfan. None of the bleeding AEs were considered related or possibly related to exa-cel.

1 (2.3%) subject with sickle cell disease had a bleeding SAE (epistaxis) which the investigator considered possibly related to busulfan and not related to exa-cel. The event occurred before platelet engraftment and resolved shortly thereafter.

There was no association between bleeding AEs or SAEs and platelet engraftment times in subjects with transfusion-dependent β-thalassemia or sickle cell disease.

Overall, for subjects with transfusion-dependent beta-thalassaemia or sickle cell disease, the incidence and severity of clinically significant bleeding events was consistent with that observed after autologous haematopoietic stem cell transplant.

Comment: bleeding is known to occur commonly after haematopoietic stem cell transplant and may occur at any site, as is described in the current studies. There is not additional comment on this issue.

Veno-occlusive Liver Disease

From the literature: Veno-occlusive liver disease is complication of haematopoietic stem cell transplant and may occur in up to 15% cases. Risk factors for development of veno-occlusive liver disease include conditioning regimen with busulfan, haematopoietic stem cell transplant (higher risk in autologous than allogeneic), very young or very old age and history of previous liver disease; patients with transfusion-dependent β-thalassemia are likely more susceptible to veno-occlusive liver disease due to liver damage associated with iron overload.

After myeloablation with busulfan and exa-cel infusion:

In subjects with transfusion-dependent β-thalassemia:

- 7 (13.0%) subjects had an AE of veno-occlusive liver disease, 2 subjects with a Grade 3 non-serious AE and 5 subjects with SAEs (Grade 2 or Grade 3); all events resolved. None of the veno-occlusive liver disease events were Grade 4.
- The time of onset for the events ranged from Study Day 13 to Study Day 32.
- All events were considered possibly related or related to busulfan; none of the events were considered related to exa-cel. All events resolved.
- All 7 subjects with Veno-occlusive Liver Disease events received Veno-occlusive Liver Disease prophylaxis starting from the time of busulfan conditioning and continuing after exa cel infusion (ursodeoxycholic acid, defibrotide or both). There was no apparent increase in risk of Veno-occlusive Liver Disease associated with different prophylaxis practices (e.g. use of Veno-occlusive Liver Disease prophylaxis) among sites.

In subjects with sickle cell disease:

- 1 (2.3%) subject had a non-serious, Grade 3 AE of Veno-occlusive Liver Disease that resolved within 12 days. The event was considered related to busulfan and not related to exa-cel.

The overall incidence and pattern of Veno-occlusive Liver Disease events is consistent with the literature for subjects with TDT or SCD undergoing busulfan-based myeloablative conditioning and autologous HSCT with no additional exa-cel specific concerns identified.

Comment: the occurrence of veno-occlusive liver disease after haematopoietic stem cell transplant in the current studies is consistent with published data. There is not additional comment on this issue.

Haemophagocytic lymphohystiocytosis

From the literature: Haemophagocytic lymphohystiocytosis is reported to occur after haematopoietic stem cell transplant in (about) 3% cases. The condition is characterised by macrophage and mononuclear cell activation in the blood and tissues, haemophagocytosis in bone marrow and reticuloendothelial organs (e.g. liver, spleen and lung) and cytopenias.

In subjects with transfusion-dependent β-thalassemia:

1 subject with prolonged high fevers, evidence of haemophagocytosis in the bone marrow, elevated ferritin and elevated soluble CD25 receptor satisfied the criteria for an SAE of haemophagocytic lymphohystiocytosis.

The subject had a significant response to therapy (glucocorticoids and anti-IL-6R therapy) which is supportive of a diagnosis of haemophagocytic lymphohystiocytosis.

A common trigger for haemophagocytic lymphohystiocytosis is infection, including viral infection. The subject had febrile neutropenia and neutropenic colitis, consistent with an infection that predated the onset of haemophagocytic lymphohystiocytosis.

The investigator considered the SAE of Haemophagocytic lymphohystiocytosis (verbatim: macrophage activation syndrome) as Grade 4 in severity and possibly related to exa-cel and not related to busulfan.

The SAE resolved within 191 days.

In subjects with sickle cell disease: no event recorded.

Overall, the incidence of these haemophagocytic lymphohystiocytosis events is within the range reported in the literature for subjects undergoing myeloablative conditioning and autologous haematopoietic stem cell transplant with no additional exa-cel specific concerns identified.

Comment: the occurrence of haemophagocytic lymphohystiocytosis after haematopoietic stem cell transplant in the current studies is consistent with published data. There is not additional comment on this issue.

Engraftment Syndrome

From the literature: Engraftment syndrome can occur in the peri-engraftment period; the syndrome includes non-infectious fever, rash (>25% of body), diarrhoea, hepatic dysfunction, renal insufficiency, transient encephalopathy and capillary leakage. Engraftment syndrome typically occurs in the early stages of neutrophil recovery and is more common after autologous- than allogeneic haematopoietic stem cell transplant. Skin rash and non-infectious fever within 7 days following haematopoietic stem cell transplant occur in (about) 60% patients

In subjects with transfusion-dependent β-thalassemia:

1 subject had a Grade 3 non-serious AE of engraftment syndrome that resolved within 13 days; the event was considered not related to exa-cel or busulfan; the subject achieved neutrophil engraftment. The subject had a concurrent SAE of related to an infection which resolved within 17 days.

In subjects with sickle cell disease: no event recorded.

Comment: information on engraftment syndrome is noted without additional comment at this stage.

Neutrophil and Platelet Engraftment

Per protocol (Study 111 and Study 121):

neutrophil engraftment was defined as the first day of 3 consecutive measurements of absolute neutrophil count (ANC) ≥500/µL on 3 different days without use of unmodified $CD34^+$ cells after reaching the nadir, defined as ANC <500/µL.

Delayed engraftment was defined as lack of engraftment of neutrophils by Study Day 43.

Engraftment failure was defined as not achieving neutrophil engraftment after exa-cel infusion and receipt of backup $CD34^+$ stem cells.

A subject was considered evaluable for neutrophil engraftment if they had achieved neutrophil engraftment or had at least 44 days of follow-up after exa-cel infusion (reached at least Study Day 43).

Platelet engraftment was defined as the first of 3 consecutive measurements on 3 separate days with platelet ≥20,000/µL (Study 111 [TDT]) or ≥50,000/µL (Study 121 [SCD]) without a platelet transfusion for 7 consecutive days.

There was not a pre-specified definition of evaluable for platelet engraftment.

No subjects have had engraftment failure and no subjects have received back up cells.

Neutrophil Engraftment

Prophylactic anti-infective agents were used in the study according to individual site practices. For subjects who completed busulfan conditioning and received exa-cel, all subjects in both studies achieved neutrophil engraftment. The median times for engraftment here reported in both studies are consistent with published data.

For subjects with transfusion-dependent β-thalassemia (n=54), the median (range) time to neutrophil engraftment was 29.0 (12 to 56) days. 53 subjects achieved engraftment by day 43; none required back up cells; 1 subject achieved engraftment at day 56 without back up cells. Use of G-CSF was allowed if engraftment did not occur by Day 21 after exa-cel infusion; of the 54 subjects who achieved neutrophil engraftment as of 16 Apr 2023, 20 (37.0%) subjects achieved neutrophil engraftment without use of G-CSF and 34 (63.0%) subjects received G-CSF before neutrophil engraftment. Subjects generally discontinued receiving G-CSF after achieving neutrophil engraftment (range: Study Day 27 to Study Day 120). Most (N = 24) of the 34 subjects discontinued receiving G-CSF within 7 days after neutrophil engraftment. Results are summarised:

Table 12-12 Subgroup Analysis: Summary of Neutrophil Engraftment by Age at Screening (FAS)

Category	Total N = 54	Age at Screening ≥12 and <18 Years N = 19	Age at Screening ≥18 and ≤35 Years N = 35
Subjects who neutrophil engraftment was evaluable, N1	54	19	35
Subjects who received backup cells	0	0	0
Subjects who achieved neutrophil engraftment[a] at any time n (%)	54 (100.0)	19 (100.0)	35 (100.0)
Time to neutrophil engraftment (days) for subjects who achieved neutrophil engraftment at any time			
Mean (SD)	29.2 (7.4)	31.0 (8.9)	28.3 (6.5)
Median	29.0	31.0	29.0
Min, Max	12, 56	19, 56	12, 40

Source: Ad hoc Table 14.3.4.6.1 (data cutoff date of 16 April 2023)

ANC: absolute neutrophil count; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N: total sample size; n: size of subsample; N1: number of subjects who achieved neutrophil engraftment or had at least 44 days after exa-cel infusion

Notes: Time to neutrophil engraftment = neutrophil engraftment date - exa-cel infusion date + 1. The percentage of subjects who achieved neutrophil engraftment was calculated relative to the number of subjects whose neutrophil engraftment was evaluable, (i.e., n/N1 × 100).

[a] Neutrophil engraftment was defined as the first day of 3 consecutive measurements of ANC ≥500/μL on 3 different days, without use of the unmodified $CD34^+$ cells after reaching the nadir, defined as ANC <500/μL.

Results for subjects ≥12 and <18 years of age and ≥18 and ≤35 years of age were consistent with the overall results from the main analyses.

Median (range) neutrophil counts were lowest at Month 1 after exa-cel infusion: 0.60 (0.03 to 33.80) × 10^9/L. Median (range) neutrophil counts increased at Month 2 (2.50 [0.47 to 8.38] × 10^9/L) and median neutrophil counts remained ≥1.5 × 10^9/L thereafter.

For subjects with sickle cell disease (n=43), the median (range) time to neutrophil engraftment was 27.0 (15 to 40) days. All subjects achieved neutrophil engraftment by Study Day 43. No subject needed back up cells.

Use of G-CSF was allowed if engraftment did not occur by Day 21 after exa-cel infusion. Of the 43 subjects who achieved neutrophil engraftment, 24 (55.8%; N = 43) subjects achieved neutrophil engraftment without use of G-CSF and 19 (44.2%; N = 43) received G-CSF prior to neutrophil engraftment. All subjects discontinued receiving G-CSF (range: Study Day 25 to Study Day 43) and discontinued G-CSF within 7 days after neutrophil engraftment.

Results are summarised on the following page.

Table 12-11 Subgroup Analysis: Summary of Neutrophil Engraftment by Age at Screening (FAS)

Parameter	Total N = 43	Age at Screening ≥12 and <18 years N = 12	Age at Screening ≥18 and ≤35 years N = 31
Subjects who neutrophil engraftment was evaluable, N1	43	12	31
Subjects who received back-up cells	0	0	0
Subjects who achieved neutrophil engraftment[a] at any time n (%)	43 (100.0)	12 (100.0)	31 (100.0)
Time to neutrophil engraftment (days) for subjects who achieved neutrophil engraftment at any time			
Mean (SD)	26.7 (6.0)	29.8 (4.6)	25.5 (6.1)
Median	27.0	28.0	26.0
Min, Max	15, 40	24, 40	15, 38

Source: Ad hoc Table 14.3.4.6.1 (data cutoff date of 16 April 2023)
ANC: absolute neutrophil count; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; N1: number of subjects who achieved neutrophil engraftment or had at least 44 days after exa-cel infusion; N: number of subjects; n: size of subsample
Note: Time to neutrophil engraftment = neutrophil engraftment date - exa-cel infusion date + 1. The percentage of subjects who achieved neutrophil engraftment was calculated relative to the number of subjects whose neutrophil engraftment was evaluable, (i.e., n/N1 × 100).
[a] Neutrophil engraftment was defined as the first day of 3 consecutive measurements of ANC ≥500/μL on 3 different days, without use of the unmodified CD34+ cells after reaching the nadir, defined as ANC <500/μL.

Results for subjects ≥12 and <18 years of age and ≥18 and ≤35 years of age were consistent with the overall results from the main analyses.

Median (range) neutrophil counts were lowest at Month 1 after exa-cel infusion: 1.24 (0.00 to 5.58) × 10^9/L. Median (range) neutrophil counts increased at Month 2 (3.50 [0.70 to 10.72] × 10^9/L) and median neutrophil counts remained ≥1.5 × 10^9/L thereafter.

Comment: although G-CSF is contra-indicated in sickle cell disease because life-threatening complications can ensue in the presence of sickle vasculopathy, a report of 62 patients ages 1-20yrs who were exposed to granulocyte colony-stimulating factor for a median of 9 days after haematopoietic stem cell transplantation has reported that G-CSF is sufficiently clinically safe to permit use for neutrophil recovery in this context; refer to Shah et al Transplant Cell Ther 2022 28:174.e1-174.e5: G-CSF following allogeneic transplantation in patients with sickle cell disease.; sickle cell disease complications were not reported.

Platelet Engraftment

Thrombopoietin receptor agonists and mimetics were used by the individual investigator according to their judgment. Of the 97 subjects in studies 111 and 121 who achieved neutrophil engraftment, 96 subjects also achieved platelet engraftment at the time of the data cutoff date.

The median (range) time to platelet engraftment was as follows:

- Subjects with transfusion-dependent β-thalassemia (N = 53): 44.0 (20 to 200) days
- Subjects with sickle cell disease (N = 43): 35.0 (23 to 126) days

1 subject with transfusion-dependent β-thalassemia was pending platelet engraftment at the time of the data cutoff date (16 Apr 2023); the subject was at Study Day 63 at the time of data cutoff date and had achieved neutrophil engraftment on Study Day 37.

The median times for engraftment here reported are consistent with published data.

Comment: more time appears to be taken for platelet engraftment in those with transfusion-dependent β-thalassemia compared to those with sickle cell disease.

In general: those who have undergone splenectomy are known to display faster platelet engraftment times relative to those with an intact spleen. A subgroup analysis of platelet engraftment by spleen status was performed (Table 23).

Table 23 → Platelet Engraftment Time by Spleen Status at Screening (Study 111): FAS

	Spleen Intact N = 38	No Spleen N = 16	Total N = 54
Platelet Engraftment[a]			
Time to platelet engraftment (days) for subjects who achieve platelet engraftment			
..N	37	16	53
..Mean (SD)	60.8 (43.5)	37.8 (14.6)	53.8 (38.5)
..Median	46.0	34.5	44.0
..Min, max	27, 200	20, 78	20, 200

Source: Study 111/Ad hoc Table 14.3.4.6.2 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; n: size of subsample; PE: platelet engraftment
Note: Time to PE = PE date - exa-cel infusion date + 1. No subject received unmodified $CD34^+$ cells (backup cells).

[a] → PE was defined as the first day of 3 consecutive measurements of unsupported (no platelet transfusions for the last 7 days) platelet ≥20,000/μL on 3 different days after exa-cel infusion after reaching nadir, defined as platelet <20,000/μL, or the first platelet transfusion whichever is earlier. For subjects who were discharged before reaching PE, PE was defined as the seventh day after the last platelet transfusion, if there were 3 subsequent and consecutive unsupported measurements of unsupported platelet ≥20,000/μL on 3 different days. This last platelet transfusion refers to the last platelet transfusion preceding these 3 measurements.

No clinically relevant sequalae were observed in subjects with longer platelet engraftment times.

Presence or absence of spleen was not assessed in subjects with sickle cell disease because this population is effectively and functionally asplenic.

Comment: the median times for platelet engraftment are similar between the sickle cell disease population and those with transfusion-dependent β-thalassemia who are asplenic i.e. about 35 days. The rationale of the company on presence / absence of spleen may be accepted.

For subjects with transfusion-dependent β-thalassemia: median (range) platelet counts were lowest at Month 1 after exa-cel infusion: 19.0 (3.0 to 307) × 10^9/L. Median (range) platelet counts increased at Month 2 (86.5 [9.0 to 507] × 10^9/L) and median platelet counts remained ≥100 × 10^9/L from Month 4 thereafter.

For subjects with sickle cell disease: median (range) platelet counts were lowest at Month 1 after exa-cel infusion: 64.0 (12 to 374) × 10^9/L. Median (range) platelet counts increased at Month 2 (122.0 [13 to 385] × 10^9/L) and median remained ≥100 × 10^9/L thereafter.

Comment: it may be acknowledged that data presented on neutrophil and platelet engraftment in studies 111 and 121 are consistent with published data and would not give particular concern.

Bleeding Adverse Events in the Context of Platelet Engraftment

There is an increased risk of bleeding events following myeloablative conditioning, with the highest risk of bleeding being after haematopoietic stem cell transplant and before platelet engraftment. Peak incidence is at the second week after transplant with decreasing incidence of events thereafter.

In subjects with transfusion-dependent β-thalassemia:

From exa-cel infusion to Month 24, bleeding events occurred in 37 (68.5%; N = 54) subjects. Consistent with myeloablative conditioning and platelet recovery, the incidence of bleeding events was highest before platelet engraftment (33 [61.1%; N = 54] subjects) and decreased after platelet engraftment (11 [20.8%] subjects; N = 53).

The most common bleeding events (occurring in ≥10% subjects) after exa-cel infusion were epistaxis (20 [37.0%; N = 54] subjects), petechiae (12 [22.2%; N = 54] subjects), haematuria (7 [13.0%; N = 54] subjects), and gingival bleeding (6 [11.1%; N = 54] subjects).

There were no bleeding events related to exa-cel only.

In subjects with sickle cell disease,

From exa-cel to Month 24, bleeding events occurred in 18 of 43 (41.9%) subjects. Consistent with myeloablative busulfan conditioning and platelet recovery, most bleeding events occurred within the first month after exa-cel infusion and before the median time to platelet engraftment (35.0 days). The incidence of bleeding events was highest before platelet engraftment (16 out of 43 [37.2%] subjects) and decreased after platelet engraftment (6 out of 43 [14.0%] subjects.

Overall, the incidence and timing of bleeding events were consistent with expectations during the period of thrombocytopenia after myeloablative busulfan conditioning and haematopoietic stem cell transplant. There was no increased incidence of bleeding events in subjects with longer times to platelet engraftment. There was no association between bleeding AEs or SAEs and platelet engraftment times in subjects with transfusion-dependent β-thalassemia or sickle cell disease.

Comment: it may be acknowledged that incidence and timing of bleeding(s) are consistent with the overall procedure rather than exa-cel.

Continuing transfusion dependence
Three subjects with transfusion-dependent β-thalassemia in the Primary Efficacy Set had not achieved transfusion independence for at least 12 consecutive months. These subjects have been clinically well throughout the period after myeloablative conditioning and exa-cel infusion and have shown clinical benefit as evidenced by the decreases from baseline in red blood cell transfusion volume of 81%, 98%, and 85%.

1st participant

The assessment of bone marrow aspirate at baseline showed erythroid predominance with an M:E ratio of 0.2, consistent with β-thalassemia.

Cellularity improved after myeloablation. Additionally, the M:E had improved at Month 12 (M:E ratio 0.7). Since exa-cel infusion, there were no reports of dysplasia in any bone marrow analysis and blast counts were within normal limits at all timepoints (Months 12 and 18).

Comment: a myeloid-to-erythroid (M:E) ratio is calculated by examining 500 cells and dividing the number of granulocytic cells, including mature granulocytes, by the number of nucleated erythroid cells. A decreased M:E ratio may mean a decrease in granulocytes or an increase in erythroid cells.

The reference M:E ratio in healthy adults varies from about 2:1 to 5:1.
The bone marrow in clinically severe thalassaemia is extremely cellular mainly as a result of marked erythroid hyperplasia; the M:E ratio may be 0.5 or even less.
(The M:E ratio in sickle cell disease is generally about 1:1).

2nd participant
The assessment of bone marrow aspirate at baseline showed erythroid predominance with an M:E ratio of 0.5, consistent with β-thalassemia.
As expected with exa-cel treatment response, cellularity improved after myeloablation. Additionally, the M:E had improved at Month 12 (M:E ratio: 1.0).

3rd participant
The assessment of bone marrow aspirate at baseline showed erythroid predominance with an M:E ratio of 0.1, consistent with β-thalassemia.
Cellularity improved after myeloablation. Additionally, the M:E had improved at Month 12 (M:E ratio: 0.5).

Summary

As of the data cutoff date of 16 April 2023, all 3 subjects have stopped receiving red blood cell transfusions and have been transfusion free for 8.1, 7.0 and 0.5 months, respectively, starting 60 days after the last RBC transfusion.

Overall, for all 3 subjects, the benefit-risk profile is considered to be favourable.

Comment: the company reports on 3 subjects with β-thalassemia who have not achieved being transfusion-free for 12 months; it is expected that the company will continue to provide updates on the progress of these subjects; the attitude of the company towards these 3 subjects is considered acceptable.

Overall, for all 3 subjects, the benefit-risk profile is considered to be favourable.

Laboratory safety
Laboratory evaluations including haematology, chemistry, coagulation, immunology and urinalysis were performed in Studies 111 and 121.

Laboratory testing was performed at screening, baseline, before the start of mobilization, before conditioning, before exa-cel infusion and at regular intervals (at least monthly through Month 6 visit and then every 3 months) after exa-cel infusion up to the Month 24 visit.

Haematology variables / coagulation tests / liver function tests / routine chemistry results over time were generally consistent for the transfusion-dependent β-thalassemia or sickle cell disease patient population and for subjects undergoing busulfan myeloablation and autologous haematopoietic stem cell transplant.

Comment: in general, 'routine' laboratory results reverted to pre-procedure values by (about) month 2-3.

Vital signs
- No clinically relevant trends in vital signs have been observed.
- No clinically relevant trends in 12-lead ECG results have been observed.

Additional aspects of safety
Exa-cel has not been studied in patients with hepatic impairment.

Exa-cel has not been studied in patients with renal impairment.

As exa-cel is an autologous cell product, drug-drug interactions that can alter the pharmacokinetic profiles of co-administered medications are not anticipated.

Female subjects who were lactating were excluded from participation. After start of myeloablation or exa-cel infusion, no pregnancies have been reported and therefore there is no relevant data to inform on the safety of exa-cel use and pregnancy.

Sex and race: clinically relevant differences attributable to exa-cel were not identified based on sex or race.

Genotype: clinically relevant differences attributable to exa-cel were not identified amongst genotypes in either Study 111 or Study 121.

Age

In both Studies 111 and 121, the observed safety profile was generally similar between subjects ≥12 and <18 years of age and ≥18 and ≤35 years of age; AEs were considered consistent with myeloablative busulfan conditioning, haematopoietic stem cell transplant and underlying disease.

No differences attributed to exa-cel were identified. In each study, the incidence of AEs and SAEs after exa-cel infusion to Month 24 for the 2 age groups (≥12 and <18 years and ≥18 and ≤35 years of age) was generally similar (Table 30).

Table 30 Overview of Adverse Events by Age Group at Screening for the Exa-cel to M24 Interval (Studies 111 and 121): FAS

	Age at Screening			
	TDT (Study 111)		SCD (Study 121)	
	≥12 and <18 years n (%)	≥18 and ≤35 years n (%)	≥12 and <18 years n (%)	≥18 and ≤35 years n (%)
Evaluable subjects, N1	19	35	12	31
Subjects with				
any AEs	19 (100.0)	35 (100.0)	12 (100.0)	31 (100.0)
any AEs related or possibly related to exa-cel	5 (26.3)	9 (25.7)	2 (16.7)	11 (35.5)
any AEs related or possibly related to busulfan	18 (94.7)	35 (100.0)	12 (100.0)	31 (100.0)
Grade 3 or 4 AEs	19 (100.0)	29 (82.9)	10 (83.3)	31 (100.0)
SAEs	6 (31.6)	13 (37.1)	4 (33.3)	12 (38.7)
SAEs related or possibly related to exa-cel	1 (5.3)	1 (2.9)	0	0
SAEs related or possibly related to busulfan	4 (21.1)	5 (14.3)	0	4 (12.9)
AEs leading to study discontinuation	0	0	0	0
AEs leading to death[a]	0	0	0	1 (3.2)

Source: Study 111/Table 14.3.1.1.4 and Study 121/Table 14.3.1.1.4 (data cutoff date of 16 April 2023)

AE: adverse event; exa-cel: exagamglogene autotemcel; FAS: Full Analysis Set; M24: Month 24 Visit; N: total sample size; n: size of subsample; PT: preferred term; SAE: serious adverse event; SAS: Safety Analysis Set; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia

Notes: MedDRA version 26.0. Evaluable subjects, N1: the number of subjects in the SAS who were on or after the day of exa-cel infusion (i.e., FAS). Percentages were calculated as n/N1*100. When summarizing number of events for each study interval, a subject with multiple events within a category and study interval was counted multiple times in that category and study interval. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. An AE with relationship missing to busulfan/exa-cel is counted as related to busulfan/exa-cel in this table. Table shows exa-cel to M24 study interval: day of exa-cel infusion to Month 24 visit or end of study visit.

[a] As reported in the initial MAA, 1 subject died due to COVID-19 infection that resulted in respiratory failure, not related to exa-cel (Section 4.4)

Comment: adverse events are universal and serious adverse events occur in (about) 35% subjects in both age groups described; the overview of adverse events by age does not appear to show difference between those 12 to 17yrs and those ≥18yrs old.

Engraftment

Clinically relevant differences in achievement of engraftment (neutrophil or platelet), time to neutrophil engraftment or time to platelet engraftment based on age were not observed in Studies 111 or 121. Times to neutrophil and platelet engraftment are shown:

Neutrophil Engraftment

For subjects with transfusion-dependent thalassaemia (Study 111), times to neutrophil engraftment by age group were as follows:

Subjects ≥12 to <18 years of age (N = 19): mean 31.0 days; median 31.0 days; range: 19 to 56 days.

Subjects ≥18 to ≤35 years of age (N = 35): mean 28.3 days; median 29.0 days; range 12 to 40) days.

For subjects with sickle cell disease (Study 121), times to neutrophil engraftment by age group were as follows:

Subjects ≥12 to <18 years of age (N = 12): mean 29.8 days; median 28.0 days; range: 24 to 40 days.

Subjects ≥18 to ≤35 years of age (N = 31): mean 25.5 days; median 26.0 days; range 15 to 38) days.

Comment: the times to neutrophil engraftment appear similar in both studies and in the different age groups described; up to 56 days is described for neutrophil engraftment.

Platelet Engraftment

For subjects with transfusion-dependent thalassaemia (Study 111), times to platelet engraftment by age group were as follows:

Subjects ≥12 to <18 years of age (N = 18): mean 63.9 days; median 45.0 days; range: 20 to 199 days.

Subjects ≥18 to ≤35 years of age (N = 35): mean 48.6 days; median 40.0 days; range 24 to 200 days.

For subjects with sickle cell disease (Study 121), times to platelet engraftment by age group were as follows:

Subjects ≥12 to <18 years of age (N = 12): mean 46.2 days; median 44.5 (range: 23 to 81) days, respectively.

Subjects ≥18 to ≤35 years of age (N = 31): mean 42.0 days median 32.0 days; range 23 to 126) days.

Comment: the times to platelet engraftment appear similar in the different age groups described. There is a wider spread of times taken to engraftment of platelets (compared to neutrophil engraftment) in each study with those subjects with thalassaemia demonstrating the higher range up to 200 days versus up to 126 days in sickle cell disease.

Data are noted without additional comment.

Overdose: not applicable; exa-cel is an autologous drug product

Drug abuse: as the entire dose (all vial[s]) of exa-cel is administered as a one-time infusion and exa-cel is an autologous product, there is no potential for abuse.

Withdrawal and rebound: as exa-cel is a one-time autologous drug product, the treatment cannot be discontinued after administration. As such, no studies or systematic analyses to evaluate the potential withdrawal and rebound effects of exa-cel were conducted. Based on the autologous nature of the product and single-time administration, no withdrawal or rebound effects are expected.

No studies on the effects of exa-cel on the ability to drive or operate machinery or impairment of mental ability have been performed. Based on the mechanism of action, exa-cel is not expected to affect the ability to drive or operate machinery. After exa-cel infusion, subjects are hospitalised until neutrophil engraftment is achieved and stabilisation of major medical issues has occurred, thus patients are not driving or operating machinery during this time. Therefore, exa-cel has no influence on these activities.

Safety During Mobilization and Apheresis
Studies 111 and 121 each consist of a mobilization and apheresis period with either a dual agent (granulocyte colony stimulating factor and plerixafor) in subjects with transfusion-dependent thalassaemia or a single agent (plerixafor) in subjects with sickle cell disease.

The treatments used for mobilization/apheresis have well-characterised safety profiles and each have marketing authorisation for use prior to allogeneic haematopoietic stem cell transplant.

Comment: to note that the company employed granulocyte colony stimulating factor and plerixafor outside the terms of the UK-based licences.

In Studies 111 and 121, the total exposure from the start of mobilization to the day before the start of myeloablative conditioning with busulfan was 948.67 patient-months (418.1 patient-months for transfusion-dependent thalassaemia and 530.57 patient-months for sickle cell disease.

Discontinuations

3 subjects with transfusion-dependent thalassaemia and 11 subjects with sickle cell disease discontinued the respective studies after initiating mobilization and were not subsequently dosed with exa-cel. The reasons for discontinuations included the following:

• For subjects with transfusion-dependent thalassaemia: withdrawal of consent for undisclosed reasons (1 subject); did not want to undergo a second apheresis procedure (1 subject); concerns with continued study participation (1 subject).

• For subjects with sickle cell disease: inadequate cell collection (6 subjects); no longer meeting eligibility criteria (1 subject); non-compliance (1 subject); withdrawal of consent (2 subjects); [removed to protect personal information] (1 subject [not reported as an AE])

Comment: inadequate cell collection is notably more evident in those with sickle cell disease and presumably reflects the underlying pathophysiology.

Overview of Adverse Events

An overview of AEs is presented by study for the interval from the start of mobilization to the day before the start of myeloablative busulfan conditioning in Table 31.

Table 31 Overview of AEs From Mobilization to <Conditioning (Studies 111 and 121): SAS

	TDT (Study 111) n (%)	SCD (Study 121) n (%)
Evaluable subjects, N1	59	58
Subjects with		
any AEs	49 (83.1)	57 (98.3)
Grade 3/4 AEs	13 (22.0)	40 (69.0)
SAEs	8 (13.6)	35 (60.3)
AEs leading to study discontinuation	0	0
AEs leading to death	0	0
AEs by strongest relationship to plerixafor		
Not related	25 (42.4)	21 (36.2)
Unlikely related	2 (3.4)	3 (5.2)
Possibly related	13 (22.0)	19 (32.8)
Related	9 (15.3)	14 (24.1)
AEs by strongest relationship to G-CSF		
Not related	15 (25.4)	NA
Unlikely related	0	NA
Possibly related	6 (10.2)	NA
Related	28 (47.5)	NA

Source: Study 111/Table 14.3.1.1.2 and Study 121/Table 14.3.1.1.2 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; G-CSF: granulocyte colony-stimulating factor; n: size of subsample; NA: not applicable; SAE: serious adverse event; SAS: Safety Analysis Set; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia
Notes: MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of the study interval. Percentages were calculated as n/N1*100 within each interval, unless otherwise specified. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. An AE with relationship missing to plerixafor/G-CSF was counted as related to plerixafor/G-CSF in this table. Table shows mobilization to <conditioning study interval: start of first mobilization cycle to the day before the start of busulfan conditioning.

Most subjects had at least 1 AE.

No subject in either study has discontinued the study or failed to complete mobilization / apheresis due to an AE.

Comment: adverse events in general, serious adverse events and grade 3 & 4 adverse events appear to be more common percentage-wise in those with transfusion-dependent thalassaemia; data are noted without additional comment.

Common Adverse Events

The most common AEs during mobilization (occurring in >10% of subjects) are presented by study in Table 32 (transfusion-dependent thalassaemia) and Table 33 (sickle cell disease).

For each study, most AEs occurring in >10% of subjects were consistent with the known safety profile of granulocyte colony stimulating factor (Study 111 only) or plerixafor, the apheresis procedure and / or underlying disease of transfusion-dependent thalassaemia or sickle cell disease.

Table 32 AEs Occurring in ≥10% of Subjects With TDT by PT From Mobilization to <Conditioning (Study 111): SAS

Preferred Term	TDT (Study 111) n (%)
Evaluable subjects, N1	59
Subjects with any AEs	49 (83.1)
Bone pain	20 (33.9)
Headache	15 (25.4)
Vascular access site pain	15 (25.4)
Nausea	12 (20.3)
Back pain	9 (15.3)
Hypokalaemia	9 (15.3)
Neck pain	8 (13.6)
Hypocalcaemia	7 (11.9)
Hypomagnesaemia	7 (11.9)
Procedural pain	7 (11.9)
Catheter site pain	6 (10.2)
Pain in extremity	6 (10.2)
Vomiting	6 (10.2)

Source: Study 111/Table 14.3.1.2.2 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; n: size of subsample; PT: preferred term; SAS: Safety Analysis Set; TDT: transfusion-dependent β-thalassemia
Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of the study interval. Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table is sorted in descending order of frequency by PT. Table shows mobilization to <conditioning: start of first mobilization cycle to the day before the start of busulfan conditioning.

Table 33 AEs Occurring in ≥10% of Subjects With SCD by PT From Mobilization to <Conditioning (Study 121): SAS

Preferred Term[a]	SCD (Study 121) n (%)
Evaluable subjects, N1	58
Subjects with any AEs	57 (98.3)
Nausea	31 (53.4)
Sickle cell anaemia with crisis	22 (37.9)
Hypomagnesaemia	20 (34.5)
Vascular access site pain	20 (34.5)
Hypocalcaemia	20 (34.5)
Paraesthesia	17 (29.3)
Abdominal pain	15 (25.9)
Vomiting	13 (22.4)
Headache	12 (20.7)
Hypokalaemia	12 (20.7)
Pruritus	12 (20.7)
Constipation	11 (19.0)
Arthralgia	10 (17.2)
Pain	9 (15.5)
Pain in extremity	9 (15.5)
Back pain	8 (13.8)
COVID-19	6 (10.3)
Diarrhoea	6 (10.3)
Fatigue	6 (10.3)
Paraesthesia oral	6 (10.3)
Pyrexia	6 (10.3)

Source: Study 121/Table 14.3.1.3.2 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; n: size of subsample; PT: preferred term; SAS: Safety Analysis Set; SCD: sickle cell disease
Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of the study interval. Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table is sorted in descending order of frequency by PT. Table shows mobilization to <conditioning: start of first mobilization cycle to the day before the start of busulfan conditioning.

Comment: about 83% of subjects with transfusion-dependent thalassaemia and about 98% subjects with sickle cell disease exhibited adverse events associated with the procedure; this would be consistent with experience of the procedure. There is not additional comment.

Adverse Events by Relationship to granulocyte colony stimulating factor and Plerixafor

Overall, 36 (61.0%) subjects with transfusion-dependent thalassaemia and 33 (56.9%) subjects with sickle cell disease had at least 1 AE considered related or possibly related to the mobilization regimens used. AEs considered related or possibly related to plerixafor and/or granulocyte colony stimulating factor occurring in >1 subject are presented by study in Table 34 (transfusion-dependent thalassaemia) and Table 35 (sickle cell disease).

Table 34 AEs Related to Plerixafor and/or G-CSF Occurring in >1 Subject With TDT by PT for the Enroll to Month 24 Interval (Study 111): SAS

Preferred Term	TDT (Study 111) n (%)
Evaluable subjects, N1	59
Subjects with any AEs	36 (61.0)
Bone pain	20 (33.9)
Headache	11 (18.6)
Nausea	7 (11.9)
Neck pain	5 (8.5)
Back pain	5 (8.5)
Abdominal pain	4 (6.8)
Pain	4 (6.8)
Pain in extremity	4 (6.8)
Vomiting	4 (6.8)
Leukocytosis	2 (3.4)
Pyrexia	2 (3.4)
Hypokalaemia	2 (3.4)
Hypoaesthesia oral	2 (3.4)
Diarrhoea	2 (3.4)

Source: Study 111/Table 14.3.1.3.4 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; M24: Month 24 Visit; n: size of subsample; PT: preferred term; SAS: Safety Analysis Set; TDT: transfusion-dependent β-thalassemia
Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of the Enroll to M24 interval and have received each study drug. Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. "Related", "Possibly Related", and "Missing" are considered as "Related" in this table. Table is sorted in descending order of frequency by PT. Table shows Enroll to M24 study interval: enrollment to Month 24 Visit or end of study visit.

Table 35 AEs Related to Plerixafor Occurring in >1 Subject With SCD by PT for the Enroll to Month 24 Interval (Study 121): SAS

Preferred Term	SCD (Study 121) n (%)
Evaluable subjects, N1	58
Subjects with any AEs	33 (56.9)
Nausea	26 (44.8)
Abdominal pain	9 (15.5)
Headache	7 (12.1)
Vomiting	7 (12.1)
Pain	5 (8.6)
Sickle cell anaemia with crisis	5 (8.6)
Back pain	4 (6.9)
Bone pain	4 (6.9)
Diarrhoea	4 (6.9)
Neck pain	3 (5.2)
Pain in extremity	3 (5.2)
Arthralgia	2 (3.4)
Fatigue	2 (3.4)
Hypomagnesaemia	2 (3.4)

Source: Study 121/Table 14.3.1.3.5 (data cutoff date of 16 April 2023)
AE: adverse event; exa-cel: exagamglogene autotemcel; M24: Month 24 Visit; n: size of subsample; PT: preferred term; SAS: Safety Analysis Set; SCD: sickle cell disease
Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of the Enroll to M24 interval and have received each study drug. Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. "Related", "Possibly Related", and "Missing" are considered as "Related" in this table. Table is sorted in descending order of frequency by PT. Table shows Enroll to M24 study interval: enrollment to Month 24 Visit or end of study visit.

Comment: adverse events reported as related to granulocyte colony stimulating factor and plerixafor are consistent with known adverse events and are mainly events of pain; 'sickle cell anaemia with crisis' in noted against plerixafor yet is not reported in the SmPC for Plerixafor (see additional comment below); events described may be clinically managed; there would not be additional comment.

Serious Adverse Events

Study 111

Eight (13.6%; N = 59) subjects with transfusion-dependent thalassaemia (study 111) had at least 1 SAE that occurred during mobilization up to the day before the start of myeloablative busulfan conditioning; none of the SAEs was considered related or possibly related to plerixafor or granulocyte colony stimulating factor.

Study 121

Thirty-five (60.3%; N = 58) subjects with sickle cell disease (study 121) had at least 1 SAE that occurred during mobilization up to the day before the start of myeloablative busulfan conditioning (Table 36).

Table 36 SAEs Occurring in ≥2 Subjects With SCD by PT From Mobilization to <Conditioning (Study 121): SAS

Preferred Term	SCD (Study 121) n (%)
Evaluable subjects, N1	58
Subjects with any SAEs	35 (60.3)
Sickle cell anaemia with crisis	20 (34.5)
Abdominal pain	4 (6.9)
Acute chest syndrome	3 (5.2)
Back pain	3 (5.2)
Vascular device infection	3 (5.2)
Anxiety	2 (3.4)
Bacteraemia	2 (3.4)
Bone pain	2 (3.4)
Pulmonary embolism	2 (3.4)
Staphylococcal bacteraemia	2 (3.4)

Source: Study 121/Table 14.3.2.2.2 (data cutoff date of 16 April 2023)
exa-cel: exagamglogene autotemcel; n: size of subsample; PT: preferred term; SAE: serious adverse event; SAS: Safety Analysis Set; SCD: sickle cell disease
Notes: AEs were coded using MedDRA version 26.0. Evaluable subjects, N1: The number of subjects in the SAS who were on or after the start date of the study interval. Percentages were calculated as n/N1*100. When summarizing number and percentage of subjects for each study interval, a subject with multiple events within a category and study interval was counted only once in that category and study interval. Table is sorted in descending order of frequency by PT. Table shows mobilization to <conditioning: start of first mobilization cycle to the day before the start of busulfan conditioning.

8 (13.8%) subjects had at least 1 SAE considered related or possibly related to plerixafor. Sickle cell anaemia with crisis (3 [5.2%] subjects), followed by bone pain and abdominal pain (2 [3.4%] subjects each) were the most common SAEs considered related or possibly related to plerixafor.

Comment: serious adverse events appear to be more common in those with sickle cell disease compared to thalassaemia; serious adverse events reported (mainly events of pain) may be understood in the context of the procedure(s); 'sickle cell anaemia with crisis' is noted (and see additional comment below); events described may be clinically managed; there would not be additional comment.

Study 121

During the mobilization and apheresis period but before conditioning, a total of 22 (37.9%; N = 58) subjects had an AE of sickle cell anaemia with crisis and 4 (6.9%) subjects had an AE of acute chest syndrome; of those, 3 subjects had AEs of both sickle cell anaemia with crisis and acute chest syndrome. Such events were Grade 2 or 3 in severity and most were considered not related to plerixafor and occurred >7 days after any plerixafor dose.

Within 7 days after any plerixafor dose, 9 (15.5%; N = 58) subjects had an SAE of sickle cell anaemia with crisis and 1 (1.7%) subject had an SAE of ACS. This incidence within 7 days following plerixafor is similar to that observed in another study (Tisdale JF et al. Am J Hematol. 2020;95(9):e239-e242.) in a sickle cell disease population undergoing mobilization/apheresis with plerixafor (20%).

SAEs of sickle cell anaemia with crisis and SAEs of acute chest syndrome that were considered related or possibly related to plerixafor occurred in 3 (5.2%) subjects and 1 (1.7%) subject, respectively.

Comment: the company provides published evidence that ‘sickle cell anaemia with crisis’ is known in association with the Plerixafor and the procedure; there is not additional comment.

Discontinuation of Plerixafor or granulocyte colony stimulating factor

One (1.7%) subject with transfusion-dependent thalassaemia discontinued granulocyte colony stimulating factor due to a Grade 1 AE of splenomegaly. The subject continued to receive plerixafor and completed mobilization. The event was considered related to granulocyte colony stimulating factor and resolved after [no. days removed to protect from personal protected data].

No subjects with transfusion-dependent thalassaemia discontinued plerixafor.

No subjects with sickle cell disease discontinued plerixafor.

Interruption of Plerixafor or granulocyte colony stimulating factor

Transfusion-dependent thalassaemia

Three (5.1%) subjects with transfusion-dependent thalassaemia had AEs (hypocalcaemia, diarrhoea, leucocytosis, and bone pain) that led to interruption of granulocyte colony stimulating factor and 1 (1.7%) subject had an AE (hypocalcaemia) that led to interruption of plerixafor. For all subjects, the events resolved and mobilization resumed.

Sickle cell disease

Two (3.4%) subjects with sickle cell disease had AEs that led to interruption of plerixafor: 1 subject with a Grade 3 SAE of acute chest syndrome and a Grade 1 AE of C-reactive protein (CRP) increased and 1 subject with a Grade 3 SAE of vascular device infection. For both subjects, the events resolved and mobilization resumed.

Overall comment on aspects of safety during mobilisation and apheresis:
aspects of safety reported for the mobilisation and apheresis procedures are known and are amenable to clinical management; there would not be particular concern.

Post-marketing data
Not applicable: other than this authorisation which has only very recently been granted, exa-cel has not yet been approved in any country or region for marketing. In the intervening period between GB CMA approval and the drafting of this public report, exa-cel is now approved in Bahrain for both TDT and SCD (02 Dec 2023) and is also approved in the US for SCD (08 Dec 2023).

Summary of clinical safety

Most harms encountered by subjects in studies 111 and 121 were in relation to mobilisation of cells from the bone marrow, apheresis and conditioning of bone marrow prior to administration of the engineered cells. Most adverse events occurred within 6 months of the transplantation procedure and declined thereafter. Adverse events associated with G-CSF, plerixafor, busulfan and the transplantation procedure in general are known and so may be anticipated and mitigated for.

Primary graft failure, secondary graft failure, graft rejection, acute graft-versus-host-disease and chronic graft-versus-host-disease have not been reported.

Subjects with transfusion-dependent β-thalassemia achieved neutrophil engraftment at a median of 29 days and platelet engraftment at a median of 44 days.

Subjects with sickle cell disease achieved neutrophil engraftment at a median of 27 days and platelet engraftment at a median of 35 days.

Prophylactic antibiotics and G-CSF were employed during the above periods.

The times reported for engraftment are consistent for subjects undergoing haematopoietic stem cell transplant.

Conclusion on clinical safety

Aspects of safety would be known to clinicians who are experienced in the bone marrow transplantation procedure and so may be managed accordingly.

Aspects of safety thus far described would not give rise to particular concern.

In the context of a novel product with a novel mechanism of action, however, there may be aspects of safety that have yet to reveal themselves such as new malignancies or pathologies of the blood-forming organs; these as-yet-unknown aspects of clinical safety may be addressed by an acceptable risk management plan; refer to the risk management assessor.

IV.6 Risk Management Plan (RMP)

The MAH has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance and risk minimisation measures have been proposed:

Longer time to platelet engraftment (Important identified risk)	
Evidence for linking the risk to the medicine	In the pivotal Phase 1/2/3 clinical study in subjects 12 to 35 years of age with TDT (Study 111) and SCD (Study 121), median time to platelet engraftment after CASGEVY infusion was comparatively longer than reported in allogeneic HSCT; however, it was consistent with the median time reported in other genetic therapies involving HSCT. There was no association observed between bleeding AEs and time to platelet engraftment after CASGEVY infusion. However, thrombocytopenia following myeloablative conditioning is a risk factor for serious bleeding-related complications, with the highest risk occurring prior to platelet engraftment. As such, longer time to platelet engraftment is considered and important identified risk.
Risk factors and risk groups	Following infusion with CASGEVY, subjects with TDT without a spleen (i.e., splenectomised) had an earlier median time to platelet engraftment than subjects with an intact spleen. This finding is similar to data from allogenic HSCT and other genetic therapies for β-thalassemia major.
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Sections 4.2 and 4.4: • Indication for treatment of patients with β-haemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of CASGEVY must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with β-hemoglobinopathies, as stated in SmPC Section 4.2. • Recommendations for monitoring platelet counts and managing symptoms of bleeding are provided in SmPC Section 4.4. PL Sections 2 and 4: • Advice to on how to identify symptoms of bleeding and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine Additional Risk Minimisation Measures • Patient Alert Card • Guide for Patients/Carers

Additional pharmacovigilance activities	• Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD aged 12 to 35 years • Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.
Neutrophil engraftment failure (Important potential risk)	
Evidence for linking the risk to the medicine	Neutrophil engraftment failure is considered an important potential risk because of the possibility for neutrophil engraftment failure to be an outcome of any myeloablation and bone marrow transplantation. Failure to achieve neutrophil engraftment would require a subsequent HSCT procedure with unmodified rescue $CD34^+$ stem cells, thereby negating beneficial effects of CASGEVY gene therapy. However, in the pivotal Phase 1/2/3 clinical studies in subjects 12 to 35 years of age with TDT (Study 111) and SCD (Study 121), there was no evidence of neutrophil engraftment failure after CASGEVY infusion, and this risk is considered potential.
Risk factors and risk groups	As no subjects with TDT or SCD failed to achieve neutrophil engraftment following CASGEVY infusion, no risk factors or risk groups were identified in the clinical programme.
Risk minimisation measures	<u>Routine Risk Minimisation Measures</u> SmPC Sections 4.2 and 4.4: • Indication for treatment of patients with β-haemoglobinopathies for whom HSCT is appropriate, as stated in SmPC Section 4.1. • Administration of CASGEVY must be performed in a treatment centre by physician(s) with experience in HSCT and in the treatment of patients with βhemoglobinopathies, as stated in SmPC Section 4.2. • Collection of unmodified rescue $CD34^+$ stem cells is required prior to myeloablative conditioning and infusion with CASGEVY, as outlined in SmPC Section 4.2. • Guidance for administering unmodified rescue cells in the event of neutrophil engraftment failure is provided in SmPC Sections 4.2 and 4.4. • Recommendations for monitoring neutrophil counts and managing infections are provided in SmPC Section 4.4. PL Sections 2 and 4: • Information on what to expect if engraftment fails is provided in PL Section 2. • Advice on how to identify symptoms of infection and when to contact the doctor is given in PL Sections 2 and 4. Restricted prescription medicine <u>Additional Risk Minimisation Measures</u> • Guide for Patients/Carers
Additional pharmacovigilance activities	• Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD ages 12 to 35 years • Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.
Gene editing-related oncogenesis (Important potential risk)	
Evidence for linking the risk to the medicine	Gene editing-related oncogenesis is considered an important risk as it is possible after Casgevy infusion. In the clinical programme, there have been no reports of blood cancers due to treatment with Casgevy and no potential identified in nonclinical and in silico studies; therefore, this risk is considered potential.
Risk factors and risk groups	There have been no reports of malignancy after Casgevy in follow-up of up to 4 years after Casgevy infusion; therefore, no risk factors or risk groups were identified in the clinical programme.
Risk minimisation measures	<u>Routine Risk Minimisation Measures</u> Restricted prescription medicine <u>Additional Risk Minimisation Measures</u> None

Additional pharmacovigilance activities	• Study 131 Long-term follow-up study in subjects with TDT and SCD • Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.
Medication error due to Casgevy storage and administration (Important potential risk)	
Evidence for linking the risk to the medicine	To date, there have been no reports of medication errors in the clinical programme. In the post-market setting, exa-cel will be handled and administered by experienced HCPs at authorised treatment centres who can perform and manage complex HSCT procedures. Exa-cel must be administered under controlled and specific preparation and handling conditions. Due to the importance of cell viability and administering a patient's own cells, medication error is a potential risk.
Risk factors and risk groups	To date, there have been no reports of medication error; therefore, no specific risk factors or risk groups were identified.
Risk minimisation measures	Routine Risk Minimisation Measures Restricted prescription medicine Additional Risk Minimisation Measures • Handling and Administration Guide
Additional pharmacovigilance activities	• Study 111 in subjects with TDT ages 12 to 35 years • Study 121 in subjects with SCD aged 12 to 35 years See Section II.C of this summary for an overview of the post-authorisation development plan.
Long-term safety and efficacy (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.4: • Recommendation for long-term follow up is provided in SmPC Section 4.4. PL Section 2: • Expectations for long-term monitoring are described in PL Section 2. Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 131 Long-term follow-up study in subjects with TDT and SCD • Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.
Pregnancy and lactation (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures SmPC Section 4.6: • Recommendations for contraception use, breastfeeding, and pregnancy, including a negative pregnancy test prior to the start of any treatment, are provided in SmPC Section 4.6. • CASGEVY must not be administered during pregnancy or breastfeeding due to risks associated with myeloablative conditioning, as stated in SmPC Section 4.6. The benefits of breastfeeding should be considered along with the mother's clinical need for CASGEVY and any potential effects on the breastfed child from CASGEVY or from the underlying maternal conditions. PL Section 2: • Expectations for use of contraception, pregnancy testing, and breastfeeding are described in PL Section 2. • Advice for talking to the doctor prior to starting treatment is given in PL Section 2. Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 131 Long-term follow-up study in subjects with TDT and SCD • Study 101 (PASS; pregnancy outcomes)

	See Section II.C of this summary for an overview of the post-authorisation development plan.
Use in patients >35 years of age (Missing information)	
Risk minimisation measures	Routine Risk Minimisation Measures Restricted prescription medicine Additional Risk Minimisation Measures None
Additional pharmacovigilance activities	• Study 101 (PASS) See Section II.C of this summary for an overview of the post-authorisation development plan.

AE: adverse event; HSCT: haematopoietic stem cell transplant; PASS: post-authorisation safety study; PL: Package Leaflet; SCD: sickle cell disease; SmPC: Summary of Product Characteristics; TDT: transfusion-dependent β-thalassemia

This is acceptable.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

1. Transfusion-dependent β-thalassemia

Disease or condition

β-thalassemia is an inherited autosomal recessive disorder caused by genetic mutations that reduce or eliminate the expression of β-globin resulting in ineffective erythropoiesis and haemolysis in the peripheral circulation. Only about 65% survive to 50 years of age; death is usually a result of heart failure.

Current management

People with transfusion-dependent β-thalassemia are anaemic and require frequent blood transfusions resulting in iron overload and end-organ damage that affects heart, liver, skeletal and endocrine systems. Iron overload occurs despite administration of iron chelating agents. Stem cell transplant from a healthy donor may be offered to those with significant disease.

Summary of favourable effects

There are 29 adults and 13 paediatric subjects (ages 12 < 18yrs) in the primary efficacy set now submitted by the company; the median age was 20yrs; 25 subjects had a β0/β0-like genotype and 30 subjects had an intact spleen.

For the 2 years before screening: the baseline median (range) annualised units of thalassaemia-related red blood cell transfusions per year was 35.0 (20.5 to 71.0) units and the

baseline median (range) annualized volume of thalassaemia-related red blood cell transfusions was 201.0 (115.2, 330.9) mL/kg per year.

39/42 subjects achieved the primary outcome by maintaining a weighted average Hb ≥9 g/dL without red blood cell transfusions for at least 12 consecutive months any time after exa-cel infusion.

For those who achieved the primary outcome:

- the median time to achieve 'free from transfusion' was (about) 1 month and the maximum time was (about) 3 months.
- the total duration of being transfusion-free ranged from (about) 13 to 24 months
- Mean HbF increased from trace concentrations at baseline to 10.8g /dL by month 6 and remained so for the duration of follow-up.

For the 3/42 subjects who did not achieve the primary outcome: there was a reduction in annualized red blood cell transfusion volume by at least 80%

Uncertainties and limitations about favourable effects

The design of the submitted study was single-arm and open-label; outcome for each subject was compared to his / her status prior to administration of Casgevy; the design of the study is associated with bias that may be unduly favourable towards the product.

Subjects enrolled were able to carry out normal activities without special care needs; efficacy in a less-able population has not been investigated.

Subjects in the primary efficacy set were between 12yrs to 35yrs old; the company intends to extend investigation to a younger age group; efficacy in an older age group has not been investigated / established.

Consistent long-term maintenance of efficacy has not yet been established.

Summary of unfavourable effects

Unfavourable effects reported by the company are, in the main, related to the auto-transplant procedure i.e. (i) cell mobilisation with granulocyte cell stimulation factor and plerixafor, (ii) apheresis / harvest of cells and (iii) conditioning of bone marrow with busulfan.

Unfavourable effects in relation to the procedure of autologous haematopoietic stem cell transplant are well known to the haematology physician with experience in this procedure; such effects may be anticipated and managed accordingly.

Uncertainties and limitations about unfavourable effects

The number of subjects exposed to Casgevy is small; knowledge of clinical safety is therefore limited and may only be improved by increased exposure; this may be addressed by a robust risk management plan.

The duration of efficacy is not yet established and may only become known with long-term follow-up.

Importance of favourable and unfavourable effects
There is high value attached to an outcome of being free of the need for regular red blood cell transfusions for those with transfusion-dependent β-thalassemia; the value is both personal (not being exposed to potential infectious agents in blood / blood products; no longer need to attend hospital for transfusions) and societal (less demand for blood and blood products; re-deployment of transfusion staff etc.).

Unfavourable effects appear to be mainly related to the transplantation procedure; these effects are not slight and should be a matter of discussion between the patient and the attending clinician.

The importance of long-term effects (new malignancy and new or worsening haematological disorders) is currently unknown; their potential should also a matter of discussion between the patient and the attending clinician.

Balance of benefits and risks
The benefit of being free of the need for regular blood transfusions is considered to outweigh the risks (though this will be a matter for the patient and clinician to decide upon).

The claimed indication is:
Treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

The overall benefit-risk balance of Casgevy in the claimed indication of transfusion-dependent β-thalassemia, as described, is considered to be positive.

2. Sickle cell disease

Disease or condition background
Sickle cell disease is caused by a single-nucleotide substitution in DNA resulting in valine replacing glutamic acid at position 6 of the β-globin chain of haemoglobin.

This form of haemoglobin - HbS - polymerises in the deoxygenated state causing distortion of the shape of red blood cells; these sickle cells have a reduced lifespan and may clump and block blood vessels resulting in painful crises, organ failure and early mortality. The most common causes of death are cardio-pulmonary, cerebrovascular and renal; there is a high risk of sudden death; the median age at death is 45 years.

Current management
Management of sickle cell disease is aimed at avoiding pain episodes, relieving symptoms and preventing complications. Subjects are advised to reduce the chances of a sickle crisis by maintaining hydration and keeping warm. Hydroxycarbamide (hydroxyurea), crizanlizumab or voxelotor have been shown to reduce sickling episodes. Management includes pain relief (both for the acute crisis and for chronic pain), prevention of infections and blood transfusions; stem cell transplant from a healthy donor may be considered for subjects who have significant symptoms and complications.

Main clinical studies
The company submits interim data from one clinical study: trial CTX001-121, data cut-off date on 16 Apr 2023; this trial has a single-arm, open-label design. 63 subjects have been enrolled. There are 43 subjects in the full analysis set (31 adults and 12 adolescents). There are 29 subjects in the primary efficacy set.

Subjects have been administered between (2.9×10^6) and (14.4×10^6) $CD34^+$ cells/kg. Subjects have been followed up for between 1.2 and 25.6 months (long-term follow-up will be conducted via trial 131).

Summary of favourable effects
The company reports on a primary efficacy set of 23 adult subjects and 6 adolescents; 28/29 subjects achieved the primary outcome by not experiencing any severe vaso-occlusive crisis for at least 12 consecutive months after exa-cel infusion.

For those who achieved the primary outcome: 27/28 subjects remained vaso-occlusive crisis free until the end of study date or the interim data cut date, whichever was earlier

All 29 subjects remained free from in-patient hospitalisation (sustained for at least 12 months after exa-cel infusion) for severe vaso-occlusive crises.

There were increases in mean total Hb and HbF concentrations for subjects in the primary efficacy set, which occurred early (Month 3) and were maintained over time.

Mean (SD) total Hb levels were 12.1 (1.3) g/dL at Month 3, increased to 12.7 (1.7) g/dL at Month 6 and were maintained ≥12 g/dL over the duration of follow-up.

All 29 (100%) subjects in the primary efficacy set sustained HbF ≥20% for at least 12 months.

Uncertainties and limitations about favourable effects
The design of the submitted study was single-arm and open-label; outcome for each subject was compared to his / her status prior to administration of Casgevy; the design of the study is associated with bias that may be unduly favourable towards the product.

Subjects enrolled were able to carry out normal activities without special care needs; efficacy in a less-able population has not been investigated.

Subjects in the primary efficacy set were all 12 to 35yrs old; the company intends to extend investigation to a younger paediatric age group; efficacy in an older age group has not been investigated / established.

Consistent long-term maintenance of efficacy beyond 36 months has not yet been established.

Summary of unfavourable effects
Unfavourable effects reported by the company are, in the main, related to the auto-transplant procedure i.e. (i) cell mobilisation with granulocyte cell stimulation factor, (ii) apheresis / harvest of cells and (iii) conditioning of bone marrow with busulfan.
Unfavourable effects in relation to the procedure of autologous haematopoietic stem cell transplant are well known to the haematology physician with experience in this procedure; such effects may be anticipated and managed accordingly.

Uncertainties and limitations about unfavourable effects
The number of subjects exposed to Casgevy is small; knowledge of clinical safety is therefore limited and may only be improved by increased exposure; this may be addressed by a robust risk management plan.

3 subjects had recurrence of crises that may / may not represent loss of efficacy.
The duration of efficacy is not yet established and may only become known with long-term follow-up.

Importance of favourable and unfavourable effects
There is high value attached to an outcome of reduction in pain severity / frequency and an outcome of reduction in the need for medicinal products currently indicated for the management of sickle cell disease because these medicinal products are associated with adverse effects. The value is both personal (reduction in need for pain relief) and societal (less demand for hospital admissions).

Unfavourable effects appear to be mainly related to the transplantation procedure; these effects are not slight and should be a matter of discussion between the patient and the attending clinician.

The importance of long-term effects (new malignancy and new or worsening haematological disorders) is currently unknown; their potential should also a matter of discussion between the patient and the attending clinician.

Balance of benefits and risks
The benefit of a reduction in severity and frequency of pain is considered to outweigh the risks (though this will be a matter for the patient and clinician to decide upon).

The claimed indication is:

Treatment of sickle cell disease in patients 12 years of age and older with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom haematopoeitic stem cell transplantation is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available.

The overall benefit-risk balance of Casgevy in the claimed indication of sickle cell disease, as described, is considered to be positive.

Casgevy has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

The grant or renewal that has been made is conditional upon the fulfilment of the following conditions:

Description	**Due date**
In order to confirm the efficacy and safety of exa-cel in patients with TDT aged 12 years and older, the Marketing Authorisation Holder (MAH) should submit the final clinical study report from the pivotal study, Study 111. The clinical study report should be submitted to the MHRA.	**08/2026**
In order to confirm the efficacy and safety of exa-cel in patients with severe SCD aged 12 years and older, the MAH should submit the final clinical study report from the pivotal study, Study 121. The clinical studyreport should be submitted to the MHRA.	**08/2026**
In order to confirm the efficacy and safety of exa-cel in patients with TDT and severe SCD aged 12 years and older, the MAH should submit an interim clinical study report from Study 111 and Study 121 subjects in Study 131 by end of August 2026.The MAH will also submit annual updates of study 131 until study completion (study follow up of patient will be for 15 years).	**08/2026**

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

Annex 1
Summary of fulfilment of the criteria for orphan drug designation
(*β thalassaemia intermedia and major*)

Product:	***Casgevy 4-13 × 10^6 cells/mL dispersion for infusion***
Active substance:	***exagamglogene autotemcel*** **(Autologous $CD34^+$ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene)**
Orphan Designation Number:	***PLGB 22352/0019/OD1***

Background:
This application was evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered fulfilled. Opinion on orphan status was made on the first-submitted report of the company. Please note the figures presented in this annex are as per those presented to the CHM, recent data is included in the main report.

Evaluation:

Orphan condition
The orphan condition is β thalassaemia intermedia and major.

Orphan indication
The treatment of transfusion-dependent β-thalassemia in patients 12 years of age and older for whom a human leukocyte antigen-matched related haematopoietic stem cell donor is appropriate and a human leukocyte antigen matched related haematopoietic stem cell donor is not available'

Life threatening/ debilitating condition
Current management of transfusion-dependent β-thalassemia involves regular red blood cell (RBC) transfusions, iron chelation therapy, allogeneic hematopoietic stem cell transplantation and use of Reblozyl (luspatercept). Reblozyl blocks the Smad2/3 signalling pathway that is overactive in subjects with thalassaemia; about 20% recipients show a 33% or more reduction in blood transfusion requirements.

Historically, patients with severe thalassemia syndromes often do not survive into adulthood without RBCtransfusions.

Transfusion therapy and iron chelation interventions improve lifespan and reduce the risk of co-morbidities yet are associated with multiple side effects and require lifelong adherence to treatment. About 30% of patients with transfusion-dependent β-thalassemia do not survive beyond age 35yrs despite access to adequate treatment

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects <1 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of treatment

During late fetal gestation, the predominant form of haemoglobin is fetal haemoglobin (HbF), which is composed of 2 α-globin chains and 2 γ-globin chains. Shortly before birth, there is a switch from HbF to HbA, where the γ-globin chains are replaced by β-globins. HbA normally accounts for >95% of the total haemoglobin in adults with only traces of HbF present.

β-thalassemia is an inherited autosomal recessive disorder caused by genetic mutations that reduce or eliminate the expression of β-globin; this results in a deficiency of oxygen-carrying HbA and an excess of unpaired α-globin chains; unpaired α-globin chains precipitate in cells so leading to destruction of erythroid precursors, ineffective erythropoiesis in bone marrow and peripheral haemolysis.

β-thalassemia major is a clinical diagnosis referring to a patient who has a severe form of the disease and requires lifelong chronic transfusions beginning within the first year of life; these subjects are unable to produce sufficient amounts of β-globin or HbA as the expression of γ-globin decreases.

β-thalassemia intermedia is a clinical diagnosis of a patient characterized by a less severe chronic anaemia and a more variable clinical phenotype although some patients develop a transfusion requirement as they reach adolescence or develop additional comorbidities. Patients who require regular blood transfusions based on their disease and clinical status are categorised as having 'transfusion-dependent β-thalassemia'.

Patients with transfusion-dependent β-thalassemia may be homozygous or heterozygous for the mutations that result in absent synthesis of β-globin (β0) or they may have a combination of mutations that lead to reduced β-globin (β+).

Current interventions

Current intervention management is with RBC transfusions and iron chelation medications throughout the patient's lifetime. Most patients will not survive past the age of 10 without regular blood transfusions. A list of current treatment methods approved in Great Britain is provided in Table 3.

The improvements in blood supply, transfusion protocols and the availability of multiple chelation formulations over the preceding decades has increased overall survival although comorbidities remain a significant concern in the transfusion-dependent β-thalassemia population. With current management: about 70% of patients with transfusion-dependent β-thalassemia are alive at 35 years of age.

Regular RBC transfusions lead to iron accumulation and overload that result in systemic organ damage. Complications include cardiomyopathy, liver fibrosis / cirrhosis and endocrinopathies.

Subjects also exhibit delayed growth during childhood, gallstones, cholecystitis, skeletal abnormalities, osteoporosis and reduced fertility; dyserythropoiesis causes bone marrow expansion and skeletal deformities of the bones; chronic anaemia leads to reduced growth and development; haemolysis leads to damage of the vasculature, thrombosis and pulmonary hypertension.

The most common cause of mortality in patients with transfusion-dependent β-thalassemia is cardiac failure related to iron overload. RBC transfusions carry the risk of exposure to infectious disease, transfusion reactions and alloimmunisation.

Table 3 describes current treatment methods approved in the Great Britain.

Table 3 Medicinal Products Approved For Management and Treatment of β-thalassemia

Product	Indication
Products supporting transfusion therapy	
Deferiprone (Ferriprox® [31], Deferiprone Lipomed® [32])	• Monotherapy is indicated for the treatment of iron overload in patients with thalassemia major when current chelation therapy is contraindicated or inadequate. • In combination with another chelator is indicated in patients with thalassemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction.
Deferasirox (Exjade® [33])	• Treatment of chronic iron overload due to frequent blood transfusions (≥7 mL/kg/month of packed red blood cells) in patients with β-thalassemia major aged 6 years and older.
Deseferrioxamine Mesilate® [34]	• Treatment of iron overload. Monotherapy iron chelation treatment of chronic iron overload
Products for the treatment of βthalassemia	
*Reblozyl (luspatercept)[35]	• Treatment of transfusion-dependent anemia associated with β-thalassemia

Source: References [31-35]
*Not yet marketed in Great Britain

Justification of significant benefit
The MAH reports on 27 subjects who needed repeated RBC transfusions and who were administered the current product in submitted study 111. 24/27 subjects maintained a weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time after exa-cel (casgevy) infusion; The MAH claims clinical efficacy.

Exa-cel offers the significant benefit of improved efficacy over existing therapies by providing a 1-time functional cure that eliminates or reduces the need for frequent RBC transfusions. It is expected that the reduction in RBC transfusions may reduce iron overload and patients may be able to reduce or eliminate the use of iron chelation therapies.

Allo-HSCT is the only approved (potentially) curative treatment option but its use is limited by the need for an HLA-matched donor i.e. a matched sibling donor before iron overload due to the association of iron overload with long-term complications. Long-term complications include chronic graft versus host disease, secondary malignancy risk related to multi-agent conditioning and infections.

Some patients may pursue a matched unrelated allogeneic or an umbilical cord stem cell transplant yet these experimental approaches have not yielded long-term outcomes comparable to matched related transplants.

Transfusion therapy requires access to a transfusion centre, cross-matching and time spent in treatment suites to receive the appropriate therapy; transfusions are associated with risks of

infectious disease, alloimmunization and transfusion reactions. Repeated RBC transfusions are also associated with iron overload in β-thalassemia patients and contribute to many of the co-morbidities that affect survival and quality of life.

Iron chelation medications are effective at reducing iron overload; the availability of oral chelation drugs has significantly improved survival. All 3 available iron chelation agents (deferasirox, deferiprone, and deferoxamine) require regular administration (up to 3 times daily) and have significant side effect profiles that can include gastrointestinal, hepatic, renal, haematopoietic, auditory, ocular and bone toxicities. These side effects can limit the ability to administer the products resulting in continued iron loading and consequences. Even with the availability of oral chelators, compliance with lifetime therapy remains a challenge in specific patients and age groups.

In a pivotal trial: 10% of subjects exposed to Reblozyl (luspatercept) achieved transfusion independence during any 8-week interval compared with 1.8% in the placebo arm. 4% of patients receiving luspatercept (and 0 patients receiving placebo) achieved Hb > 9g/dL and absence of transfusions for 12 consecutive months.

Luspatercept also has the risk of thromboembolic events and hypertension and is only indicated in adults.

Methods for the treatment of the orphan condition already exist in GB. Suitable justification has been provided that *Casgevy* provides a significant benefit to those affected by the condition as specified in the orphan indication.

Conclusion: It may be accepted that significant benefit over existing methods has been demonstrated.

Conclusion on acceptability of orphan designation
The MAH has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: 15 November 2023

Annex 2
Summary of fulfilment of the criteria for orphan drug designation
(*Sickle cell disease*)

Product:	***Casgevy 4-13 × 10^6 cells/mL dispersion for infusion***
Active substance:	***(Autologous $CD34^+$ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene)***
Orphan Designation Number:	***PLGB 22352/0019/OD2***

Background:
This application was evaluated for fulfilment of orphan designation criteria by the Commission on Human Medicines (CHM) and the designation criteria were considered fulfilled. Opinion on orphan status was made on the first-submitted report of the company. Please note the figures presented in this annex are as per those presented to the CHM, recent data is included in the main report.

Evaluation:

Orphan condition
The orphan condition is sickle cell disease.

Orphan indication
Treatment of sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises who have the βS/βS, βS/β+ or βS/β0 genotype, for whom a human leukocyte antigen (HLA)-matched related haematopoietic stem cell (HSC) donor is not available.

Life threatening/ debilitating condition
Sickle cell disease is a chronic disease characterised by recurrent acute vaso-occlusive crises that lead to acute pain, haemolysis, anaemia, progressive tissue injury and organ dysfunction.

The disease affects many organs, causing acute and chronic complications such as acute chest syndrome, stroke, priapism, splenic sequestration, osteonecrosis, renal failure, pulmonary hypertension, liver disease, bone damage, increased susceptibility to infections, fatigue and progressive cognitive decline.

About a third of people with sickle cell disease develop chronic kidney disease / end-stage renal failure.

For many patients, pain becomes chronic and contributes to significant morbidity and poor quality of life.

People with sickle cell disease have a reduced life-expectancy.

Prevalence of the Condition in Great Britain (GB)
Suitable evidence has been provided that demonstrates that, at the time of orphan designation, the condition affects 2.17 – 3.2 in 10,000 people in GB. This does not exceed the upper limit of prevalence for orphan designation, which is 5 in 10,000 people in GB.

Existing methods of treatment
The following methods for the management and treatment of sickle cell disease have been identified:

Table 2 Medicinal Products Approved For Management and Treatment Of Sickle Cell Disease

Product	Indication
Siklos® (hydroxycarbamide)[56]	• Prevention of recurrent painful VOCs including acute chest syndrome in adults, adolescents, and children older than 2 years suffering from symptomatic sickle cell syndrome
Xromi® (hydroxycarbamide)[57]	• Prevention of vaso-occlusive complications of SCD in patients over 2 years of age
Adakveo® (crizanlizumab)[58]	• Prevention of recurrent VOCs in sickle cell disease patients aged 16 years and older. It can be given as an add-on therapy to HC/HU or as monotherapy in patients for whom HC/HU is inappropriate or inadequate
Oxbryta® (voxeletor)[59]	• Treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide

Sources: References[56-59]
HC: hydroxycarbamide; HU: hydroxyurea; SCD: sickle cell disease; VOC: vaso-occlusive crisis.
Note: No treatments are curative.

Other treatments for sickle cell disease include allogeneic haematopoeitic stem cell transplantation and RBC transfusions.

Justification of significant benefit

Study 121 enrolled patients with severe sickle cell disease; patients were administered exa-cel (Casgevy). The interim report for study 121 reported that 16/17 (94.1%) subjects in the primary efficacy set achieved the primary outcome of not experiencing any severe vaso-occlusive crisis for at least 12 consecutive months after exa-cel (casgevy) infusion.

To note that 15 of the 16 subjects in the primary efficacy set who had achieved the primary outcome in study 121 remained vaso-occlusive crisis free until the end of study date or the interim data cut date, whichever was earlier.

In relation to other lines of management:
Allogeneic haematopoietic stem cell transplant has the potential to be curative yet is limited to the 18% of patients with sickle cell disease who have a suitable matched related sibling donor. Haematopoietic stem cell transplant is associated with significant risks including transplant-related mortality, primary and secondary graft failure, acute and chronic graft-versus-host-disease and other severe complications related to the need for immunosuppressive therapies.

RBC transfusions do not offer a cure yet are used to manage acute and chronic complications of sickle cell disease. The response to transfusion therapy is variable. A single-centre retrospective study of 52 patients in a chronic (≥1 year duration) automated exchange transfusion programme reported on a limited response whilst in the East London Newborn

Cohort enrolling children and young adults with sickle cell disease, 31/53 patients receiving chronic transfusions had at least 1 vaso-occlusive crisis during 2015 to 2018 and 34/53 patients had any acute complication of sickle cell disease during the same period. Further: long-term transfusion therapy can result in iron overload (responsible for about 11% deaths in sickle cell disease), alloimmunisation (present in about 30% patients and associated with haemolytic transfusion reactions) and transmission of transfusion-associated infections.

Hydroxyurea is a ribonucleotide reductase inhibitor that promotes production of HbF up to 40% of total Hb. A study has reported that median rates for vaso-occlusive crises were 2.5 crises per year in the hydroxyurea group versus 4.5 crises per year in the placebo group. When only crises severe enough to cause hospitalization were considered, the median annual rates were 1.0 and 2.4, respectively ($p \leq 0.001$). Hydroxyurea is known to have myelosuppressive effects; patients receiving hydroxyurea must have regular monitoring of blood counts and must discontinue treatment if bone marrow function is markedly depressed; the most common sign of myelosuppression is neutropenia. Hydroxyurea is contraindicated for patients with severe hepatic or renal impairment and should be used with caution in patients with moderate impairment.

Oxbryta (voxelotor) is a small-molecule HbS polymerization inhibitor and was approved in the UK in July 2022 for patients aged 12 years and older. Voxelotor is indicated for the treatment of haemolytic anemia (Hb ≤10.5 g/dL) in adult and paediatric patients 12 years and older with sickle cell disease. Voxelotor can be administered alone or in combination with hydroxyurea. Exposure to voxelotor results in a decrease in haemolysis markers (concentration of 'indirect' bilirubin in serum, serum lactate dehydrogenase activity and numbers of circulating reticulocytes). In a recent trial: 46/90 patients achieved a mean Hb increase of at least 1.0 g/dL with voxelotor at 24 weeks compared with 6/92 in the placebo group.

Adakveo (crizanlizumab) is a humanized monoclonal antibody P-selectin blocker that reduces the frequency of vaso-occlusive crises. It was approved in the UK in January 2021 to prevent recurrent vaso-occlusive crises in patients with sickle cell disease ages 16 years and older. Blocking P-selectin on the surface of the activated endothelium and leukocytes has been shown in vitro and in animal models to reduce interactions between endothelial cells, platelets, RBCs and leukocytes, thereby decreasing the likelihood of vaso-occlusion. The SUSTAIN trial found that the median rate of sickle cell-related vaso-occlusive crises per year was 1.63 for those treated with high-dose crizanlizumab compared with 2.98 for those treated with placebo, representing a 45% reduction in annual vaso-occlusive crises. There was also a 41.8% reduction in annual rate of days hospitalised.

Other authorised therapies address some of the disease symptoms but do not offer a functional cure for sickle cell disease. Further, they are chronic therapies that require prolonged, regular dosing, and are associated with substantial safety, patient compliance, and tolerability issues.

Methods for the treatment of the orphan condition already exist in GB. Suitable justification has been provided that Casgevy provides a significant benefit to those affected by the condition as specified in the orphan indication.

Conclusion:

Conclusion on acceptability of orphan designation
The MAH has demonstrated fulfilment of the criteria for approval as an orphan medicinal product.

All medicines that gain an orphan marketing authorisation from the UK Licensing Authority are listed on its publicly available Orphan Register until the end of the market exclusivity period. The authorised orphan indication defines the scope of orphan market exclusivity.

Decision: Grant

Date: *15 November 2023*

Annex 3 – Handling and Administration Guide

Handling and Administration Guide

Important Information for Healthcare Professionals About CASGEVY®▼ (exagamglogene autotemcel)

CASGEVY (exagamglogene autotemcel) is a genetically modified autologous CD34⁺ cell enriched population that contains human haematopoietic stem and progenitor cells (HSPCs) edited *ex vivo* by CRISPR/Cas9 at the erythroid-specific enhancer region of the *BCL11A* gene.

CASGEVY is approved for the following indications:

- Treatment of transfusion dependent β-thalassemia (TDT) in patients 12 years of age and older for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related HSC donor is not available.
- Treatment of sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs) who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype, for whom haematopoietic stem cell transplantation is appropriate and a human leukocyte antigen matched related HSC donor is not available.

This guide provides important information on the handling and administration of CASGEVY.

It does not contain all the information about this product. Please always consult the Summary of Product Characteristics (SmPC) for full prescribing information.

▼ **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions as described in Section 8 of this Guide.**

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casgevy▼ (exagamglogene autotemcel)

1. Precautions to take before handling and administering CASGEVY

- This medicinal product contains human blood cells. Healthcare professionals handling CASGEVY should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

2. Receipt and storage of CASGEVY

- CASGEVY is shipped to the treatment centre frozen in the vapour phase of liquid nitrogen.
- Confirm patient identifiers on the product label(s) and lot information sheet.
- If there are any concerns about the product or packaging upon receipt, contact Vertex at +44 (0) 800-028-2616.
- Store in the vapour phase of liquid nitrogen at ≤ –135 °C until ready for thaw and administration.

3. How to prepare for CASGEVY infusion

- Coordinate the timing of CASGEVY thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CASGEVY is available for infusion when the patient is ready, as CASGEVY must be administered within 20 minutes of thawing the vial.
- Assemble supplies needed to thaw and withdraw the product from the vial(s). With the exception of the water bath, these supplies are single use. Assemble sufficient supplies for each vial to be administered:
  - Water bath
  - Alcohol swabs
  - Vial adapter (to allow for needle-less extraction)
  - 18 micron stainless steel filter
  - 30 mL luer-lock syringe
  - 0.9% sodium chloride (saline, 5 to 10 mL needed for each vial)
  - 10 mL luer-lock syringe for saline rinse

4. How to check CASGEVY vials prior to thawing

- Before thaw, **confirm the patient's identity matches the patient information on the CASGEVY vial(s).**
- Do not remove the CASGEVY vials from cryo storage if the information on the patient specific label does not match the intended patient.
- A dose of CASGEVY may be contained in one or more cryopreserved patient specific vial(s). **Account for all vials and confirm each vial is within the expiry date using the accompanying lot information sheet.**
- Inspect the vial(s) for any breaks or cracks prior to thawing. If a vial is compromised, do not infuse the contents. Call Vertex at +44 (0) 800-028-2616.

5. How to thaw CASGEVY

- When the dose consists of multiple vials, thaw and administer one vial at a time. While thawing a vial, remaining vials must remain in cryo storage at ≤ –135 °C.
- Thaw each vial at 37 °C using a water bath. Ensure water bath temperature does not exceed 40 °C.
- Thaw each vial holding the vial neck, gently agitating clockwise and counterclockwise. This can take between 10 to 15 minutes.
- Do not leave vial unattended during thaw.
- Thawing is complete when ice crystals are no longer visible in the vial.
- Remove vial from water bath immediately once thawed.
- The thawed product should appear as a translucent cell dispersion, which may contain visible particles.
- Infuse within 20 minutes of thaw.

6. How to administer CASGEVY

CASGEVY is for autologous use only. The patient's identity must match the patient identifiers on the CASGEVY vial(s). Do not infuse CASGEVY if the information on the patient specific label does not match the intended patient.

A patient's dose may consist of multiple vials. All vials must be administered. The entire volume of each vial provided should be infused. If more than one vial is provided, administer each vial completely before proceeding to thaw and infuse the next vial.

- After completion of the myeloablative conditioning regimen, a minimum of 48 hours or the length of time taken for elimination of the conditioning agent (whichever is longer) must elapse before CASGEVY infusion. CASGEVY must be administered within 7 days of the last dose of myeloablative conditioning.
- It is recommended that pre-medication with paracetamol and diphenhydramine, or equivalent medicinal products, be administered per institutional guidelines, before the infusion of CASGEVY, to reduce the possibility of a hypersensitivity reaction. CASGEVY is administered as an intravenous bolus through a central venous catheter. The total volume of CASGEVY administered within one hour must not exceed 2.6 mL/kg.
- Please consult the Summary of Product Characteristics (SmPC) Section 6.6 for information on attaching the vial adapter and filter as well as withdrawal of CASGEVY from the vial. The optional product/patient identifier label can be peeled from the lot information sheet and affixed to the syringe.
- CASGEVY must be administered within 20 minutes of product thaw.
- Perform a **two-person confirmation and verification of patient's identification at the bedside prior to the infusion of each vial(s).**
- Do not use an inline filter when infusing CASGEVY.
- After administration of each vial of CASGEVY, flush the primary line with 0.9% sodium chloride solution.

7. Additional information regarding mobilisation, apheresis, and pre-treatment conditioning

Mobilisation and apheresis

- Patients are required to undergo CD34+ HSPC mobilisation followed by apheresis to isolate the CD34+ cells for medicinal product manufacturing.
- Each mobilisation and apheresis cycle must be separated by a minimum of 14 days.
- In patients with TDT:
  - Prior to apheresis procedure, it is recommended that patients receive red blood cell (RBC) transfusion(s) with a goal to maintain total haemoglobin (Hb) concentration ≥ 11 g/dL.
  - Granulocyte colony-stimulating factor (G-CSF) dosage should be reduced for splenectomised patients per local/institutional guidelines.
- In patients with SCD:
  - Prior to apheresis it is recommended that patients receive RBC exchange or simple transfusions to achieve target HbS levels < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL, for a minimum of 8 weeks before the planned start of mobilisation.
  - At initiation of RBC exchange or simple transfusions, discontinue disease modifying therapies (e.g., hydroxyurea/hydroxycarbamide, crizanlizumab, voxelotor).
  - GCSF should not be administered for mobilisation in patients with SCD.

Pretreatment conditioning

- Full myeloablative conditioning must be administered before infusion of CASGEVY. Consult prescribing information for the myeloablative conditioning agent(s) prior to treatment.
- If busulfan is used as a single agent for myeloablation, there are important considerations regarding administration. Key points are outlined below. Please refer to the UK Public Assessment Report for further details.
  - Busulfan should be administered for 4 consecutive days intravenously via a central venous catheter at a starting dose of 3.2 mg/kg/day once daily or 0.8 mg/kg every 6 hours. Busulfan plasma levels should be measured by serial blood sampling and the dose adjusted to maintain exposure in the target range:
    - For once daily dosing, the four-day target cumulative busulfan exposure of 82 mg*h/L (range 74 to 90 mg*h/L), corresponding to $AUC_{0\text{-}24h}$ of 5000 µM*min (range: 4500 to 5500 µM*min).
    - For dosing every 6 hours, the four-day target cumulative busulfan exposure of 74 mg*h/L (range 59 to 89 mg*h/L), corresponding to $AUC_{0\text{-}6h}$ of 1125 µM*min (range 900 to 1350 µM*min).

- In patients with TDT, if transfusions were not continued to maintain Hb at ≥ 11 g/dL after apheresis, reinitiate at least 60 days prior to myeloablative conditioning to achieve the same target total Hb levels.
- In patients with SCD:
  - If exchange or simple transfusions were paused after apheresis, reinstate for at least the 8 weeks prior to the start of myeloablative conditioning, to achieve the same target total Hb and HbS (%) levels.
  - At initiation of RBC exchanges or simple transfusions, discontinue disease modifying therapies (e.g., hydroxyurea/hydroxycarbamide, crizanlizumab, voxelotor).
- Iron chelation therapy should be stopped at least 7 days prior to myeloablative conditioning.
- Prophylaxis for seizures should also be considered. Refer to the prescribing information of the conditioning agent used for information on drug interactions.
- Prophylaxis for hepatic venoocclusive disease (VOD)/hepatic sinusoidal obstruction syndrome should be considered, per institutional guidelines.

8. Reporting of adverse drug reactions (ADRs)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:

- The Yellow Card website https://yellowcard.mhra.gov.uk/.
- The free Yellow Card app available from the Apple App Store or Google Play Store.

Any suspected adverse reactions to CASGEVY should also be reported to Vertex Pharmaceuticals (UK) Ltd on +44 (0) 800-028-2616 or at vertexmedicalinfo@vrtx.com.

Annex 4 – Patient Alert Card

Patient Name	
Date of CASGEVY infusion	
CASGEVY Patient ID number	

CASGEVY Treating Physician Name	
CASGEVY Treating Physician Contact Information	
CASGEVY Treating Physician Contact Information After Hours	

VERTEX

Patient Alert Card

Important information regarding CASGEVY® ▼ (exagamglogene autotemcel)

Carry this card with you at all times (duplicates or pictures kept on your smart device are recommended). Show it to any doctor who sees you and when you go to any hospital or healthcare clinic.

Tell any healthcare provider who sees you that you have been treated with CASGEVY (exagamglogene autotemcel).

As you have been treated with CASGEVY, you should never donate blood, organs, tissues or cells.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. If you experience any side effects after your treatment with CASGEVY, talk to your doctor or nurse. You can also report side effects directly via the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/.

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casgevy▼ (exagamglogene autotemcel)

Annex 5 – Guide for Patients and Carers

Guide for Patients and Carers

Important Information About CASGEVY®▼ (exagamglogene autotemcel)

CASGEVY (exagamglogene autotemcel) is a one-time gene therapy that can be used to treat:

- People 12 years of age and older with beta thalassemia who need regular blood transfusions.
- People 12 years of age and older with sickle cell disease and frequent painful crises (called vaso-occlusive crises) who have the β^S/β^S, β^S/β^+ or β^S/β^0 genotype.

Carers: Please support the patient you are caring for in understanding this guide.

This Guide provides information on two important side effects of CASGEVY:

- Prolonged period of time after treatment with CASGEVY for the body to produce adequate levels of platelets (known as longer time to platelet engraftment). Platelets are the blood cells that stick together to stop bleeding. When platelet levels are inadequate, there is an increased risk of bleeding.

- The possibility that after treatment with CASGEVY neutrophils fail to re-establish in the body (known as neutrophil engraftment failure). Neutrophils are a type of white blood cell that protects the body from infections. A failure to re-establish these cells increases the risk of infections.

This Guide does not contain all the information about CASGEVY. Please read the Patient Information Leaflet and talk with your doctor for further information.

▼ **This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects that you, or the person you are caring for, experience from being treated with CASGEVY (see Section 5 of this Guide).**

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casgevy▼ (exagamglogene autotemcel)

1. About CASGEVY

CASGEVY is a one-time gene therapy. In the case of CASGEVY, a change is made in a specific gene that controls a special type of haemoglobin called fetal haemoglobin (HbF). This change increases the production of HbF. Having more HbF increases overall haemoglobin levels in the body and has been shown to improve the production and function of red blood cells in carrying oxygen through your body.

CASGEVY is made specifically for each patient, using the patient's own blood stem cells.

Glossary	
Stem cells	Special type of cell that can develop into many different cell types, such as blood cells
Blood stem cells	A type of stem cell found in your bone marrow that can develop into red blood cells, platelets, or white blood cells
Platelets	Blood cells that stick together to stop bleeding
White blood cells	Blood cells that are a part of the immune system. They are important for protecting the body from infection
Neutrophils	A type of white blood cell
Red blood cell	A type of blood cell that carries oxygen throughout the body

To produce CASGEVY for you, your blood stem cells are collected from you and are genetically changed outside of your body. The genetically changed cells are then given back to you through a haematopoietic (hee-MA-toh-poy-EH-tik) stem cell transplant, also called a bone marrow transplant. A haematopoietic stem cell transplant is a treatment that replaces unhealthy blood stem cells with the genetically changed healthy cells. Some of your original stem cells will not be genetically changed and will be stored as "rescue cells" in case there is a problem with your treatment.

Before treatment with CASGEVY, you will go through two pre-treatment stages.

- Stem Cell Mobilisation: In this stage, you will be given medicines that move the blood stem cells from the bone marrow into the blood stream so they can be more easily collected from the body via procedure called apheresis. Apheresis is a process in which a portion of the blood is temporarily removed from the body to collect blood stem cells. After the cells are collected, the person's blood is returned to their body. It is possible that you may need to repeat this stage if not enough cells are collected the first time. The cells collected during mobilisation will be used to make CASGEVY which will be given to you after conditioning.

- Conditioning: In this stage, you will be given a conditioning medicine (a type of chemotherapy) as an infusion into a vein for a few days in the hospital. This will remove most of your blood stem cells that are not working properly from the bone marrow to create space for the genetically changed blood stem cells (CASGEVY) received on the transplant day to grow.

2. Important side effects

After being given CASGEVY, you will have fewer blood cells in your body until the genetically changed stem cells received on transplant day are successfully accepted by your body and begin to grow (or engraft). This means that, at first, you will have higher risk of bleeding (due to low platelets) or infection (due to low neutrophils) until these cells re-establish themselves.

While in the hospital, your doctor will monitor your blood cell counts, including your platelets and neutrophils (white blood cells), with regular blood tests. You will stay in the hospital until your neutrophils have returned to a level that enables you to fight infection.

There is a possibility that after treatment with CASGEVY neutrophils fail to re-establish in the body. If this happens, it may be necessary to return to your body your own untreated stem cells (rescue cells) that were collected and stored before you received CASGEVY. If this is the case, you will not receive any benefit from CASGEVY treatment.

Once you leave the hospital, your platelet levels may still not have returned to normal. There may be a prolonged period of time after treatment with CASGEVY for your body to produce adequate levels of platelets. Your doctor will continue to monitor your platelet counts with blood tests after you are discharged from the hospital. Until your platelets return to an adequate level, you will be at risk for bleeding. It is very important that you watch for any symptoms that could be a result of bleeding.

Some symptoms of bleeding are listed below. However, this list does not cover every symptom of bleeding.

Tell your doctor right away if you have any symptoms of bleeding, even if not listed here:

- Abnormal bruising
- Prolonged bleeding
- Severe headache
- Bleeding without injury such as:
  - Nosebleeds
  - Bleeding from gums
  - Blood in your urine, stool, or vomit
  - Coughing up blood

When you are leaving the hospital, your doctor will give you a Patient Alert Card. Keep this card with you at all times to remind you of the symptoms of bleeding, and show the card to all your doctors.

This Guide does not contain all the information about CASGEVY. Please read the Patient Information Leaflet and talk with your doctor for further information.

3. Other important information

As CASGEVY is a gene therapy, once you have been treated with CASGEVY, you should never donate blood, organs, tissues, or cells.

4. CASGEVY long-term study

As with all new treatments, there is limited information on the effects of CASGEVY over the long term. A study has therefore been set up to follow over a longer period of time patients who have received CASGEVY.

If you do take part in this study, you **will not** be required to undergo any additional tests, treatments or visits to the doctor beyond your routine tests, treatments, or visits. If you choose not to take part, **your choice will not affect the care that you receive**, and your doctor will continue to treat you in a way that is in your best medical interests. Please talk to the doctor who treated you with CASGEVY to find out more about the study.

5. Reporting side effects

If you, or the person you are caring for, experience any side effects after your treatment with CASGEVY, talk to your doctor or nurse. This includes any side effects, not just those addressed in this Guide.

You can also report side effects directly via the Yellow Card Scheme at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects, you are helping to provide more information on the safety of this treatment.

Any suspected adverse reactions to CASGEVY should also be reported to Vertex Pharmaceuticals (UK) Ltd on +44 (0) 800-028-2616 or at vertexmedicalinfo@vrtx.com.