Exa-cel for Transfusion-dependent β-thalassaemia - Assessment and Work up

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1.0 Introduction

1.1 Exa-cel is indicated for the treatment of transfusion-dependent β-thalassaemia 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.

2.0 Scope

2.1 This document describes the process involved from the initial assessment of suitability for gene therapy, through to the point of admission.

3.0 Abbreviations & Definitions

BMT CNS: Bone Marrow Transplant Clinical Nurse Specialists

HPC: Haematopoietic Progenitor Cell

HSCT: Haematopoietic Stem Cell Transplantation Programme

WCTU: Wolfson Cellular Therapy Unit

4.0 Stakeholders/Responsibilities

Personnel involved include the:-

- Haematology, Red Cell or Paediatric Oncology Consultant referring the patient for gene therapy,
- Clinicians from the disease specific teams at Specialist Registrar (SpR) or Consultant level.
- The Bone Marrow Transplant Clinical Nurse Specialists (CNSs)
- Additional nursing staff that have undergone apheresis training.

5.0 Related Documents

Reference to other controlled documents required to perform the procedure, such as forms. These documents shall be hyperlinked to ensure easy-access and availability.

6.0 Assessment of patient fitness for treatment with Exa-cel:

Patients should be screened for their fitness and suitability of treatment. The criteria will evolve as increased clinical experience is accrued. At the current time it is advised that when assessing patients, we consider the study criteria:

6.1 Patient 12 to 35 years of age

6.2 Able to give informed consent. Alternatively, for patients who do not yet have competence, or who have long-term loss of capacity to provide informed consent themselves, decision to proceed has been made after careful consideration of patient's best interests, and local frameworks followed to document this.

6.3 Genotyping for thalassaemia (*HBA1 HBA2* and *HBB* loci) including alpha multiplications have been confirmed. Demonstrating a diagnosis of transfusion-dependent β-thalassaemia (TDT) as defined by:

- Documented homozygous β-thalassaemia (including B+ or B0 / B0-like) or compound heterozygous β-thalassaemia including β-thalassaemia /haemoglobin E (HbE) and a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the prior 2 years

6.4 Karnofsky performance status of ≥80% for patients ≥16 years of age. Lansky performance status of ≥80% for patients <16 years of age.

6.5 Fit for myeloablative autologous stem cell transplant on the judgement of transplant physician with experience of transplantation for haemoglobinopathies. This will be assessed post workup investigations to confirm absence of:

- a known and available fully matched HLA related donor.
- Prior allogeneic HSCT.
- Patients with associated α-thalassaemia and >1 alpha deletion or alpha multiplications. Patients with sickle cell β-thalassaemia variant.
- Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the attending physician.
- White blood cell count $<3\times10^9$/L or platelet count $<50\times10^9$/L not related to hypersplenism.
- History of a significant bleeding disorder.
- Any prior or current malignancy or myeloproliferative disorder or a significant immunodeficiency disorder
- Advanced liver disease; in the CTX111 study this was defined as:

    a) Aspartate transaminase (AST), alanine transaminase (ALT) >3 × the upper limit of normal (ULN), or conjugated bilirubin value >2.5 × ULN, or:

b) Baseline prothrombin time (International Normalized Ratio; INR) >1.5 × ULN, or

c) History of cirrhosis or any evidence of bridging fibrosis on a prior liver biopsy, if available

d) Patients with active hepatitis infection.

e) Patients with history of chronic hepatitis infection are also excluded unless liver biopsy within 3 months prior to or at screening shows no evidence of bridging fibrosis or cirrhosis

f) Liver iron content (LIC) ≥15 mg Fe/g dry weight on R2 or T2* MRI of liver unless liver biopsy within three months prior to or at screening shows no evidence of bridging fibrosis or cirrhosis.

- A cardiac T2* <10 ms by MRI or left ventricular ejection fraction (LVEF) <45% by echocardiogram
- Baseline estimated glomerular filtration rate <60 mL/min/1.73 m2.
- Diffusion capacity of the lungs for carbon monoxide (TLco) <50% of predicted (corrected for haemoglobin and/or alveolar volume).
- Prior treatment with gene therapy/editing product.
- Intolerance, contraindication, or known sensitivity to plerixafor, G-CSF products (e.g. filgrastim), or Busulfan. Prior anaphylaxis with excipients of Exa-cel product (dimethyl sulfoxide [DMSO], Dextran).

6.6 Agreement to use effective contraception from the point of mobilisation until at least 6 months after Exa-cel infusion.

7.0 Work-up investigations and processes

7.1 Patient approval steps:

1) Red cell consultant presents at HCC MDT with representation from local HCC gene editing team present, if consensus for treatment with Exa-cel reached then refer to the NHP
2) NHP discussion and approval where appropriate
3) Discussion at UK Haemoglobinopathy transplant group for cases where suitability for exa-cel treatment is unclear e.g. abnormal organ function.

7.2 Pre-transplant tests (generally investigations should be completed within the 3 months prior to apheresis).

- Routine bloods and infectious disease markers (IDMs) as per local policies and Vertex Technical Requirements
- Globin gene sequencing (*HBA1, HBA2* and *HBB*) (if not already completed)
- Blood group genotype or extended phenotype, and RBC Ab screen
- HRCT chest- if any previous lung pathology
- Lung function
- ECG
- Cardiac echo, with pulmonary arterial pressure estimation
- Isotopic GFR or GFR as per local policy
- Protein: creatinine ratio (urine)
- T2* MRI heart and Ferriscan® or T2* MRI liver - aiming for patient's tissue iron to be <7mg/g. . Iron chelation should be optimised with local red cell team
- Liver Fibroscan or locally available non-invasive liver assessment e.g., MR liver

7.3 Fertility

Males would be offered sperm cryopreservation routinely where available and/or appropriately counselled. Female patients will be offered fertility preservation assessment and counselled to locally available options. If gamete collection is not possible consideration should be given to storage of gonadal tissue after appropriate counselling. Clarification of the length of time gametes or tissues can be stored for, and options for storage at the end of these periods should be discussed with each patient.

7.4 Patient assessment:

Compliance with eligibility criteria should be confirmed between local HCC gene editing centre and local HCC MDT for treatment with Exa-cel. If a positive recommendation is forthcoming then further approval should be sort through the NHP. Prior to these referrals patients should be comprehensively counselled to the benefits and risks of treatment with myeloablative chemotherapy such as Busulfan and treatment with Exa-cel including the risk of off target gene editing, the unknown long term graft stability of edited HSCs and the risk of secondary malignancies. Patients should be counselled with the most current relevant data. Counselling should be delivered by red cell and transplant physicians with relevant experience. Patients should also have the opportunity to discuss the treatment plan and receive support from a psychologist with relevant experience. Furthermore, ongoing access to such a psychologist is central to delivering good care, and ensuring inappropriate patients do not proceed further with these therapies.

Only once screening investigations have been carried out, approvals obtained and a patient is clear they want to proceed should they progress on to mobilisation.

Psychological support should remain available during mobilisation, the transplant process and beyond.

7.5 Concomitant medications during treatment

7.5.1 Iron Chelation:

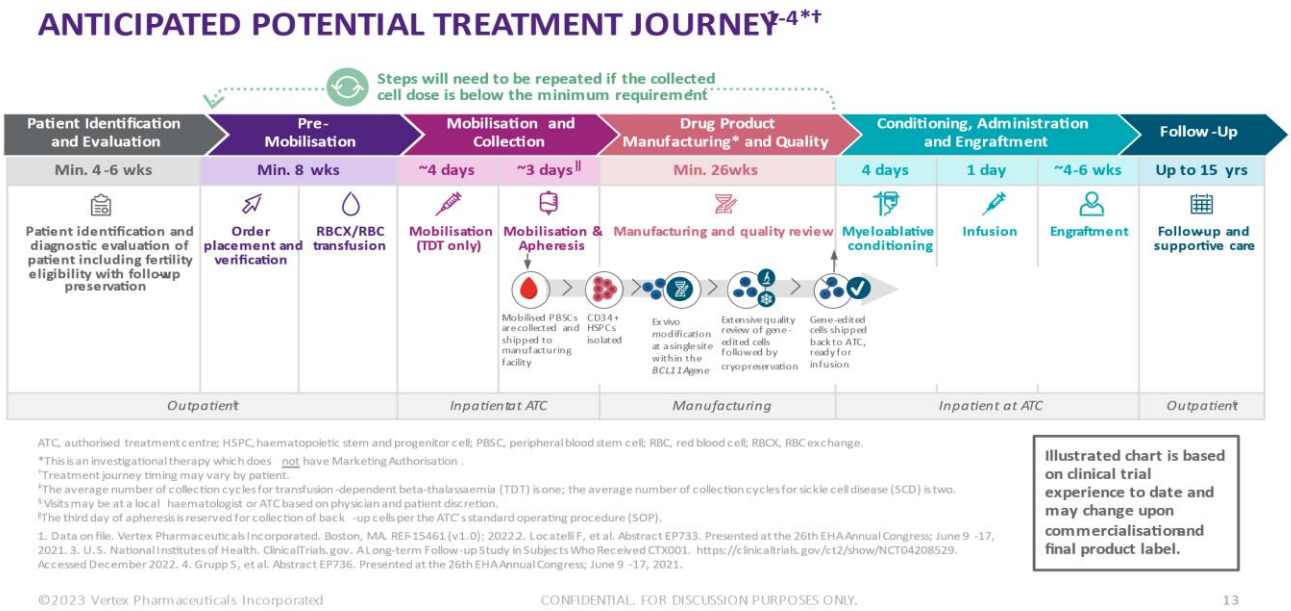
Consideration of pausing iron chelation e.g. Deferiprone prior to mobilisation. If possible, all iron chelation should be stopped 2 weeks prior to mobilisation and recommenced post-apheresis. All iron chelation drugs should be discontinued at least 7 days prior to starting myeloablative conditioning.

Note: If needed, iron chelation with deferasirox or deferoxamine is recommended not to be restarted until at least 3 months following Exa-cel infusion to allow for stable hematopoietic recovery and avoid a potential myelosuppressive effect. Deferiprone should not be started until at least 6 months post Exa-cel infusion. Patients should be evaluated regularly to determine whether chelation is required. Management of chelation should be as per institutional guidelines. Caution should be exercised in completely stopping chelation in patients who are maintaining Hb levels of 80 to 100 g/L post-treatment because iron may continue to be hyper-absorbed in the gut and released from the tissue macrophages.

7.5.2 The following medication should be avoided:

Granulocyte colony-stimulating factor (G-CSF): G-CSF should not routinely be administered after exa-cel infusion, however, G-CSF may be administered if engraftment is not achieved by Day 21.

8.0 Treatment Plan



8.1 Mobilisation

Once assessed as appropriate and fit for treatment with Exa-cel, patients will be mobilised with G-CSF and plerixafor. G-CSF products (e.g., filgrastim) will be administered subcutaneously or intravenously at a dose of 5 µg/kg/dose approximately every 12 hours (q12h) for at least 5 days, or 10mcg/Kg/dose once per day for at least 5 days. Our preference is for once per day dosing.

Splenectomised patients should receive a lower dose of G-CSF at 5 µg/kg once per day for at least 5 days to reduce the risk of significant hyperleukocytosis. Dosing of G-CSF and plerixafor should be reviewed if WBC count is > 70 x109/L. Conversely G-CSF dosing may need to be increased e.g. the splenectomised dose regimen may be increased to BD, if there is no significant increase in WBC or peripheral blood CD34+ count during mobilisation. Dose adjustment will be performed for obese patients or for patients with renal or hepatic impairment as per local standard of care. Plerixafor will be administered after the patient has received G-CSF for 4 days. Plerixafor is to be administered via subcutaneous injection; the recommended dose is 0.24 mg/kg administered approximately 4 to 6 hours prior to planned apheresis. This dose will be based on a FBC performed as patients start mobilisation and on the fourth, and fifth days of G-CSF to monitor WBC. It is good practice to check CD34+ cell count in peripheral blood after the first dose of plerixafor pre apheresis procedure.

Table 1: Mobilisation and Apheresis Timing

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7 (only if needed)
Filgrastim 5mcg/kg SC OD dosing (if weight >48kg without spleen)	6pm	6pm	6pm	6pm	6pm	6pm (only if day 7 required)	
Filgrastim 10mcg/kg SC OD dosing (if weight >48kg with intact spleen)	6pm	6pm	6pm	6pm	6pm (post apheresis)	6pm (post apheresis if day 7 required)	
Plerixafor 0.24mg/kg SC OD	-	-	-	-	6am (4 to 6 hours pre-apheresis)	6am (4 to 6 hours pre-apheresis)	6am (4 to 6 hours pre-apheresis)
Apheresis	-	-	-	-	10:00am	10:00am	10:00am

8.2 For TDT patients Prior to Apheresis and Conditioning

Prior to start of apheresis procedure and at least 60 days prior to planned initiation of busulfan conditioning, patients' transfusion plan should be tailored to achieve a pre-transfusion Hb ≥110 g/L. This is performed to suppress ineffective erythropoiesis and allow for a more successful engraftment.

8.3 Apheresis Procedure

CD34+ HSC will be collected per institutional site SOPs for up to 3 consecutive days, apheresis may require 3 blood volumes to be processed. Patients should be transfused with a goal of pre-transfusion Hb ≥110 g/L prior to apheresis collection. Patients will undergo apheresis for 2 consecutive days to collect HSC for Exa-cel manufacturing. The targeted CD34+ cell collection is at least 20 × 10^6 CD34+ cells/kg in order to achieve a minimum target dose of 3 × 10^6 CD34+ cells/kg. On these days, collected cells intended for manufacturing will be shipped same-day at 2°C to 8°C to the manufacturing facility. An additional 2 × 10^6 CD34+ cells/kg will be collected as backup for rescue therapy in an event of non-engraftment. These cells will be cryopreserved on site. Only once both manufacturing is satisfactorily completed and backup HSC acquired can patients proceed to conditioning.

8.4 Shipment to Manufacturing Facility

At the end of each day of apheresis for manufacturing, collected cells will be shipped at 2°C to 8°C to the manufacturing facility. Cells collected for a backup dose will be cryopreserved and stored on site.

8.5 Manufacture of Exa-cel

Manufacturing and release of the cell product inclusive of quality release testing is expected to take approximately 5-8 months (from apheresis to point of infusion).

8.6 Shipment of Exa-cel Product to Treatment Site

Exa-cel (packaged in vial(s)) will be shipped cryopreserved to the clinical sites in sealed dry nitrogen shippers (≤ -135°C) validated for at least 10 days. On receipt, package integrity will be checked and the cellular product label(s) will be confirmed against the donor's unique identifier. Vial(s) will be labelled for "autologous use only" with donor identification, batch number, and expiry date in accordance with local regulatory requirements.

8.7 Storage of Exa-cel Product

Exa-cel will be stored at the site in the frozen state at a temperature of ≤ -135°C until just prior to the scheduled infusion.

8.8 Cell product

Exa-cel will have a minimum CD34 cell dose of 3.0 × 106 cells/kg, and is routinely returned through a central venous catheter.
Transplant procedure

8.9 Pre-Conditioning checks

Once patients have had backup HSC stored on site and Exa-cel product has passed quality release and is on site can patients proceed to myeloablative conditioning and Exa-cel infusion. Pre myeloablation patients should be transfused with a goal of pre-transfusion Hb of ≥110 g/L at least 60 days prior to planned initiation of busulfan conditioning. If a patient is deemed not yet to be eligible for myeloablative conditioning, this procedure can be delayed until the expiry date of the patient's Exa-cel product. If 3 months pass from the time of workup investigations to the start of myeloablation PFTs and echocardiogram should be performed within 30 days prior to busulfan administration to confirm ongoing fitness to proceed. If 6 months pass from the time of workup investigations to the planned start of myeloablation, MRIs will also be repeated to confirm ongoing fitness to proceed. If repeat LIC is ≥15 mg Fe/g dry weight, then consideration may be given to a liver biopsy -if this shows no evidence of bridging fibrosis or cirrhosis the patient may proceed to myeloablative conditioning. Conditioning should only start once Exa-cel is received and safely stored at the transplant site.

8.10 Transfusion for TDT conditioning and Exa-cel Infusion

During hospitalization for busulfan conditioning and Exa-cel infusion patients should be supported with packed RBC and platelet transfusions as per standard or institutional practices (recommended to keep Hb ≥80 g/L) for patients undergoing HSCT.

8.11 Busulfan Administration

Busulfan will be administered IV daily at a starting dose of 3.2 mg/kg/day for 4 consecutive days (based on weight collected within 3 to 7 days prior to the first day of busulfan administration). Once-daily dosing is the preferred schedule, but the busulfan dose regimen may be adjusted to be given every 6 hours (QDS) for 4 consecutive days, per the site's standard practice. A test dose of busulfan may be performed within 30 days (consistent with institutional guidelines) prior to initiation of busulfan. The dose of busulfan will be adjusted based upon first dose busulfan PK in order to maintain appropriate levels for myeloablation.

Patient weight	Q6h dosing	OD dosing
>34 kg	0.8 mg/kg/dose	3.2 mg/kg/dose
>23 to 34 kg	0.95 mg/kg/dose	3.8 mg/kg/dose
16 to 23 kg	1.1 mg/kg/dose	4.4 mg/kg/dose

Dose adjustment will be performed for obese patients or patients with renal or hepatic impairment per local label and standard of care.

Target busulfan AUC or cumulative exposure for each dosing regimen will remain the same across all age groups.

The per dose target AUC for once-daily dosing is 20.5 mg*h/L (range: 18.5 to 22.5 mg*h/L) and total AUC target 82 mg*h/L (range: 74 to 90 mg*h/L).
The per dose target AUC for q6h dosing is 4.6 mg*h/L (range: 3.7 to 5.6 mg*h/L) and total AUC target 74 mg*h/L (range: 59 to 89 mg*h/L).

See Appendix B for suggested Busulfan dose adjustments based on PK analysis- this PK sampling should be carried out on day 1 of busulfan administration and be available prior to day 3 doses being given.

During busulfan conditioning, anti-seizure prophylaxis (per institutional guidelines for medications, except Phenytoin which is contraindicated) and other supportive measures should be instituted as per hospital guidelines. Suggested prophylaxis includes VZV/HSV, PCP and antifungal given the cellular product returned is CD34 selected and neutrophil engraftment occurs at a median of 29 days (EHA abstract 2023).

Infusion of busulfan should not take place if:

- • Exa-cel integrity has been compromised in some way and is no longer suitable for infusion (e.g., damage to the product container in transit to the clinical site).

- • The patient has any clinical condition which, in the opinion of the attending physician would put the patient at unacceptable risk for transplantation.

8.12 Exa-cel Infusion Procedures, Dose, and Administration

Exa-cel will be formulated in CryoStor CS5 medium which contains 5% DMSO and Dextran-40. Histamine release associated with DMSO can result in symptoms such as, adverse effects including nausea, vomiting, diarrhoea, flushing, fevers, chills, headache, dyspnoea, rashes, bronchospasm, anaphylaxis, vasodilation and hypotension, and mental status changes. Given the risk of these side effects, patients will be pre-medicated with an antihistamine (e.g., chlorpheniramine) and paracetamol) before infusing Exa-cel. Emergency medical equipment should be available during the infusion. Exa-cel must be given at least 48 hours and within 7 days after the last busulfan dose. If not given by 7 days post completion of myeloablation then infusion of backup HSC should be considered. Exa-cel vial(s) should be thawed just prior to the scheduled infusion as per local site SOPs and infused within 20 minutes of thaw. For further detailed instructions for the thaw and infusion of cells aee separate infusion SOP. Each vial should be check to ensure minimum patient identifiers are present and correct prior to infusion.

8.13 Post-Infusion Infection Prophylaxis and Surveillance

Patients will undergo infectious surveillance and prophylaxis (bacterial, viral, fungal) as per local guidelines for HSCT but it is suggested patients receive HSV/VZV, fungal and PCP prophylaxis until evidence of adequate immune reconstitution, and measures to monitor for, and treat neutropaenic sepsis should be in place. Female patients where appropriate should receive menstrual suppression until platelets >$50x10^9$/L.

8.14 Veno-occlusive disease

It is strongly advised in the absence of contra-indications that patients receive prophylaxis with ursodeoxycholic acid from admission to at least day 28. In the event of evidence of veno-occlusive disease early treatment with defibrotide is additionally recommended.

8.15 Seizure prophylaxis

Seizure prophylaxis should be given e.g. Levetiracetam from the day before busulfan conditioning starts to 48 hours post the last dose.

8.16 Other supportive care

Supportive care medications e.g. stress-ulcer prophylaxis should be given as per local guidelines. This guidance would also recommend careful monitoring and replacement of fluid balance, electrolytes and platelets as per local guidelines. Hypertension should also be monitored for, and where appropriate careful treated. Patients should be carefully monitored for clinical evidence of VOD.

8.17 Discharge

Patients are eligible for discharge when neutrophil engraftment has occurred (G-CSF can be considered from D21 post Exa-cel infusion), and any infections are adequately controlled. If engraftment (neutrophils >0.5 for 2 consecutive days) has not occurred by D29 (median neutrophil engraftment from CTX001-111 study, and day 44 for platelet engraftment) then ongoing review of the need to administer ‘back up HSC’ should take place, bearing in mind patients may still engraft up to at least day 56 (latest recorded engraftment without use of ‘back up HSC’ in CTX001 cohort).

9.0 Post-Exa-cel Infusion

9.1 Transfusions post-Exa-cel Infusion

During the 24-month follow-up period after infusion of Exa-cel, it is recommended that patients receive packed RBCs if required to maintain for Hb ≤70g/L or for clinical symptoms. Transfusions should be avoided for Hb ≥90g/L, unless considered clinically important (e.g., surgery).

9.2 Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years after expiry date of the product.

9.3 Blood, organ, tissue and cell donation

Patients treated with Exa-cel must not donate blood, organs, tissues and cells for transplantation.

9.4 Vaccinations

Revaccination programme should be commenced as per local guidance; this is suggested to commence from 6-12 months post Exa-cel if evidence of expected immune reconstitution.

10.0 Acceptable End-Points and the Range of Expected Results

N/A

11.0 Process Indicators/Quality Controls

N/A

12.0 Limitations/ Planned Deviations

12.1 Patients are always given the opportunity to meet with the BMT CNS and/or the Adolescent Transplant CNS and discuss any aspect of their care at any time and so there are circumstances where it is appropriate for meetings to take place on more than one occasion.

12.2 Virology and / or microbial screening results may need to be repeated if they become outdated prior to harvest. Circumstances in which this can occur may be a delay in the harvest attempt and therefore the patient will require repeat screening.

12.3 Where the collection has failed or the GM – CFU assays are insufficient, the results are discussed with the patients Consultant directly or at the disease specific transplant meeting. Following discussion with the patient at a scheduled clinic appointment, the decision is made by the Consultant whether to proceed with another mobilisation attempt. In such cases, the above procedure is repeated in its entirety.

12.4 Alterations to a patient's plan of care may be necessary at any time because of patient disease status and / or overall health in pre-harvest work-up and prior to admission for the transplant procedure. Any modifications are communicated directly to the patient's medical team, apheresis staff, theatre staff, WCTU, and radiotherapy unit (where indicated) by the Paediatric and/or BMT CNS.

12.5 Where and when required, the patient is recalled to UCLH for a reassessment by their medical team and Paediatric and/or BMT CNS as to their current health state and appropriateness to continue with the proposed treatment.

13.0 Training

Details of how staff competence shall be demonstrated and recorded for this PPG.

Type of Training	1. **Minor Document Change.** All **NEW** users unfamiliar with previous version of this PPG must undergo training, or 2. **Major Document Change.** Training required and defined.
Method of competency assessment	1. Read and Aware Assessment Form, 2. Competency Assessment Quiz, 3. Supervised Practical Assessment, 4. Supervised Stepwise Practical Assessment, or 5. any other method as defined and approved by the author and QMG
List Staff required for Training and Competency Assessment	List of all appropriate staffing groups
Who is to perform this training	N/A.

Appendix I: Busulfan dosing calculation

Blood samples should be collected after the first dose of Busulfan at T=0h, 3h 5min, 3h 15min, 3h 30min, 4h, 5h, 7h, on the first day of Busulfan administration.

Once the Busulfan AUC is reported, the consultant/speciality doctor on service in the HSCT unit needs to calculate the predicted cumulative AUC, by multiplying the actual AUC result by the total number of doses in the conditioning protocol.

For example, if the AUC after the first dose of Busulfan is 25mg*h/L, the predicted cumulative AUC is: 25mg*h/L x 4 (for Busulfan once daily dosing) = 100mg*h/L

A) If the predicted cumulative AUC is within the target range, there is no need for a dose adjustment and the same dose should be prescribed for any remaining Busulfan doses.

B) If the predicted cumulative AUC is outside the target range, the remaining Busulfan doses need to be adjusted to achieve the target range. To calculate the adjusted Busulfan dose follow the below steps (if calculating after 2 doses have been given using OD dosing):

B1. Calculate the cumulative AUC achieved from the Busulfan doses that have already been given: **actual dose AUC x 2** (number of doses given if using once daily dosing)

B2. Calculate the cumulative AUC to target from the remaining Busulfan doses: **Target cumulative AUC – actual predicted cumulative AUC (B1)**

B3. Calculate the target AUC for each of the remaining doses: **B2 ÷ 2** (3rd and 4th Busulfan doses if using once daily dosing)

B4. Calculate the adjusted Busulfan dose, according to the formula below:

$$\textbf{Adjusted Busulfan dose (mg)} = \frac{\textbf{actual Busulfan dose given (mg) x calculated target AUC (B3, above)}}{\textbf{actual Busulfan AUC}}$$

The BMT doctor needs to prescribe the remaining adjusted Busulfan doses. The maximum permissible increase in an individual Busulfan dose is 50%.

For example, using the once daily dosing schedule, if the Bu AUC after the first dose of 160mg is 17.5mg*h/L, the predicted cumulative AUC is 70 (=17.5mg*h/L x 4). This is outside the Busulfan target range of 74-90mg*h/L. The remaining Busulfan doses need to be adjusted.

1. The cumulative AUC for the first 2 doses of busulfan is 35 (=17.5mg*h/L x 2)
2. The cumulative AUC to target for the remaining 2 doses of busulfan is 45 (80mg*h/L - 35mg*h/L)
3. The target AUC for each of the remaining 2 doses is 22.5 (45 ÷ 2)
4. The adjusted busulfan dose is 206mg ((160mg x 22.5) ÷ 17.5mg*h/L)

Note, 206mg is less than a 50% increase from the calculated busulfan dose.

Appendix II: Adverse events

Adverse events attributed to Exa-cel in TDT patients

System organ class	Very common (≥10%)	Common (≥1% - <10%)
Blood and lymphatic system disorders	Lymphopenia *, †	Thrombocytopenia *, Neutropenia *, Anaemia *, Leukopenia *
Immune system disorders		Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		Hypocalcaemia *
Nervous system disorders		Headache *, Paraesthesia
Cardiac disorders		Tachycardia *
Respiratory, thoracic and mediastinal disorders		Acute respiratory distress syndrome, Idiopathic pneumonia syndrome *, Epistaxis *
Skin and subcutaneous tissue disorders		Petechiae *
General disorders and administration site conditions		Chills *, Pyrexia *
Injury, poisoning and procedural		Delayed engraftment *, Infusion related reactions ‡

* At least one event was also attributed to haematopoietic stem cell transplantation complications.
† Lymphopenia included CD4 lymphocytes decreased and lymphocyte count decreased.
‡ Infusion related reactions includes chills, sinus tachycardia and tachycardia.

Adverse events attributed to myeloablative condition in TDT patients

System organ class	Very common (≥10%)	Common (≥1% - <10%)
Infections and infestations		Pneumonia, Klebsiella sepsis, Sepsis
Blood and lymphatic system disorders	Thrombocytopenia, Febrile neutropenia, Neutropenia, Anaemia, Lymphopenia *, Leukopenia	Splenomegaly
Metabolism and nutrition disorders	Decreased appetite, Hypokalaemia, Fluid retention, Hypophosphataemia	Hypoalbuminaemia, Hypomagnesaemia, Hypocalcaemia
Nervous system disorders	Headache	Cerebellar haemorrhage, Hydrocephalus, Neuralgia
Eye disorders		Vision blurred
Cardiac disorders		Tachycardia
Vascular disorders		Hypotension
Respiratory, thoracic and mediastinal disorders	Epistaxis	Idiopathic pneumonia syndrome, Oropharyngeal pain, Cough, Dyspnoea
Gastrointestinal disorders	Mucositis †, Nausea, Abdominal pain ‡, Vomiting, Diarrhoea, Constipation	Colitis, Gastritis, Gingival bleeding, Dyspepsia, Dysphagia, Gastrointestinal inflammation, Haematochezia, Mouth ulceration
Hepatobiliary disorders	Venoocclusive liver disease, Alanine aminotransferase increased	Hepatomegaly, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Alopecia, Petechiae, Pigmentation disorder §	Rash #, Dry skin, Pruritus, Erythema
Musculoskeletal and connective tissue disorders	Musculoskeletal pain **	Arthralgia
Renal and urinary disorders		Haematuria
Reproductive system and breast disorders		Amenorrhoea, Premature menopause
General disorders and administration site conditions	Pyrexia, Fatigue	
Investigations		C-reactive protein increased, International normalised ratio increased, Weight increased
Injury, poisoning and procedural		Delayed engraftment, Subcutaneous haematoma

* Lymphopenia included CD4 lymphocytes decreased and lymphocyte count decreased.
† Mucositis included anal inflammation, mucosal inflammation, pharyngeal inflammation and stomatitis.
‡ Abdominal pain included abdominal pain lower, abdominal pain upper, abdominal tenderness and epigastric discomfort.
§ Pigmentation disorder included skin hyperpigmentation.
# Rash included dermatitis, rash erythematous and rash maculo-papular.
** Musculoskeletal pain included back pain, bone pain, chest pain and pain in extremity.