Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Trecondi

Active ingredient: Treosulfan

Sponsor: Link Medical Products Pty Ltd

June 2023

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
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About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ALL	Acute lymphoblastic leukaemia
alloHSCT	Allogeneic haematopoietic stem cell transplantation
AML	Acute myeloid leukaemia
ASA	Australia specific annex
AUC	Area under the concentration-time curve
$AUC_{0\text{-inf}}$	Area under the concentration versus time curve from zero extrapolated to infinity
$AUC_{0\text{-last}}$	Area under the curve from the time of dosing to the last measurable concentration
AUC_{norm}	Area under the curve normalised for the administered dose
$AUC_{0\text{-t}}$	Area under the concentration versus time curve from time zero to the last measurable concentration
$AUC_{t,norm}$	Area under the curve from the last measurable concentration to area under the curve normalised for the administered dose
BSA	Body surface area
CI	Confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CMI	Consumer Medicines Information
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLP	Data lock point
DNA	Deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplantation
EMA	European Medicines Agency (European Union)
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration (United States of America)
GGT	Gamma-glutamyl transferase
GvHD	Graft versus host disease
GVP	Good Pharmacovigilance Practice(s)
HSCT	Haematopoietic stem cell transplantation

Abbreviation	Meaning
IPSS-R	Revised International Prognostic Scoring System
JMML	Juvenile myelomonocytic leukaemia
MDS	Myelodysplastic syndrome
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PPS	Per-protocol set
PSUR	Periodic safety update report
RMP	Risk management plan
SAE	Serious adverse event
SD	Standard deviation
S,S-DEB	(2S,3S)-1,2:3,4-diepoxybutane
S,S-EBDM	(2S,3S)-1,2-epoxy-3,4-butanediol 4-methanesulfonate
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
WHO	World Health Organization
WPPS	World Health Organization (WHO) Classification based on Prognostic Scoring System

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Trecondi
Active ingredient:	Treosulfan
Decision:	Approved
Date of decision:	19 September 2022
Date of entry onto ARTG:	23 September 2022
ARTG numbers:	369770 and 369771
Black Triangle Scheme:	Yes. This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Link Medical Products Pty Ltd 5 Apollo Street Warriewood NSW 2102
Dose form:	Powder for solution
Strengths:	1 g and 5 g
Container:	Vial
Pack sizes:	1 and 5 (single use) vials
Approved therapeutic use:	***Adults with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS)*** *Trecondi (treosulfan) is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with AML or MDS at increased risk for standard conditioning therapies.* ***Paediatric patients aged 1 month and older with malignant and non-malignant haematological diseases*** *Trecondi (treosulfan) is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with malignant and non-malignant diseases.*
Route of administration:	Intravenous infusion
Dosage:	Administration of treosulfan should be supervised by a physician experienced in conditioning treatment followed by allogeneic haematopoietic stem cell transplantation.

As with all cytotoxic substances, appropriate precautions should be taken when handling treosulfan. Trained personnel should reconstitute the medicinal product (see Method of administration, and Instructions for reconstitution, along with associated warnings in the Product Information. Vials are for single use in a single patient only

Adults with acute myeloid leukaemia or myelodysplastic syndrome

Treosulfan is given in combination with fludarabine.

The recommended dose and schedule of administration is:

- treosulfan 10 g/m^2 body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (Day -4, -3, -2) before stem cell infusion (Day 0). The total treosulfan dose is 30 g/m^2;
- fludarabine 30 mg/m^2 BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (Day -6, -5, -4, -3, -2) before stem cell infusion (Day 0). The total fludarabine dose is 150 mg/m^2;
- treosulfan should be administered before fludarabine on Days -4, -3, -2 (FT_{10};[1] regimen).

Paediatric population aged one month and older with malignant and non-malignant haematological diseases

Treosulfan is given in combination with fludarabine, with thiotepa (intensified regimen; FT_{10-14} plus thiotepa regimen) or without thiotepa (FT_{10-14} regimen).[1]

The recommended dose and schedule of administration is:

- treosulfan 10 to 14 g/m^2 BSA per day as a two-hour intravenous infusion, given on three consecutive days (Day -6, -5, -4) before stem cell infusion (Day 0). The total treosulfan dose is 30 to 42 g/m^2; The dose of treosulfan should be adapted to the patient's BSA (see Section 5.2 of the Product Information);
- fludarabine 30 mg/m^2 BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (Day -7, -6, -5, -4, -3) before stem cell infusion (Day 0). The total fludarabine dose is 150 mg/m^2;
- treosulfan should be administered before fludarabine;
- thiotepa (intensified regimen 5 mg/kg twice a day), given as two intravenous infusions over 2 to 4 hours on Day -2 before stem cell infusion (Day 0).

[1] FT_{10}: fludarabine plus 3 x 10 g/m^2 treosulfan
FT_{10-14}: fludarabine plus 3 x 10 g/m^2 to 3 x 14 g/m^2 treosulfan
FB4: full busulfan dose

	For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D
	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
	The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the submission by Link Medical Products Pty Ltd (the sponsor) to register Trecondi (treosulfan) 1 g and 5 g, powder for solution, vial for the following proposed indication:

> *Trecondi (treosulfan) is indicated as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT):*
>
> - *in adult patients with malignant and non-malignant diseases,*
> - *in paediatric patients older than one month with malignant and non-malignant diseases.*

Allogeneic haematopoietic stem cell transplantation (alloHSCT) is potentially curative for leukaemias, myelodysplastic syndromes (MDS), lymphomas and multiple myeloma. It is also increasingly used in non-malignant diseases such as primary immunodeficiency, inborn errors of metabolism, haemoglobinopathies and bone marrow failure syndromes. Patients undergoing alloHSCT are prepared with chemotherapy alone or chemotherapy combined with radiotherapy, known as a conditioning or preparative regimen. The conditioning regimen has three aims: reduction of the tumour burden when the disease is neoplastic; elimination of the self-renewing capacity of the recipient's own haematopoiesis; and suppression of the recipient's immune system in order to allow engraftment of donor stem cells.

Conditioning regimens are divided into three categories: myeloablative conditioning; reduced intensity conditioning; and non-myeloablative conditioning.[2] While myeloablative regimens cause irreversible cytopenia and stem cell support is mandatory, non-myeloablative regimens may result in only minimal cytopenia that do not require stem cell support.[3] Reduced intensity conditioning regimens cause cytopenia of variable duration and should be given with stem cell support.

[2] Giralt, S. et al. Reduced-Intensity Conditioning Regimen Workshop: Defining the Dose Spectrum. Report of a Workshop Convened by the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant,* 2009; 15(3): 367-369.

[3] Bacigalupo, A. et al. Defining the Intensity of Conditioning Regimens: Working Definitions, *Biol Blood Marrow Transplant,* 2009; 15(12): 1628-1633.

Myeloablation radiation containing regimen

High dose total body irradiation has been widely used as part of myeloablative radiation containing conditioning regimens due to its stem cell toxicity, immunosuppressive properties, effectiveness against most leukaemias and lymphomas, and ability to penetrate sanctuary sites. The majority of myeloablative radiation containing conditioning regimens combine total body irradiation with other chemotherapeutic agents, most commonly cyclophosphamide; other agents, such as cytarabine, etoposide, melphalan, and busulfan have been combined with total body irradiation as conditioning regimens;[3] but there is currently no evidence suggesting that any of these combinations are superior to cyclophosphamide and high dose total body irradiation.[3,4]

Myeloablative conditioning regimen without radiation

Although primarily developed for autologous transplantation, these regimens have also been used in the alloHSCT setting. Alkylating agents remain the mainstay of such regimen, due to their favourable toxicity profile (marrow toxicity as dose-limiting toxicity) and effect on non-dividing tumour cells, and are commonly based on busulfan and other cytotoxic agents.[2,3]

Non-myeloablative and reduced intensity conditioning regimen

For patients with haematologic malignancies, an important contributing factor is a graft versus tumour effect mediated by the allogeneic donor cells. This effect requires the permanent engraftment of donor type immunocompetent cells, which does not necessarily require a toxic myeloablative conditioning regimen. Due to its lowered toxicity, non-myeloablative conditioning prior to transplantation can be appropriate for patients older than 55 years, which is a common upper limit for standard myeloablative conditioning, and for patients with co-morbidities that would exclude them from undergoing myeloablative conditioning.[2,3]

Both non-myeloablative and reduced intensity conditioning regimens have been explored extensively and these regimens have expanded the number of patients eligible for haematopoietic stem cell transplantation (HSCT). Fludarabine has been widely incorporated into such regimens, as it is highly immunosuppressive, has anti-tumour activity in haematological malignancies, and has a low non-haematological toxicity profile. The optimum non-myeloablative and reduced intensity conditioning regimen remains to be defined.

Commonly used standard intensity myeloablative conditioning regimens such as total body irradiation with cyclophosphamide, busulfan with cyclophosphamide or combinations of busulfan with other cytotoxic agents are associated with a high risk of mortality and morbidity especially for intensively pre-treated patients. Therefore, these regimens are usually contraindicated in patients over 55 years of age, patients with an increased risk for pulmonary or hepatic complications, organ or infectious complications with previous chemotherapy, as well as patients with previous autologous stem cell transplantation. As a consequence, many efforts have been made to reduce the toxicity of these regimens while maintaining their efficacy with respect to donor cell engraftment and anti-tumour efficacy. The development of non-myeloablative and reduced intensity conditioning regimens expanded the patient population that could receive alloHSCT, but at the expense of increased relapse rates.

The sponsor states that a perfect cytotoxic agent for conditioning regimens should have the following properties:

[4] Potdar, R.R. et al. Current Status and Perspectives of Irradiation-Based Conditioning Regimens for Patients with Acute Leukemia Undergoing Hematopoietic Stem Cell Transplantation, *Clin Hematol Int*, 2019; 1(1): 19-27.

- Sufficient stem cell toxicity (with respect to primitive as well as committed stem cells) and immunosuppression to enable rapid and stable engraftment.
- Low organ toxicity, especially with respect to the liver, kidneys, lung, and the nervous system.
- Sufficient cytotoxicity to guarantee an effective treatment of the underlying haematological malignancy.
- Predictive pharmacokinetics (PK; intravenous administration, linear PK, low inter-individual variability, and no enzyme dependent drug activation).

Treosulfan has been approved in several European countries for the treatment of patients with ovarian cancer since 1973 with oral formulation and 1990 with intravenous formulation. Its dose limiting side effect is bone marrow toxicity, with a maximal tolerated dose of 10 g/m^2 when administered intravenously as a single agent without stem cell reinfusion in patients with chemotherapy refractory advanced cancer.[5] The toxicity profile of treosulfan is stated to be well known, based on its use to treat ovarian cancer. The sponsor commented that, as a single agent, Grade III/IV toxicities with treosulfan are very rarely observed. Myelosuppression is stated to be the most frequently observed side effect with treosulfan. Gastrointestinal toxicity, especially nausea or vomiting, is stated to be rarely observed with treosulfan monotherapy and seldom exceeds Grade II. In addition, the sponsor stated that the drug lacks hepatic and renal toxicity and only very rarely causes lung toxicity.

The sponsor stated that, based on the encouraging preclinical and clinical Phase I results, it was suggested that treosulfan could be an ideal drug for incorporation into a conditioning regimen prior to HSCT. Pilot studies were reported to have shown that treosulfan based conditioning regimens followed by alloHSCT are feasible, tolerable, and effective and can be used for patients who do not tolerate conventional standard intensity myeloablative conditioning treatments. In a Phase I dose escalation study of treosulfan infused intravenously over 2 hours at escalating doses (20 to 56 g/m^2) combined with autologous HSCT in patients with advanced malignancies (15 ovarian cancers; 7 other carcinomas or lymphomas), the conventional maximum tolerable dose of treosulfan (10 g/m^2) was escalated up to 5 times and a maximum tolerated dose of 47 g/m^2 was identified.[6] These results supported further clinical development of treosulfan based conditioning regimens prior to alloHSCT.

No maximum tolerable dose of treosulfan prior to alloHSCT has been established. Therefore, for conditioning treatment prior to alloHSCT the sponsor did not plan to use treosulfan doses beyond 42 g/m^2 (14 g/m^2/day x 3), as this dose represented approximately 90% of the previously defined maximum tolerable dose of 47 g/m^2 determined in the autologous HSCT setting.[6] The primary goal of the alloHSCT studies was to establish a standard intensity but reduced toxicity treosulfan based conditioning regimen, which in contrast to reduced intensity conditioning regimens retains its myeloablative and antileukaemic activities thereby reducing the risk of relapse.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

[5] Harstrick, A. et al. A Phase I Dose Escalation Trial of Intravenous Treosulfan in Refractory Cancer, *Onkologie*, 1996; 19: 153-156.

[6] Scheulen, M.E. et al. Clinical Phase I Dose Escalation and Pharmacokinetic Study of High-Dose Chemotherapy with Treosulfan and Autologous Peripheral Blood Stem Cell Transplantation in Patients with Advanced Malignancies, *Clin Cancer Res*, 2000; 6: 4209-4216.

This product received orphan drug designation on 11 June 2021 for the following indication:

> *Treosulfan is indicated for the conditioning treatment prior to haematopoietic stem cell transplantation.*

At the time the TGA considered this submission, similar submissions had been approved in the European Union (EU) on 20 June 2019, Great Britain on 20 June 2019, Canada on 25 June 2021, and Switzerland on 10 August 2020. Similar submissions were under consideration in the United States of America (submitted on 11 August 2020), and Singapore (submitted on 11 May 2022).

The following table summarises these submissions and provides the indications where approved.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	12 December 2017	Approved on 20 June 2019	*Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant and non-malignant diseases.*
Great Britain	12 December 2017;[1]	Approved on 20 June 2019;[1]	*Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases.*
United States of America	11 August 2020	Under consideration	Under consideration

Region	Submission date	Status	Approved indications
Canada	18 September 2020	Approved on 25 June 2021	*Trecondyv (treosulfan) is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT)* • *in adult patients with AML or MDS at increased risk for standard conditioning therapies, in pediatric patients older than 1 year old with AML or MDS*
Switzerland	19 November 2019	Approved on 10 August 2020	*Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non- malignant diseases, and in paediatric patients older than one month with malignant diseases.*
Singapore	11 May 2022	Under consideration	Under consideration

1 Originally submitted for approval by the European Medicines Agency via the Centralised Procedure on 12 December 2017. Subsequently approved on 20 June 2019 for use in the EU, including at that time, Great Britain. Subsequently a Centrally Authorised Product (CAP) conversion (of the baseline submission) due to Brexit was submitted to Medicines and Healthcare products Regulatory Authority (MHRA) on 9 February 2021.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2021-02707-1-6

Description	Date
Designation (Orphan)	11 June 2021
Submission dossier accepted and first round evaluation commenced	2 August 2021
First round evaluation completed	22 December 2021
Sponsor provides responses on questions raised in first round evaluation	31 March 2022
Second round evaluation completed	18 May 2022
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	29 June 2022
Sponsor's pre-Advisory Committee response	15 July 2022
Advisory Committee meeting	4 and 5 August 2022
Registration decision (Outcome)	19 September 2022
Completion of administrative activities and registration on the ARTG	23 September 2022
Number of working days from submission dossier acceptance to registration decision*	221

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

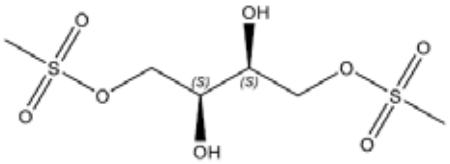
Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- Therapeutic Goods Administration, Stability Testing for Prescription Medicines, Version 1.1, March 2017.
- European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Reporting the Results of Population Pharmacokinetic Analyses, CHMP/EWP/185990/06, 21 June 2007.

Quality

Treosulfan, the drug substance of Trecondi is a prodrug of a bifunctional alkylating agent. In the body, treosulfan is converted into other compounds called epoxides with cytotoxic activity, especially against rapidly dividing cells such as those of bone marrow (haematopoietic precursor cells). It has a broad antineoplastic and antileukaemic activity. The chemical structure of treosulfan is shown in Figure 1 below.

Figure 1: Chemical structure of treosulfan



The drug product is a white lyophilised powder, packed in 30 mL type I clear glass vial with colourless glass vial with a chlorobutyl rubber stopper and aluminium cap in a carton. Each pack contains alternatively one or five vials. Each vial is for single use and contains no antimicrobial preservative.

Chemical and physical stability has been demonstrated for 24 hours at 25°C. It is recommended to store the drug product below 25°C, but not in a refrigerator (2°C to 8°C) to prevent precipitation.

Before use, the drug product is reconstituted with an appropriate amount of sodium chloride 0.45% aqueous solution at or below 30°C in the original glass container. Final concentration of treosulfan in the reconstituted liquid is 50 mg/mL. Reconstituted product can be combined in a larger glass vial, polyvinyl chloride or polyethylene bag.

The reconstituted solution appears as a clear colourless solution. Solutions showing any sign of precipitation should not be used.

Each vial is for single use only. Reconstituted treosulfan is for intravenous use as a two-hour infusion.

As with all cytotoxic substances, appropriate precautions should be taken when handling treosulfan. When handling treosulfan, inhalation, skin contact or contact with mucous membranes should be avoided. Pregnant personnel should be excluded from handling cytotoxics.

The Delegate seeks advice on whether the lower pH limit of the reconstituted solution (for the duration of in-use period) be acceptable to the ACM.

Approval for registration of the proposed product will be recommended once each issue is satisfactorily resolved by the sponsor and considered to be acceptable by the ACM.

Nonclinical

The pharmacology studies support the use of treosulfan for the proposed indication. Limited pharmacodynamic drug interactions studies support the proposed treosulfan / fludarabine combination therapy.

No nonclinical studies were submitted to support the proposed treosulfan / fludarabine / thiotepa combination.

Based on the metabolic pathway for treosulfan, drugs affecting the pH could affect the conversion of treosulfan to the active epoxides ((2S,3S)-1,2-epoxy-3,4-butanediol 4-methanesulfonate (S,S-EBDM) and (2S,3S)-1,2:3,4-diepoxybutane (S,S-DEB)). Treosulfan has the potential to alter the pharmacokinetics (PK) of drugs metabolised by cytochrome P450;[7]

[7] **Cytochrome P450 (CYP)** enzymes: CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

(CYP)2C19 and CYP3A4/5 and substrates of P-glycoprotein and multidrug and toxin extrusion protein 2K.

The collective safety studies indicate the following as potentially clinically relevant:

- gastrointestinal and dermal toxicity with the proposed treosulfan / fludarabine combination
- haematopoietic, lymphatic and immune system toxicity of treosulfan and its active moieties.

Treosulfan is mutagenic and potentially carcinogenic in animals and humans, as for other alkylating drugs.

Treosulfan (and DEB) impaired fertility and induced reproductive and developmental toxicity in rodents. A similar effect in humans is anticipated, including the potential for irreversible infertility. The proposed Product Information (PI) statement provides advice on the possibility of cryo-preservation of sperm prior to treatment of men but does not provide any equivalent advice for women.

The paediatric indication is supported by a rat juvenile toxicity study.

There are no objections on nonclinical grounds to the registration of treosulfan for the proposed indication.

Clinical

Summary of clinical studies

The clinical dossier in adult patients consisted of:

- 3 Phase II studies: Studies MC-FludT.6/L, MC-FludT.7/AML, and MC-FludT.8/MDS;
- 2 Phase III studies: Studies MC-FludT.14/L Trial I and Trial II;
- Analyses by European Group for Blood and Marrow Transplantation (EBMT (2019));[8] and Center for International Blood and Marrow Transplant Research (CIBMTR (2019));[8]

The clinical dossier in paediatric patients consisted of:

- 2 Phase II study: Studies MC-FludT.16/NM and MC-FludT.17/M.
- Comparative engraftment data
- Analyses by Peters (2011)[8] and Peters (2017)[8]

Pharmacology

Pharmacokinetics

A pharmacokinetic (PK) substudy was undertaken for a subset of adult patients (n = 24) randomised to the treosulfan arm of Study MC-FludT.14/L Trial I who had received treosulfan 3 x 14 g/m^2 administered by intravenous infusion (Study MC-FludT.14/L Trial I; PK study

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

[8] These reports are not publicly available.

report, 26 March 2012). Individual PK parameters derived from treosulfan concentrations in plasma were evaluated by standard model independent methods as well as two-compartment disposition modelling.

Pharmacokinetic data for treosulfan and its monoepoxide metabolite in paediatric patients from Studies FludT.16/NM (n = 24) and MC-FludT.17/M (n = 59) were used for the PK analysis reported in Venn Life Sciences (2020).[8] Non-compartmental analysis and two-compartment modelling analysis of PK parameters were presented in the final report.

The clinical evaluation of PK is summarised as follows:

- Treosulfan is a prodrug that has no activity by itself but needs transformation into epoxide derivatives which have cytotoxic activity. Under physiological conditions (pH 7.4; temperature 37°C), treosulfan is converted spontaneously (non-enzymatically) into an active monoepoxide intermediate and finally to L-diepoxibutane.
- The PK of treosulfan intravenously administered once daily on three consecutive days for conditioning prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adults and children have been adequately characterised by non-compartmental analysis and population pharmacokinetic (PopPK) modelling. All submitted PK studies were undertaken in patient populations, with no studies being conducted in healthy subjects.
- The duration of the treosulfan intravenous infusion was 2 hours in most studies. After intravenous administration, peak treosulfan plasma levels were reached at the end of the infusion.
  - Maximum plasma levels (mean ± standard deviation (SD)) in adult patients after 2-hour treosulfan intravenous infusions of 10, 12, and 14 g/m^2 were 306 ± 94 µg/mL, 461 ± 102 µg/mL, and 494 ± 126 µg/mL, respectively (Hilger et al. 1998,[9] Nemecek et al. 2011,[10] and PK Substudy MC-FludT.14/L).
  - The area under the concentration versus time curve from zero extrapolated to infinity ($AUC_{0\text{-}inf}$; mean ± SD) values in adult patients after 10, 12 and 14 g/m^2 were 940 ± 293 µg x h/mL, 1,365 ± 293 µg x h/mL and 1638 ± 378 µg x h/mL, respectively.
- No accumulation of treosulfan was observed between the first (Day -6) and the third (Day -4) of administration (PK Substudy MC-FludT.14/L). This is not unexpected as the terminal half-life is approximately 2 hours, indicating that treosulfan will be cleared from the plasma in approximately 10 hours (that is, 5 times half-lives).
- As treosulfan is administered by intravenous route, no food effect study or relative bioavailability studies were undertaken.
- The volume of distribution (mean ± SD) at steady state from different studies in adults was reported to range from 22.1 ± 3.8 L to 50.4 ± 43.9 L. According to the final population PK analysis of treosulfan in paediatric patients (Venn Life Sciences 2020, PopPK), the estimated volumes of distribution were 18.9 L and 20.3 L for central compartment and peripheral compartment, respectively, giving a total volume of distribution of 39.2 L.
- The mean total clearance (mean ± SD) from different studies in adults was reported to range from 154 ± 35 mL/min to 273 ± 77 mL/min. In the PK Substudy MC-Flud.T.14/L, the model dependent mean ± SD total clearance in adults treated with treosulfan 14 g/m^2 intravenously daily for 3 days was 272.58 ± 77.21 mL/min on Day -6 (that is, after the first dose) and 275.02 ± 64.79 mL/min on Day -4 (that is, after the third dose). According to the

[9] Hilger, R.A. et al. Clinical Pharmacokinetics of Intravenous Treosulfan in Patients with Advanced Solid Tumors, *Cancer Chemother Pharmacol*, 1998; 42:99-104.

[10] Nemecek, E.R. et al. Conditioning with Treosulfan and Fludarabine Followed by Allogeneic Hematopoietic Cell Transplantation for High-Risk Hematologic Malignancies, *Biol Blood Marrow Transplant*, 2011; 17: 341-350.

final population PK analysis of treosulfan in paediatric patients (Venn Life Sciences 2020, PopPK), the estimated clearance was 17.7 L/h (standard error = 0.427 L/h).

- Renal excretion of a total dose of treosulfan ranged from 14% to 41% across individual studies in adult patients. In the PK substudy (Study MC-FludT.14/L), 40.9% of an administered dose of treosulfan 14 g/m^2 intravenously to adult patients was excreted in the urine over 24 hours, with inter-subject variability (coefficient of variation %) being 21.7%. The model dependent terminal half-life in this study was approximately 2 hours on both Days -4 and -6.
- The PK of the monoepoxide metabolite of treosulfan have been investigated in children in published studies and in the Medac GmbH;[11] sponsored clinical Studies MC-FludT.16/NM and MC-FludT.17/M (Venn Life Sciences 2020; non-compartmental analysis). In a published study in children, the area under the concentration-time curve (AUC) of treosulfan was reported to be 100-fold higher than the AUC of its monoepoxide metabolite. In the Venn Life Sciences (2020) non-compartmental analysis, based on body surface area (BSA) the mean treosulfan maximum observed concentration value was approximately 54-fold higher than the mean monoepoxide maximum observed concentration value and the mean treosulfan $AUC_{0\text{-inf}}$ value was approximately 30-fold higher than the mean monoepoxide $AUC_{0\text{-inf}}$ value.
- The final PopPK model (Venn Life Sciences 2000, PopPK) for treosulfan, based on historical data and data derived from the two paediatric Studies MC-FludT.16/NM and MC-FludT.17/M, is reported to be a two compartmental model (with dosing in the central compartment) with linear elimination and inter-compartmental clearance. Inter-individual variance on clearance, central compartment, peripheral compartment, and inter-compartmental clearance was included in the final model. No deviations from dose proportionality or time dependent PK were identified during model development. A covariate analysis revealed that BSA was the only clinically relevant covariate for clearance, central compartment and peripheral compartment and inter-compartmental clearance. The reporting of the results from the final PopPK analysis are considered to meet the appropriate TGA adopted guideline.[12]
- There were no PK studies in patients with hepatic impairment or with renal impairment. Patients with severe hepatic or renal impairment were excluded from the clinical studies.
- In the PK sub-study (Study MC-FludT.14/L), linear regression analysis of the covariates of age (range: 43 to 70 years), body weight (range: 54 to 114 kg), BSA (range: 1.5 to 2.25 m^2) and creatinine clearance (range: 47 to 182 mL/min) had no statistically significant effects on AUC and AUC from time zero to the last measurable concentration ($AUC_{0\text{-t}}$). Body weight and BSA had statistically significant effects on both normalised AUC for the administered dose (AUC_{norm}) and AUC from the last measurable concentration to AUC normalised for the administered dose ($AUC_{t,norm}$), with patients with lower body weight and smaller BSA tending to have higher values.
- In the Venn Life Sciences (2020) non-compartmental analysis of PK data for treosulfan and monoepoxide from Studies MC-FludT.16/NM and MC-FludT.17/M in children were undertaken in separate subgroups based on age and BSA. With respect to the shape of the mean plasma concentration-time profiles of treosulfan, no major differences were observed between the age or BSA groups. No major differences in mean maximum observed concentration values were observed across the age or BSA groups, mean AUC from the time of dosing to the last measurable concentration ($AUC_{0\text{-last}}$) and $AUC_{0\text{-inf}}$ values were comparable across the three youngest age groups but were higher in the two oldest age groups (that is, 4 to less than 12 years and 12 years or older), and mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ values were comparable in the two lowest BSA groups (no more than 0.5 m^2, and more than 0.5 to no more than 1.0 m^2) but higher in the highest BSA group (more than 1.0 m^2).

[11] Medac GmbH is a German pharmaceutical company.

[12] European Medicines Evaluation Agency (EMEA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Reporting the Results of Population Pharmacokinetic Analyses, CHMP/EWP/185990/06, 21 June 2007.

Similarly, mean terminal half-life, clearance and volume of distribution treosulfan values were generally comparable across the three youngest age groups but were higher in the two oldest age groups, and the mean terminal half-life, clearance and volume of distribution treosulfan values were generally comparable in the two lowest BSA groups and higher in the highest BSA group.

- The final PopPK analysis (Venn Life Sciences 2020, PopPK) recommended changes to the treosulfan BSA dependent dose of treosulfan which were being used in the two paediatric clinical studies (Studies MC-FludT.16/NM and MC-FludT.17/M). According to predictions using the updated PopPK Model reported in Venn Life Sciences (2020), from a PK perspective the updated dosing scheme indicated that children with a BSA of 0.4, 0.5, 0.9 and 1.0 m^2 should receive a higher dose of treosulfan than currently being used the two paediatric studies in order to achieve target AUC exposure of 1355 µg x h/mL. Deviations ranged between 9% for BSA levels 0.6, 0.7 and 0.8 m^2, up to 20% for BSA levels 0.4 and 0.5 m^2, and up to 17% for BSA levels 0.9 and 1.0 m^2. Therefore, it was recommended that children with a BSA less than 0.4 m^2 should receive a dose of 10 g/m^2/day, while children with a BSA at least 0.4 m^2 to less than 0.9 m^2 should receive a dose of 12 g/m^2/day and children with a BSA at least 0.9 m^2 should receive a dose of 14 g/m^2/day. However, there are safety concerns with the 14 g/m^2 dose being proposed for children and adolescents with a BSA at least 0.9 m^2, as noted by the clinical evaluation (See *Safety* and *Risk-benefit analysis* sections below).
- *In vitro* data were reported to show that treosulfan was not an inducer of CYP1A2, CYP2B6 or CYP3A4 in cryopreserved human hepatocyte. The *in vitro* data showed that treosulfan was not a time dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4, but was a reversible inhibitor of CYP2C19 and CYP3A4.
- Physiologically based PK modelling investigating potential drug-drug interactions suggested that treosulfan is a weak to moderate inhibitor of CYP3A4, a weak inhibitor of CYP2C19, and a negligible inhibitor of the P-glycoprotein transporter. Based on the *in vitro* and physiologically based PK modelling data, the sponsor recommends that medicinal products with a narrow therapeutic index that are substrates for CYP3A4, CYP2C19 or P-glycoprotein should not be given during treatment with treosulfan. There were no clinical PK studies assessing potential drug-drug interactions between treosulfan and other medicines.

Pharmacodynamics

The primary pharmacodynamic effects of treosulfan in humans contribute to the benefits and risks of conditioning treatment prior to alloHSCT observed in paediatric and adult patients with malignant and non-malignant disease. Consequently, these effects are discussed in *Efficacy* and *Safety* sections below. The clinical evaluation concluded that in the evaluated clinical studies, it is not possible to dissect the different primary and secondary pharmacodynamic effects of treosulfan when it is being administered as conditioning treatment, as the drug was always administered with fludarabine in both paediatric and adult patients; or, administered with thiotepa in paediatric patients only.

Efficacy (adult population)

Dose selection for pivotal study

A dosage regimen consisting of treosulfan 14 g/m^2 (by body surface area (BSA)) given once a day for three days, in combination with fludarabine 30 g/m^2 (BSA) given once a day for five days was used for conditioning prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in the initial Phase III adult study (Study MC-FludT.14/L Trial I). However, in the first confirmatory interim analysis of 279 patients showed a higher incidence of transplant related mortality in the treosulfan 14 g/m^2 arm compared with the busulfan arm, mainly due to an

increased rate of infections because of a significantly prolonged duration of neutropenia in the treosulfan 14 g/m^2 arm compared to the busulfan arm.

The final analysis of 330 patients enrolled in Trial I of Study MC-FludT.14/L confirmed the unfavourable findings of the first confirmatory interim analysis and a decision was subsequently made to reduce the daily treosulfan dose from 14 g/m^2 to 10 g/m^2. Based on the unfavourable safety findings observed in Trial I of Study MC-FludT.14/L, this trial was prematurely terminated.

In the subsequent Trial II of Study MC-FludT.14/L (considered pivotal for this submission), the new treatment regimen for treosulfan consisting of treosulfan 10 g/m^2 given once a day for 3 days was used in order to reduce the treatment related toxicity observed with the higher dosed treosulfan regimen (treosulfan 14 g/m^2, given once a day for 3 days) used in Study MC-FludT.14/L Trial I.

Evaluable efficacy data

The clinical studies submitted for the evaluation of the efficacy and safety of treosulfan in the proposed adult population include:

- Study MC-FludT.14/L Trial II is a pivotal Phase III efficacy and safety study in adult patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) with increased risk for standard conditioning therapies;
- Study MC-FludT.7/AML and Study MC-FludT.8/MDS are Phase II, non-randomised, single arm studies of similar design investigating a conditioning regimen containing treosulfan 14 g/m^2 on Days -6 to -4 prior haematopoietic stem cell transplantation (HSCT) in adult patients with AML (Study MC-FludT.7/AML) and MDS (Study MC-FludT.8/MDS)

The treosulfan dose of 10 g/m^2 is the dose being proposed by the sponsor for approval for the treatment of malignancies in adults. The efficacy results relating to the treosulfan dose of 14 g/m^2 in combination with fludarabine for conditioning prior to alloHSCT in patients with AML and matched sibling donor used in Study MC-FludT.7/AML and Study MC-FludT.8/MDS are therefore not directly relevant to the proposed indication for adults with malignant disease. Furthermore, the majority of patients in both Studies MC-FludT.7/AML and MC-Flud.8/MDS were eligible for standard conditioning with total body irradiation or busulfan based regimens (75% and 95%, respectively). This contrasts with Study MC-FludT.14/L Trial II in which none of the 268 patients with AML or MDS were considered to be eligible for standard conditioning.

Data from the European Group for Blood and Marrow Transplantation (EBMT) Registry study (2019) was evaluated. The registry data was re-analysed for fludarabine / melphalan based and busulfan / cyclophosphamide based conditioning treatment without total body irradiation (control EBMT) compared to fludarabine / treosulfan based conditioning in adult AML and MDS patients treated in Study MC-FludT.14/L Trial II (treated chemotherapy) by using propensity score matching methods. The clinical evaluation concluded that this provides supportive data for the treosulfan combined with fludarabine conditioning regimen assessed in Study MC-FludT.14/L Trial II for the treatment of patients with AML or MDS at risk for standard conditioning therapies.

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) 2019 Registry analysis was evaluated. This report provided a comparison of alloHSCT outcomes for patients with AML or MDS treated with myeloablative or reduced intensity conditioning regimens used in the United States of America to the treosulfan / fludarabine conditioning regimen used in the Medac GmbH sponsored European Union (EU) clinical Study MC-FludT.14/L Trial II ('Trial' regimen). The clinical evaluation noted numerous limitations with this analysis (for example non-randomised, observational study subject to biases; no matched score

propensity analysis; multivariate modelling adjusted for covariates based on statistical algorithm and not on clinically relevant differences in patient and disease characteristics between comparison groups and so on) and consequently concluded that these findings should be interpreted cautiously and that outcomes should be confirmed by suitably designed randomised clinical studies.

It is noted that no pivotal clinical studies have been submitted for the following populations:

- adult patients with malignant disease other than AML or MDS;
- adult patients with non-malignant disease;
- adult patients treated with treosulfan combined with conditioning agents other than fludarabine;
- adult patients at risk with standard conditioning therapies;
- adult patients who had been previously treated with alloHSCT.

Study MC-FludT.14/L Trial II (pivotal)

Study design

Study MC-FludT.14/L Trial II is a Phase III clinical study comparing treosulfan based conditioning therapy with busulfan based reduced intensity conditioning prior to alloHSCT in patients with AML or MDS considered ineligible to standard conditioning regimens.

The trial was designed as a randomised, parallel group, open label, multicentre, international, group sequential Phase III non-inferiority trial.

A group-sequential approach was implemented consisting of three confirmatory interim analyses. The first interim analysis was performed with 220 randomised patients qualifying for full analysis set (FAS) or after 45 events to investigate the effect of dose reduction on duration of neutropenia and transplant-related mortality until Day 100. The second interim analysis was scheduled with 137 events or latest after randomisation of 460 patients qualifying for FAS. The third interim analysis was scheduled with 239 events or 700 patients in the FAS. The final analysis was planned after 481 events or inclusion of 930 patients at the latest.

After the second interim analysis, the data monitoring committee recommended stopping recruitment into the trial since the primary objective had been achieved (that is, proof of non-inferiority in 2-year event-free survival of treosulfan compared to busulfan). The sponsor followed this recommendation and stopped recruitment after a total of 570 patients had been included. The first patient was enrolled in the trial on 13 June 2013 and the last patient completed the trial (including post-surveillance) on 25 January 2018. The results for the second interim analysis (confirmatory analysis) in 476 patients were reported on 15 September 2017, and the results for the final analysis in 570 patients were reported on 5 March 2020.

Of note, following the first planned interim analysis of 279 enrolled patients in Study MC-FludT.14/L Trial I, the study was amended regarding the dose and schedule of the treosulfan regimen, as per recommendations of the Data Monitoring Committee based on unfavourable findings, that is increased cumulative incidence (95% confidence interval (CI)) of transplant-related mortality in the treosulfan group compared to the busulfan group (7.9% (4.7, 13.3) versus 4.0% (1.8, 8.7): Hazard Ratio (95.2% CI) = 2.14 (0.80, 5.72); p = 0.0630).

The Data Monitoring Committee concluded that the likely reason for the partly unfavourable findings was due to ‘imbalanced dosing’ of the treosulfan and busulfan groups. It recommended that the clinical study protocol be amended with respect to the treosulfan dose, the duration of follow-up, and the sample size. The sponsor consequently agreed to amend (Amendment 03) the clinical study protocol with respect to:

- decreasing the treosulfan dose from 3 doses of 14 g/m^2 given once a day for three days, to 3 doses of 10 g/m^2 given once a day for three days;
- shifting the treosulfan treatment days from Days -6,-5,-4 to Days -4,-3,-2 prior to alloHSCT;
- increasing the duration of follow-up for event-free survival from one to two years;
- increasing the sample size to enrol 960 patients to allow for at most 481 event-free survival events or 930 randomised patients qualifying as the FAS population.

The final analysis of Study MC-FludT.14/L Trial I in 330 patients enrolled before implementation of Amendment 03 (171 patients to the treosulfan group and 159 to the busulfan group) confirmed the unfavourable findings of the first interim analysis in 279 enrolled patients. A total of 50 patients (32.9%) receiving busulfan and 64 patients (38.1%) receiving treosulfan experienced an event-free survival event at 12 months of relapse of disease, graft failure or death. The event-free survival at 12 months (primary endpoint) was 67.5% (95% CI: 59.3%, 74.3%) in the busulfan group and 62.1% (95% CI: 54.3%, 69.0%) in the treosulfan group. The hazard ratio for event-free survival in the treosulfan group compared to the busulfan group was 1.23 (95.2% CI: 0.84%, 1.80%), adjusted for donor type, risk group and centre. The test for non-inferiority of treosulfan compared to busulfan was non-significant (adjusted p = 0.3808). Therefore, non-inferiority of treosulfan conditioning compared to busulfan conditioning for event-free survival could not be demonstrated, with 330 out of 545 planned patients included in this analysis. Consequently, no further information on non-inferiority of the treosulfan 14 g/m^2 compared to busulfan from Study MC-FludT.14/L Trial I was available. As the initially planned power of Study MC-FludT.14/L Trial I was not reached the conclusions drawn from this trial are descriptive.

As the pivotal Study MC-FludT.14/L Trial II continued with a significantly altered treosulfan treatment regimen following protocol Amendment 03, data for patients enrolled in this study were analysed separately from patients enrolled in Study MC-FludT.14/L Trial I.

Trial location

The trial was performed at 31 sites which includes 2 sites in France, 20 sites in Germany, 6 sites in Italy, 2 sites in Poland, and one site in Hungary. All sites were specialised transplantation centres.

Study objectives

The study aimed to compared event-free survival within two years after transplantation between treosulfan based conditioning and busulfan based conditioning; events were defined as disease relapse, graft failure, or death (whatever occurred first). Secondary objectives were as follows:

- Comparison of incidence of Common Terminology Criteria (CTC)[13] Grade III/IV mucositis between Day -6 and Day 28.
- Comparison of overall survival and cumulative incidence of relapse, non-relapse mortality and transplant-related mortality within 2 years after transplantation.
- Comparison of Day 28 conditional cumulative incidence of engraftment.
- Comparison of Day 28 and Day 100 incidence of complete donor type chimerism

[13] **Common Terminology Criteria (CTC)** is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 - Mild, 2 - Moderate, 3 - Severe, 4 - Life threatening, 5 - Death.

- Comparison of cumulative incidence of acute and chronic graft versus host disease (GvHD) within 2 years after transplantation
- Comparison of incidence of other CTC Grade III/IV adverse events between Day -6 and Day 28

Key inclusion and exclusion criteria

Key inclusion and exclusion criteria are outlined in Table 3 below.

Table 3: Study MC-FludT.14/L Trial II Key inclusion and exclusion criteria

Patients	**Key inclusion criteria** • Patients with AML or MDS according to the World Health Organisation 2008;[14] indicated for allogeneic haematopoietic progenitor cell transplantation but considered to be at increased risk for standard conditioning therapies according to the following criteria: patients aged ≥ 50 years at transplant and/or patients with a haematopoietic cell transplantation co-morbidity index score > 2 • Availability of an HLA-identical sibling donor or HLA-identical unrelated donor • Adult patients 18 to 70 years of age • Karnofsky Index ≥ 60 (that is, patient may require occasional assistance at most, but able to care for most of their needs) **Key exclusion criteria** • Patients considered contra-indicated for allogeneic HSCT due to severe concomitant illness (within 3 weeks prior to scheduled Day -6): severe renal impairment (on dialysis or prior renal transplantation or S-creatinine > 3.0 x ULN or calculated creatinine clearance < 60 mL/min); severe pulmonary impairment, diffusing capacity for carbon monoxide per single breath (haemoglobin adjusted)/or forced expiratory volume in one second < 50% or severe dyspnoea at rest or requiring oxygen supply; severe cardiac impairment diagnosed by electrocardiogram and left ventricular ejection fraction < 40%; severe hepatic impairment with hyperbilirubinaemia > 3 x ULN or alanine transaminase / aspartate transaminase > 5 x ULN. • Active malignant involvement of the central nervous system • Human immunodeficiency virus-positivity, active non-controlled infectious disease under treatment (no decrease of C-reactive protein or procalcitonin) including active viral liver infection. • Previous allogeneic HSCT. • Pleural effusion or ascites with volume of fluid > 1.0 L. • Pregnancy or lactation. • Known hypersensitivity to treosulfan, busulfan and/or related ingredients. • Participation in another experimental drug trial within 4 weeks prior to Day -6 of the protocol • Applicable to Germany, Hungary, Italy and Poland: patients with acute promyelocytic leukaemia with t(15;17)(q22;q12)[15] and in first complete remission. • (Applicable to France only) Patients with acute promyelocytic leukaemia with t(15;17)(q22;q12) and in first complete remission; Patients with cytogenetic

[14] World Health Organization (WHO), Edited by Swerdlow SH et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, WHO Classification of Tumours, 4th Edition, Volume 2.

[15] t(15;17)(q22;q12) is specific type of chromosome translocation.

	favourable AML ('low risk') and in CR1, who did not present unfavourable clinical or disease features like secondary or therapy related AML or insufficient response to AML induction therapy; Patients with MDS with Revised International Prognostic Scoring System 'very low risk' or 'low risk' at trial entry, who did not present unfavourable clinical features during disease history like refractory severe thrombocytopenia with severe bleeding complications, life threatening infectious complications due to severe neutropenia and/or very high red blood cell transfusion requirement and related complications.
Intervention (that is, test drug)	Treosulfan, 3 x once daily doses of 10 g/m^2 intravenously (Days -4, -3 and -2)
Comparator (that is reference drug)	Busulfan, 4 x 0.8 mg/kg given every 6 hours over 2 days (Days -4 and -3)
Endpoints	**Primary endpoint** • Event-free survival within 2 years after transplantation; events were defined as relapse of disease, graft failure or death (whatever occurred first). Event-free survival was measured from time of end of HSCT (= Day 0) to time of event. **Secondary objectives** • Primary or secondary graft failure • Overall survival • Relapse/progression (incidence of relapse) • Non-relapse mortality • Relapse mortality • Transplantation related mortality • GvHD-free relapse or progression-free survival • Chronic GvHD-free relapse or progression-free survival

Abbreviations: AML = acute myeloid leukaemia; HLA = human leukocyte antigen; GvHD = graft versus host disease; HSCT = haematopoietic stem cell transplantation; MDS = myelodysplastic syndrome; ULN = upper limit of normal.

Randomisation and blinding

Patients who met enrolment criteria were centrally randomised using a computer generated randomisation list to treatment with either busulfan or treosulfan, with randomisation performed in a 1:1 ratio and stratified by cytogenetic and/or molecular risk group for AML and the Revised International Prognostic Scoring System (IPSS-R);[16] for MDS, as well as donor type:

- *Risk group*: risk group I = low risk and intermediate risk for AML or very low, low or intermediate IPSS-R for MDS versus Risk group II = high risk for AML and high, or very high IPSS-R risk for MDS.
- *Donor type*: matched unrelated donor versus matched related donor.

Blinding of trial medication was considered not feasible due to different treatment schedules within the test (treosulfan) and reference (busulfan) groups with regard to different infusion

[16] **Revised International Prognostic Scoring System (IPSS-R)** is a standard for assessing prognosis of primary untreated adult patients with myelodysplastic syndromes. IPSS-R is based on five factors including the percentage of blasts in the bone marrow, the type and number of chromosome abnormalities in the cells and the level of red blood cells in the patient's blood.

regimens as well as the additional anticonvulsive treatment, which was mandatory in the busulfan group.

Statistical analysis

Following protocol Amendment 03, a new sample size calculation was required to assess the non-inferiority of the modified treosulfan based conditioning regimen. Only those patients enrolled after implementation of protocol Amendment 03 were included in the confirmatory analysis. The sponsor committed to randomise 930 patients (or collect data for a maximum of 481 events) qualifying for the FAS population in Study MC-FludT.14/L Trial II. The sample size estimation assumed under the alternative hypothesis that treosulfan based conditioning is equally effective as busulfan based conditioning (that is, hazard ratio = 1). The power of the trial was 80%.

The primary objective of the study was to demonstrate non-inferiority of treosulfan as an alternative conditioning agent to busulfan with respect to event-free survival. The study protocol included a comprehensive discussion of the selection of the non-inferiority margin (event-free survival at 24 months) used in the study. Event-free survival at 24 months is an accepted primary efficacy endpoint, considering both regimens achieve high rates of engraftment. The clinical evaluation concluded that selection of the event-free survival at 24 months as the primary objective of the study and the non-inferiority (θ_0) margin of 1.3 (-log hazard ratio = -0.2624) has been adequately justified.

For the secondary efficacy endpoints, data for the FAS and per-protocol set (PPS);[17] populations were analysed. For the endpoints overall survival, transplant-related mortality, GvHD-free and relapse or progression-free survival, and chronic GvHD-free and relapse or progression-free survival as well as the exploratory endpoints time to deterioration of Karnofsky Performance Score[18] by 20 points or higher and deterioration of KPS to less than 60 points, Kaplan-Meier estimates were calculated.

Participant flow

A total of 570 patients were included in the last analysis. The majority of patients were recruited in Germany (387 patients, 67.9%); recruitment numbers for other countries were Poland (77 patients, 13.5%), Italy (57 patients, 10.0%), Hungary (35 patients, 6.1%), and France (14 patients, 2.5%).

At the end of the trial, 18.6% of the 570 randomised patients were alive and had not undertaken their Month 24 visit, 43.9% terminated the study alive after 24 months, and 37.5% terminated the study prematurely. Death was the predominant reason for premature study termination, with 31.4% of patients dying within 24 months, 36.9% in the busulfan group and 25.7% in the treosulfan group.

Major protocol violations or deviations

Of the 570 randomised patients included in the study, 35.3% had a major protocol deviation. 'Missing evaluation at Baseline' was the most common subcategory of protocol deviation. It

[17] The **per-protocol (PP)** analysis is restricted to the participants who strictly adhered to the protocol. Also known as 'on-treatment' analysis.

[18] **Karnofsky Index**, also known as Karnofsky Performance Score Index allows patients to be classified as to their functional impairment. This index can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

appears unlikely that the major protocol deviations observed in the study have significantly prejudiced the efficacy and safety analyses, or exposed patients to unacceptable treatment risks.

Baseline and disease characteristics

Treatment arms were well balanced with respect to baseline demographic data.

Patients with acute myeloid leukaemia

Of the total population in the FAS (n = 551), 63.9% (352 of 551) of patients had AML, including 30.5% (168 of 551) of patients in the busulfan group and 33.4% (184 of 551) of patients in the treosulfan group. The AML disease characteristics were similar between the two groups. The proportion of patients in the two groups with cytogenetic detected markers and molecular detected markers was generally comparable. Remission status, blast count in bone marrow, and risk group stratification prior to randomisation were generally comparable in the two treatment groups.

Patients with myelodysplastic syndrome

Of the total population in the FAS (n = 551), 36.1% (199 of 551) of patients had been diagnosed with MDS, including 20.9% (115 of 551) of patients in the busulfan group and 15.2% (84 of 551) of patients in the treosulfan group. The MDS disease characteristics were similar between the two treatment groups. The proportion of patients in the two group with cytogenetic markers detected was generally comparable. Disease status, blast count in bone marrow, red blood cell transfusion dependency, IPSS-R and World Health Organization (WHO) Classification based Prognostic Scoring System (WPPS)[19] score, and risk group stratification prior to randomisation were generally comparable for the two treatment groups.

Donor type

The donor types between the two treatment groups were similar in the total population, and in AML and MDS patients.

Results

The results for event-free survival, including post surveillance evaluation, are summarised below in Table 4 for the PPS and FAS.

Table 4: Study MC-FludT.14/L Trial II Results for event-free survival including post surveillance evaluation (per-protocol set and full analysis set)

	Per-protocol set		**Full analysis set**	
	Busulfan (n = 275)	Treosulfan (n = 262)	Busulfan (n = 283)	Treosulfan (n = 268)
Median follow-up (months) (range of those surviving)	29.4 (3.9, 54.3)	29.7 (3.0, 52.1)	29.4 (3.0, 54.3)	29.7 (3.0, 52.1)
Patients with event	134 (48.7%)	96 (36.6%)	137 (48.4%)	97 (36.2%)
Death	53 (19.3%)	34 (13.0%)	56 (19.8%)	35 (13.1%)
Relapse/progression	72 (26.2%)	61 (23.3%)	72 (25.4%)	61 (22.8%)
Primary graft failure	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Secondary graft failure	8 (2.9%)	0 (0.0%)	8 (2.8%)	0 (0.0%)

[19] **World Health Organization (WHO) Classification based Prognostic Scoring System (WPPS)** evaluates prognosis of patients with myelodysplastic syndrome.

	Per-protocol set		Full analysis set	
	Busulfan (n = 275)	Treosulfan (n = 262)	Busulfan (n = 283)	Treosulfan (n = 268)
Patients without event	141 (51.3%)	166 (63.4%)	146 (51.6%)	171 (63.8%)
EFS at 12 months (%) (95% CI)	60.5 (54.5, 66.0)	69.7 (63.7, 74.9)	60.8 (54.9, 66.3)	70.0 (64.1, 75.1)
EFS at 24 months (%) (95% CI)	51.1 (44.8, 57.0)	65.3 (59.0, 70.9)	51.2 (45.0, 57.0)	65.7 (59.5, 71.2)
EFS at 36 months (%) (95% CI)	49.6 (43.1, 55.7)	58.9 (51.5, 65.6)	49.7 (43.3, 55.7)	59.5 (52.2, 66.1)
Hazard ratio (treosulfan / busulfan) (95% CI)	0.64 (0.48, 0.84)		0.64 (0.49, 0.84)	
Hazard ratio (treosulfan / busulfan) (99.7476% CI)	0.64 (0.42, 0.97)		0.64 (0.42, 0.97)	
p-value for testing non-inferiority of treosulfan compared to busulfan	0.0000001		0.0000001	
p-valued for testing superiority of treosulfan compared to busulfan	0.0005777		0.0005787	
p-valued for testing difference	0.0011553		0.0011574	

Abbreviations: CI = confidence interval; EFS = event-free survival.

In the final analysis, non-inferiority of treosulfan compared to busulfan with respect to event-free survival at 24 months was demonstrated in both the PPS and FAS populations. Since statistically significant non-inferiority of treosulfan compared to busulfan was shown in the FAS, superiority testing was undertaking in this analysis set. The results showed that event-free survival at 24 months in the FAS was statistically significantly superior in the treosulfan group compared to the busulfan group. The results for event-free survival in the final analysis were consistent with those observed in the second interim (confirmatory).

Secondary endpoints

Overall survival: at the time of the post-surveillance evaluation, more patients were alive in the treosulfan group than in the busulfan group (69.8% versus 60.4%, respectively). The Kaplan-Meier estimate for overall survival at 24 months after alloHSCT was higher in the treosulfan group than in the busulfan group (72.7% versus 60.2% respectively).

Relapse or progression: the proportion of patients in the two treatment groups experiencing relapse or progression was similar in the busulfan and treosulfan groups (25.4% versus 22.8%, respectively), as was the cumulative incidence of relapse or progression at 24 months after alloHSCT (25.2% versus 22.0%, respectively).

Graft failure: more patients in the busulfan group than in the treosulfan group experienced graft failure (3.2% versus 0.4% respectively). The cumulative incidence of graft failure at 24 months

after alloHSCT was higher in the busulfan group than in the treosulfan group (3.2% versus 0.4%, respectively).

Non-relapse mortality: the cumulative incidence of non-relapse mortality at 24 months was notably higher in the busulfan group than in the treosulfan group (20.4% versus 12.0% respectively).

Relapse mortality: the proportion of patients who had died after experiencing disease relapse or progression was comparable between the busulfan and treosulfan groups (18.0% versus 16.8%, respectively). The cumulative incidence of relapse mortality at 24 months was greater in the busulfan group than in the treosulfan group (17.6% versus 14.9%), but the cumulative incidence of relapse mortality at 36 months was comparable between the two groups (20.8% versus 18.6%).

Transplantation related mortality: a greater proportion of patients in the busulfan group than in the treosulfan group had died from transplantation related causes (20.5% versus 12.3%, respectively). The Kaplan-Meier estimate of transplant-related mortality at 24 months was notably greater in the busulfan group than in the treosulfan group (24.1% versus 12.8%, respectively). The proportion of patients in the FAS who died with infection as cause of death was higher in the busulfan group (40 patients, 14.1%) than in the treosulfan group (25 patients, 9.3%); similarly, the proportion of patients in the FAS who died due to events other than infection was higher in the busulfan group (18 patients, 6.4%) than in the treosulfan group (8 patients, 3.0%).

Engraftment: the conditional cumulative incidence of reconstitution of granulopoiesis at 28 days after alloHSCT in was similar in the busulfan and treosulfan groups, and the maximum conditional cumulative was 100% in both treatment groups.

The conditional cumulative incidence of reconstitution of leukopoiesis at 28 days after alloHSCT was similar in the busulfan and treosulfan groups, and the maximum conditional cumulative was 100% in both treatment groups.

The conditional cumulative incidence of reconstitution of thrombopoiesis higher than 20 x 109/L at 28 days after alloHSCT was higher in the busulfan group than in the treosulfan group, however, the maximum conditional cumulative incidence was similar in the two treatment groups (99.6% versus 99.2%, respectively).

The conditional cumulative incidence of reconstitution of thrombopoiesis higher than 50 x 109/L at 28 days after alloHSCT was higher in the busulfan group than in the treosulfan group, however, the maximum conditional cumulative incidence was similar in the two treatment groups (98.8% versus 98.9%, respectively).

Complete donor type chimerism: the incidence of complete donor type chimerism at both the Day 28 and Day 100 visits was higher in the treosulfan group than in the busulfan group.

Graft versus host disease-free and relapse or progression-free survival: at the end of the study, the proportion of patients who were alive and had not experienced GvHD or relapse or progression was higher in the treosulfan group than in the busulfan group (51.5% versus 40.3%, respectively). The Kaplan-Meier estimate of GvHD-free and relapse or progression-free survival at 24 months was greater in the treosulfan group than in the busulfan group (50.3% versus 37.1%, respectively).

Chronic graft versus host disease-free and relapse or progression-free survival: at the end of the study, the proportion of patients who were alive and had not experienced chronic GvHD or relapse or progression was higher in the treosulfan group than in the busulfan group (52.2% versus 40.6%, respectively). The Kaplan-Meier estimate of chronic GvHD-free or relapse or

progression-free survival at 24 months was greater in the treosulfan group than in the busulfan group (51.4% versus 37.2%).

Efficacy (paediatric population)

Dose selection for pivotal studies

The treosulfan dose being proposed by the sponsor for registration in the paediatric population with malignant and non-malignant disease based on body surface area (BSA) less than 0.4 m^2, from 0.4 to less than 0.9 m^2, or more than or equal to 0.9 m^2 is 10, 12 or 14 g/m^2, respectively. The proposed treosulfan dose in the paediatric population is based on PopPK modelling using historical data and data derived from the paediatric Studies MC-FludT.16/NM and MC-FludT.17/M (Venn Life Sciences 2020).

The recommended BSA dependent dose of treosulfan being proposed by the sponsor for the paediatric population with malignant and non-malignant disease differs from that administered in Studies MC-FludT.17/M and FludT.16/NM.

The concern relating to the use of a 14 g/m^2 dose in children and adolescents with a BSA at least 0.9 m^2 is discussed in *Risk-benefit analysis* section below.

Evaluable efficacy data

The clinical studies submitted for the evaluation of the efficacy and safety of treosulfan in the proposed paediatric population include:

- Study MC-FludT.17/M is a multinational, multicentre, open label, non-randomised, non-controlled, single arm (treosulfan 10 to 14 g/m^2) Phase II study in 70 paediatric patients with haematological malignancies (that is., acute lymphoblastic leukaemia (ALL), AML, MDS or juvenile myelomonocytic leukaemia (JMML)) requiring myeloablative conditioning treatment prior to alloHSCT. This was the key study submitted to support approval of treosulfan based conditioning for the treatment of malignant disease in paediatric patients aged 28 days to 17 years.
- Study MC-FludT.16/NM is a multinational, multicentre, open label, randomised, controlled Phase II study in paediatric patients with non-malignant diseases requiring myeloablative conditioning treatment prior to alloHSCT

In addition to the above, the submission also included an EBMT Registry study in patients below 18 years with malignant or non-malignant disease who underwent autologous or allogeneic HSCT between January 2005 and July 2010 (Peters 2011), and an EBMT Registry study in patients below 18 years with non-malignant disease who underwent allogeneic HSCT between January 2010 and December 2014 (Peters 2017).

Study MC-FludT.17/M (pivotal study)

Study design

Study MC-FludT.17/M is a clinical Phase II trial designed to describe the safety and efficacy of treosulfan based conditioning therapy prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients with haematological malignancies.

This was a prospective, single arm, open label, multicentre, multinational, non-controlled, Phase II clinical trial with 4 phases:

- Treatment phase: 7 days with 3 days of treosulfan administration
- Observation phase: until Day 100 after HSCT

- Follow-up phase: until 12 months after HSCT
- Longer term follow-up phase: a minimum of 3 years after HSCT

The study included paediatric patients aged 28 days to 17 years with haematological malignant disease, who required myeloablative conditioning for first or second alloHSCT due to disease relapse, graft failure or secondary malignancy after previous HSCT.

Study objectives

The study's primary objective was to estimate the freedom from transplant (treatment) related mortality, defined as death from any transplant related cause from the day of first administration of trial medication (treosulfan) until Day 100 after HSCT in paediatric patients with haematological malignant diseases. This is a combined endpoint comprising transplant-related mortality evaluated from the end of alloHSCT until Day 100 after HSCT, and treatment related mortality which extends from the first dose of fludarabine (that is, visit Day -7) until Day 100 after alloHSCT.

Secondary objectives

- Evaluation of engraftment after HSCT (the first of 3 consecutive days for each of the following 4 criteria: Leucocytes more than 1 x 10^9/L, absolute neutrophil count more than 0.5 x 10^9/L, platelets at least 20 x 10^9/L in the absence of platelet transfusion, and platelets at least 50 x 10^9/L in the absence of platelet transfusion.
- Evaluation of safety until Day 100 after HSCT, serious adverse reactions (SARs) until the end of the longer term follow-up phase.
- Evaluation of hepatic sinusoidal obstruction syndrome, lung toxicity, hepatic toxicity and infections, until Day 100.
- Evaluation of donor type chimerism on Day 28, Day 100, and 12 months after HSCT.
- Evaluation of non-relapse mortality, transplant-related mortality, graft failure rate, incidence of relapse or progression, relapse-free survival or progression-free survival, and overall survival until 12 months after HSCT.
- Evaluation of incidence and severity of acute graft-versus-host disease (GvHD) (until Day 100) and chronic GVHD (until 12 months after HSCT).
- Evaluation of use of rescue therapies including donor lymphocyte infusions and further conditioning regimen.
- Evaluation of pharmacokinetic (PK) parameters of treosulfan and its epoxides, and to develop a PK model for assessing relevant covariates.
- Evaluation of non-relapse mortality, transplant-related mortality, secondary graft failure, relapse or progression, relapse-free survival or progression-free survival, overall survival and chronic GVHD during the longer term follow-up phase.

Trial location and dates

The trial was performed at 18 sites in total, in 5 countries, including 10 sites in Germany, 4 sites in Poland, 2 sites in Italy, and 1 site each in the United Kingdom, and Czechia. The first patient was enrolled on 21 November 2014, the patient completed the 12-month follow-up visit on 14 September 2014, and the last patient completed the follow-visit on 30 September 2019.

Inclusion and exclusion criteria

Key inclusion criteria include:

- haematological malignant disease indicated for alloHSCT (that is, acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), myelodysplatic syndromes (MDS), or Juvenile myelomonocytic leukaemia (JMML);
- indication for first alloHSCT or second alloHSCT due to disease relapse, graft failure, or secondary malignancy after previous HSCT;
- available matched sibling donor, matched family donor, or matched unrelated donor. For bone marrow and peripheral blood, match was defined as 9 of 10 or 10 of 10 allele match after 4-digit typing in human leukocyte antigens (HLA) A, B, C, and DRB1 and DQB1;
- subjects with ALL or AML in complete morphologic remission (blast counts less than 5% in bone marrow) and subjects with MDS or JMML with blast counts less than 20% in bone marrow at trial entry;
- age from 28 days to less than 18 years of age;
- Lansky Index;[20] (subjects aged less than 16 years) or Karnofsky Index;[18] (subjects aged 16 years or higher) performance score of at least 70%.

Key exclusion criteria include:

- third or subsequent alloHSCT;
- haematopoietic stem cell transplantation from haploidentical or umbilical cord blood donor;
- central nervous system involvement;
- treatment with cytotoxic drugs within 10 days prior to Day -7;
- body mass index more than 30 kg/m^2;
- Fanconi anemia and other deoxyribonucleic acid (DNA) breakage repair disorders; secondary leukaemia developed from the Fanconi anaemia or other DNA breakage repair disorders;
- impaired liver function, significant coagulopathy, impaired renal function, impaired cardiac function;
- severe active infection requiring deferral of conditioning.

Study treatments

All patients were treated with treosulfan intravenously over 2 hours on three consecutive days (Days -6, -5, and -2) prior to alloHSCT. The required total dose of treosulfan was based on the patient's BSA (Mosteller formula):

- BSA (m^2) no more than 0.5 received treosulfan dose 10 g/m^2/day
- BSA (m^2) more than 0.5 to 1.0 received treosulfan dose 12 g/m^2/day
- BSA (m^2) more than 1.0 received treosulfan dose 14 g/m^2/day

The study allowed administration of two different treosulfan based conditioning regimens for the treatment of ALL, AML, MDS, and JMML: a standard fludarabine containing regimen (regimen A); and an intensified regimen with fludarabine and thiotepa (regimen B). The regimen was selected by the investigator for each individual subject.

The total administered of fludarabine intravenously was 150 mg/m^2 (given after treosulfan); the total dose for thiotepa was 10 mg/kg intravenously (an interval of 24 hours between administration of treosulfan and thiotepa was required). Other concomitant medication (for

[20] **Lansky Index,** also known as Lansky Play - Performance Scale for Paediatric Functional Status uses parent description of child's activity to assess ability and response to treatment.

example prophylaxis for GvHD, infection or mucositis; growth factors; rescue therapies) could be administered according to the hospital practice.

The clinical evaluation highlights that the treosulfan dose based on the BSA in paediatric patients used in Study MC-FludT.17/M (as above) differs from the proposed treosulfan dose based on BSA for children aged more than one month to less than 18 years.

Statistical analysis

The study was descriptive in nature and not intended to test any pre-specified hypotheses. All analyses were exploratory. No confirmatory interim analysis was pre-specified. No covariate adjustments were made. No multivariate assessments were performed because of the small number of events and subjects in the subgroups.

Within the agreed EMA paediatric investigation plan, the Paediatric Committee requested enrolment of at least 70 evaluable subjects aged from 28 days to less than 18 years of age, and consisting of at least 30 patients aged from 28 days to less than 10 years, at least 30 patients aged from 10 to 18 years, and least 50 patients receiving a first HSCT. In accordance with the EMA-approved paediatric investigation plan, engraftment data for treosulfan from Study MC-FludT.17/M were to be compared with historical paediatric engraftment data as well as with adult engraftment data from Study MC-FludT.14/L Trial II. The results of the comparison were presented in a report (comparison of engraftment data version 1.0) dated 25 July 2017. In this report, paediatric data from Study MC-FludT.17/M were compared with historical paediatric data from the published literature and adult data from Studies MC-FludT.14/L Trial I and Trial II. The report included data from 330 patients included in Study MC-FludT.14/L Trial I and 460 patients included in the interim analysis of Study MC-FludT.14/L Trial II.

Participant flow

Study MC-FludT.17/M included a total of 70 patients for analysis. At the end of the longer term follow-up period, 14 (20%) patients had discontinued the study prematurely (death in 12 patients and lost to follow-up and withdrawal by one patient each), and 56 (80%) patients had completed the study and were alive. In the total patient population (n = 70), treosulfan intravenously BSA-adapted doses of 10 g/m^2, 12 g/m^2 and 14 g/m^2 were given to 6 (8.6%), 26 (37.1%) and 38 (54.3%) patients, respectively. Of the 70 subjects in the analysis, the 'intensified regimen' with thiotepa (Regimen B) was given to 65 (92.9%) patients.

Baseline data

The median age of the total population was 9.5 years (range: 0 to 17 years); all patients were White. The population included more males (62.9%) than females (37.1%).

More subjects included in the trial had AML (41.4%) and ALL (38.6%) than MDS (14.3%) or JMML (5.7%). More subjects had had matched unrelated donor transplantations (80.0%) than matched related donor transplantations (20.0%). The majority of subjects (54.3%) received a treosulfan dose of 14 g/m^2/day, and the majority of subjects (92.9%) received a first HSCT.

The median follow-up for the 70 patients was 41.8 months, with the range for those surviving being 24.2 to 57.5 months. The ages of the 70 patients were 28 days to 23 months (12.9%), 2 to 11 years (40.0%), and 12 to 17 years (47.1%). The treosulfan dose was adapted individually based on BSA (that is, no more than 0.5 m^2, more than 0.5 to 1 m^2, and more than 1 m^2 received treosulfan 10 g/m^2 (6 patients, 8.6%), 12 g/m^2 (26 patients, 37.1%) or 14 g/m^2 (38 patients, 54.3%), respectively).

Primary endpoint results (safety)

The rate for freedom from transplant (treatment) related mortality until 100 days after alloHSCT was 98.6% (90% CI: 93.4, 99.9). Only one of the 70 patients died due to transplant (treatment) related mortality until 100 days after alloHSCT (that is, one patient with AML aged 12 to 17 years treated with treosulfan 14 g/m^2 (intensified regimen with thiotepa)).

Secondary efficacy endpoints

Engraftment:

- Reconstitution of granulopoiesis = 98.6%
  - Conditional cumulative incidence at 14 days post alloHSCT = 28.6%
  - Conditional cumulative incidence at 28 days post alloHSCT = 86.9%
  - Median duration of neutropenia = 22 days (range: 7 to 44 days)
- Reconstitution of leucopoiesis = 98.6%
  - Conditional cumulative incidence at 14 days post alloHSCT = 30.0%
  - Conditional cumulative incidence at 28 days post alloHSCT = 95.6%
  - Median duration of leukopenia = 20 days (range: 11 to 42 days)
- Reconstitution of thrombopoiesis (platelets more than 50 x 10^9/L) = 90.0%
  - Conditional cumulative incidence at 14 days post alloHSCT = 15.7%
  - Conditional cumulative incidence at 28 days post alloHSCT = 62.2%

Complete donor chimerism (at least 95% donor cells):

- At Day 28 = 94.2%
- At Day 100 = 91.3%
- At month 12 = 91.2%

Transplant related mortality:

- At end of longer term follow-up period = 5.7%
- Kaplan-Meier estimates of transplant-related mortality at Day 100, 12 months, 24 months and 36 months after alloHSCT were 1.4%, 1.4%, 4.6%, and 4.6% respectively

Non-relapse mortality:

- At end of longer term follow-up period = 2.9%
- Cumulative incidence of non-relapse mortality at 12 months = 1.4%, and 2.9% at both 24 and 36 months after HSCT

Overall survival:

- Median duration of follow-up = 41.8 months (range: 24.2 to 57.5 months)
- At end of longer term follow-up period, overall survival = 82.9%
- Kaplan-Meier estimates of overall survival at 12, 24 and 36 months after alloHSCT were 91.4%, 85.7% and 84.3%, respectively
- Overall survival results at 36 months in disease subgroups:
  - Acute lymphoblastic leukaemia (n = 27): 81.5%
  - Acute myeloid leukaemia (n = 29): 86.2%
  - Myelodysplastic syndrome (n = 10): 90.0%

  - Juvenile myelomonocytic leukaemia (n = 4): 75.0%

Relapse or progression

- At end of longer term follow-up period = 22.9%
- Cumulative incidence of relapse or progression at 12, 24 and 36 months was 15.7%, 23.0% and 23.0%, respectively
- Relapse or progression in disease subgroups (overall survival):
  - Acute lymphoblastic leukaemia (n = 27): 29.6%
  - Acute myeloid leukaemia (n = 29): 17.2%
  - Myelodysplastic syndrome (n = 10): 0%
  - Juvenile myelomonocytic leukaemia (n = 4): 75.0%

Relapse-free survival or progression-free survival

- Kaplan-Meier estimates of relapse-free survival or progression-free survival at 12, 24, and 36 months after HSCT were 82.9%, 72.7% and 72.7%, respectively.

Graft failure

- None of the 70 patients experienced a primary graft failure.
- One (1.4%) patient with ALL aged 12 to 17 years experienced a secondary graft failure. This patient had been treated with treosulfan 14 g/m^2/day using the intensified regimen with thiotepa.

Event-free survival

- At the end of the longer term follow-up period, event-free survival = 27.1%
  - two (2.9%) deaths
  - sixteen (22.9%) disease relapse or progression
  - one (1.4%) secondary graft failure
- Kaplan-Meier estimate of event-free survival at 12 months after HSCT = 81.4%, after 24 months = 72.7%, after 36 months = 72.7%
- Event-free survival results at 36 months in disease subgroups:
  - Acute lymphoblastic leukaemia (n = 27): 66.7%
  - Acute myeloid leukaemia (n = 29): 79.3%
  - Myelodysplastic syndrome (n = 10): 88.9%
  - Juvenile myelomonocytic leukaemia (n = 4): 25.0%

Evaluation of rescue therapies

- At the end-of the longer term follow-up period, 15.7% of patients treated with treosulfan based conditioning received rescue therapies, that is
  - 7.1% received donor lymphocyte infusions
  - 5.7% received stem cell boost
  - 2.9% received chemotherapy due to relapse
  - no patients received further conditioning treatment
  - 4.3% received other rescue therapies

Graft versus host disease

See *safety* section below.

Pre-specified comparison

The agreed paediatric investigation plan between the sponsor and the EMA specified a comparison relating to engraftment (reconstitution of granulopoiesis) between the paediatric data for patients with haematological malignancies treated with treosulfan based conditioning from Study MC-FludT.17/M and both historical paediatric data for patients with haematological malignancies treated with treosulfan based and busulfan based conditioning and adult data for patients with malignancies treated with treosulfan based and busulfan based conditioning from Study MC-FludT.14/L Trials I and II.

Comparison between paediatric data from Study MC-FludT.17/M and published paediatric trials:

- Maximum cumulative engraftment rate for Study MC-FludT.17/M of 96.9% (90% CI: 93.3, 100) for reconstitution of granulopoiesis was reported to be within the range found in published paediatric historical trials (94% to 100% for treosulfan based conditioning regimens and 89% to 100% for busulfan based conditioning regimens.
- One-year overall survival of 88.2% in Study MC-FludT.17/M was reported to be above the range reported in the literature for both treosulfan based (82% to 85%) and busulfan based (78% to 88%) conditioning regimens.
- One major limitation relates to the impact of different treosulfan based conditioning regimen in the studies (Study MC-FludT.17/M and historical) compared.

Comparison between paediatric data from Study MC-FludT.17/M and adult data from Study MC-FludT.14/L:

- Maximum cumulative engraftment rate for Study MC-FludT.17/M of 96.9% for the reconstitution of granulopoiesis was within the range observed in adult patients in Study MC-FludT.14/L Trials I and II (95.7% to 99.3%).
- One-year overall survival of 88.2% in Study MC-FludT.17/M was higher compared to adult patients treated with treosulfan based conditioning in Study MC-FludT.14/L Trials I and II (68% and 75.3%, respectively) and in patients treated with busulfan based conditioning in the two Study MC-FludT.14/L trials (67.8% to 74.3%).
- Limitations of the comparison relate to the different patient populations (paediatric versus adult) and the different treosulfan based condition regimens, which predominantly included thiotepa in paediatric patients but excluded thiotepa in adult patients.

European Group for Blood and Marrow Transplantation Registry study meta-analysis (Peters 2011)

In the EBMT Registry study (Peters 2011), patients below 18 years with malignant or non-malignant disease who underwent HSCT between January 2005 and July 2010 and were registered in the EBMT database were eligible for inclusion in the meta-analysis. The objectives of the analysis were to evaluate the efficacy and safety of treosulfan based conditioning prior to alloHSCT and autologous HSCT.

A total of 626 patients were included into the analysis; 41 (7%) were aged less than 0.5 years, 65 (10%) were aged 0.5 to 1 year, 358 (57%) were aged 1 to 12 years, and 162 (26%) were aged 13 through 18 years. There were 270 (43%) patients with malignant disease and 356 (57%) patients with non-malignant disease. A total of 533 (85%) patients had received an alloHSCT and 93 (15%) patients an autologous HSCT. A total of 513 (83%) patients had received their first transplant, 98 (16%) patients had received their second transplant, and 9 (1%) patients had received their third transplant. Donors representing at least 20% were identical sibling

(123 donors, 20%) and unrelated donors (208 donors, 33%). A total of 513 (83%) of patients had received a treosulfan based conditioning regimen during their first HSCT.

Of the 533 patients who had received an alloHSCT, 177 (33%) had malignant disease (76 with ALL, 62 with AML, 26 with other leukaemia or lymphoma, and 13 with other solid tumours), and 356 (67%) had non-malignant disease.

For alloHSCT, the median total treosulfan dose was 42 g/m^2. There were 24 (5%) patients received less than 33 g/m^2, 153 (29%) patients received between 33 and 39 g/m^2, 332 (62%) patients received between 39 and 45 g/m^2, and 13 (2%) patients received more than 45 g/m^2. For autologous HSCT the median treosulfan dose was 36 g/m^2.

A total of 521 alloHSCT (165 patients with malignant disease and 356 patients with non-malignant disease) and 83 autologous HSCT had been completely documented for the most important prognostic factors and were included in the outcome evaluation.

Outcomes (allogeneic haematopoietic stem cell transplantation)

Engraftment: 96% of patients with malignant disease; absolute neutrophil count at least 0.5 x 10^9/L.

Engraftment: 94% patients with non-malignant disease; absolute neutrophil count at least 0.5 x 10^9/L.

Overall survival: the 3-year probabilities of overall survival were 75% versus 84% versus 70% versus 60% in patients aged less than 6 months versus 6 months to 1 year versus 1 to 12 years versus more than 12 years, respectively (p = 0.053). The 3-year probabilities of transplant related mortality were not markedly different across the age groups.

Event-free survival: the 3-year probabilities of event-free survival significantly decreased with increasing age: 75% versus 75% versus 62% versus 53% in patients aged less than 6 months, 6 months to less than one year, 1 to 12 years and more than 12 years, respectively, p = 0.028.

Disease related mortality and transplant related mortality: there was no statistically significant relationship between treosulfan dose and disease related mortality (24% versus 15% versus 13% for no more than 3 x 11 g/m^2 versus more than 3 x 11 g/m^2 to 3 x 13 g/m^2 versus more than 3 x 13 g/m^2, respectively, p = 0.415) or between treosulfan dose and transplant related mortality (12% versus 14% versus 11% for no more than 3 x 1 g/m^2 versus more than 3 x 11 g/m^2 to 3 x 13 g/m^2 versus more than 3 x 13 g/m^2, respectively, p = 0.659).

European Group for Blood and Marrow Transplantation Registry study meta-analysis (Peters 2017)

In the EBMT Registry study (Peters 2017), patients below the age of 18 years with non-malignant disease who underwent alloHSCT between January 2010 and December 2014 and were registered in the EBMT database were eligible for inclusion in the meta-analysis. The objectives were to analyse the efficacy and safety of treosulfan based or busulfan based conditioning regimens in paediatric patients with non-malignant disease.

The study included 2187 patients who were grouped according to the given combination conditioning regimen, that is, treosulfan / fludarabine in 422 patients; busulfan / fludarabine in 1063 patients; treosulfan / fludarabine / thiotepa in 473 patients; and busulfan / fludarabine / thiotepa in 229 patients.

The median age at transplantation in the total population was 3.7 years (range: 0 to 18 years), and the median age was significantly different (p < 0.0001) for the conditioning groups

(1.5 versus 4 versus 4.8 versus 4.5 years for the treosulfan / fludarabine, busulfan / fludarabine, treosulfan / fludarabine / thiotepa and busulfan / fludarabine / thiotepa groups, respectively).

There were a number of different non-malignant diseases included in the dataset. Conditions reported in at least 10% of patients were haemoglobinopathies (590 patients, 27.0%), other inherited disorders (351 patients, 16.1%), primary immunodeficiency or severe combined immunodeficiency (320 patients, 14.6%), and primary immunodeficiency or other (324 patients, 14.8%). Patients with Fanconi anaemia were excluded. More patients with haemoglobinopathies received a treosulfan containing and a thiotepa containing regimen compared to histiocytic disorders. In contrast, more patients with bone marrow failure syndromes were conditioned with busulfan containing regimen. The median dose of busulfan, fludarabine, treosulfan and thiotepa was comparable in the 4 different conditioning regimens. The median doses in the total population were as follows: treosulfan dose was 42.0 g/m^2 (range: 20.0 to 57.0 g/m^2); busulfan dose was 16.0 mg/kg (range: 0.2 to 35.6 mg/kg); fludarabine dose was 160.0 mg/m^2 (range: 120.0 to 185.7 mg/m^2); and the thiotepa dose was 10.0 mg/kg (range: 4.0 to 16.0 mg/kg).

Outcomes

Primary efficacy outcomes: one-year overall survival was significantly different across the 4-conditioning regimen, with the best one-year overall survival of 89.5% was reported for the treosulfan / fludarabine / thiotepa group; the lowest treatment related mortality at Day 100 (4.8%) and at one year (8.3%) after HSCT was obtained for the treosulfan / fludarabine / thiotepa group.

Secondary efficacy outcomes

- In univariate analysis, disease-free survival after one year was best for the treosulfan / fludarabine / thiotepa group (86%) compared with each of the other three groups.
- Neutrophil engraftment at Day 28 after transplantation was identical (87.1%) in the treosulfan / fludarabine and treosulfan / fludarabine / thiotepa groups, and was higher in both of these groups higher than in the busulfan / fludarabine (84.7%) and busulfan / fludarabine / thiotepa (74.8%) groups, while engraftment at Day 100 after transplantation was similar in the treosulfan / fludarabine / thiotepa (96.1%), treosulfan / fludarabine (95%) and busulfan / fludarabine (95%) groups and notably higher in these three groups than in the busulfan / fludarabine / thiotepa (83.5%) group.
- In the multivariate analyses, overall survival was significantly better in the treosulfan / fludarabine group compared to the busulfan / fludarabine group, but there were no significant differences between the treosulfan / fludarabine group and either the treosulfan / fludarabine / thiotepa group or the busulfan / fludarabine / thiotepa group. There were no significant differences between the treosulfan / fludarabine group and each of the three other groups as regards transplant related mortality, disease-free survival, and incidence of disease recurrence in the multivariate analyses.
- Causes of death: The most common causes of death after HSCT for non-malignant disease were infection, GvHD, the original disease and transplant associated organ complications.

Study MC-FludT.16/NM (pivotal)

Study design

Study MC-FludT.16/NM is a clinical Phase II trial comparing treosulfan based conditioning therapy with busulfan based conditioning prior to alloHSCT in paediatric patients with non-malignant diseases.

This was a prospective, randomised, open label, multicentre, multi-national, active controlled, parallel group, clinical trial to describe the safety and efficacy of intravenous treosulfan compared with the conventional (myeloablative) dose of intravenous busulfan, each administered as part of a standardised fludarabine containing conditioning regimen.

The study consisted of 4 phases:

- Treatment phase: 7 days with 3 days of treosulfan (or 4 days of busulfan) administration.
- Observation phase: until Day 100 after HSCT.
- Follow-up phase: until 12 months after HSCT,
- Longer term follow-up phase: a minimum of 3 years after HSCT.

The treatment phase, observation phase and follow-up phase have been completed; the longer term follow-up phase is ongoing.

The study included paediatric subjects aged 28 days to 17 years with non-malignant disease, who required first myeloablative conditioning treatment followed by first alloHSCT.

The current clinical trial report cut-off data date was 7 June 2021. Longer term follow-up data will be collected until the last recruited subject has completed visit Month 36 and will be presented in an updated version of the Clinical Trials Regulation expected in 2023.

Study objectives

The study's primary objective was the comparative evaluation of freedom from transplantation (treatment) related mortality, defined as death from any transplantation (treatment) related cause from start of conditioning treatment (visit Day - 7) until Day 100 after HSCT. This was the primary study endpoint; a primary efficacy variable was not defined in this study.

Secondary objectives included:

- evaluation of engraftment after HSCT (the first of 3 consecutive days for each of the following 4 criteria: Leucocytes more than 1 x 10^9/L, absolute neutrophil count more than 0.5 x 10^9/L, platelets at least 20 x 10^9/L in the absence of platelet transfusion, and Platelets at least 50 x 10^9/L in the absence of platelet transfusion;
- evaluation of safety until Day 100 after HSCT, serious adverse events (SAEs) until the end of the longer term follow-up phase;
- evaluation of hepatic sinusoidal obstruction syndrome, lung toxicity, hepatic toxicity and infections, until Day 100;
- evaluation of donor type chimerism on Day 28, Day 100, and 12 months after HSCT;
- evaluation of overall survival until 12 months after HSCT;
- evaluation of primary and secondary graft failure until 12 months after HSCT;
- evaluation of incidence and severity of acute GvHD (until Day 100) and cGVHD (until 12 months after HSCT);
- evaluation of use of rescue therapies including donor lymphocyte infusions, stem cell infusions, re-occurrence of transfusion dependence;
- evaluation of PK parameters of treosulfan and its epoxides, and to develop a PK model for assessing relevant covariates;
- evaluation of secondary graft failure, cGVHD, donor type chimerism, overall survival and transplant-related mortality during the longer term follow-up phase;
- additional secondary endpoints event-free survival, GvHD-free survival, and chronic GvHD-free survival were also derived and evaluated.

Secondary efficacy endpoints included: engraftment (neutrophil, leucocyte, platelet), donor type donor chimerism, overall survival, graft failure, and evaluation of use of rescue therapies.

Trial location and dates

The trial was conducted at 27 sites in 6 countries, where 9 of these sites did not include any subjects (inactive sites): 11 sites (4 inactive) in Germany; 4 sites (one inactive) in Poland; 9 sites (2 inactive) in Italy; and one site in the Czechia. One site each in Austria and Romania were inactive.

Inclusion and exclusion criteria

Key inclusion criteria include:

- non-malignant disease indicated for first myeloablative alloHSCT (inborn errors of metabolism, primary immunodeficiencies, haemoglobinopathies, and bone marrow failure syndromes);
- first alloHSCT;
- available matched sibling donor, matched family donor, or matched unrelated donor. For bone marrow and peripheral blood, at least 9 of 10 allele matches after 4 digit typing in human leucocyte antigen (HLA) -A, -B, -C, -DRB1, and -DQB1 antigens. Umbilical cord blood match was defined as at least 5 of 6 matches after 2 digit typing in human leukocyte antigen-A and -B and 4 digit typing in -DRB1 antigens;
- age from 28 days to less than 18 years of age;
- Lansky Performance Index (subjects aged less than 16 years) or Karnofsky Performance Index (subjects aged 16 years or older) score of at least 70%.

Key exclusion criteria include:

- second or subsequent alloHSCT;
- HSCT from mismatched donor;
- pre-term newborn infants (less than 37 weeks gestational age) and term newborn infants aged 0 to 27 days at time of registration;
- body mass index more than 30 kg/m^2;
- Fanconi anaemia and other DNA breakage repair disorders; radiosensitive disorders; and dyskeratosis congenita;
- treatment with cytotoxic drugs within 10 days prior to Day -7;
- impaired liver function, significant coagulopathy, impaired renal function, impaired cardiac function, active infectious hepatitis with clinical evidence;
- severe active infection requiring deferral of conditioning.

Study treatments

Treosulfan: Subjects randomised to treosulfan were treated with treosulfan intravenously over on 4 consecutive days (Days -7, -6, -5, and -4) prior to alloHSCT (Day 0). The required total dose of treosulfan was based on the patient's BSA (Mosteller formula):

- BSA (m^2) no more than 0.5 received treosulfan dose 10 g/m^2/day
- BSA (m^2) more than 0.5 to 1.0 received treosulfan dose 12g/m^2/day
- BSA (m^2) more than 1.0 received treosulfan dose 14g/m^2/day

However, the BSA groups for the treosulfan based dosing scheme were subsequently modified based on the updated dosing model for treosulfan (PopPK modelling, Venn Life Sciences, November 2018) indicating that children with a BSA of more than 0.3 m^2 to no more than 0.5 m^2 and more than 0.8 m^2 to no more than 1.0 m^2 should receive a higher treosulfan dose than initially defined to reach the target exposure for the AUC of 1355 µg/h*mL:

- BSA (m^2) no more than 0.3 received treosulfan dose 10 g/m^2/day
- BSA (m^2) more than 0.3 to 0.8 received treosulfan dose 12 g/m^2/day
- BSA (m^2) more than 0.8 received treosulfan dose 14 g/m^2/day

In the updated regimen, treosulfan was administered intravenously over 2 hours on 3 consecutive days (visit Day -6, -5, and -4). In general, the administered dose of treosulfan was not to differ by more than 10% from the calculated dose. The modification of the individual BSA related dose calculation did not change the initially defined treosulfan dose range of 10 g/m^2 to 14 g/m^2.

Busulfan: Subjects randomised to busulfan received a total dose calculated with regard to the European Summary of Product Characteristics for Busilvex (busulfan) on the basis of the actual body weight within groups:

- less than 9 kg received busulfan dose 4.0 mg/kg/day
- 9 to less than 16 kg received busulfan dose 4.8 mg/kg/day
- 16 to 23 kg received busulfan dose 4.4 mg/kg/day
- more than 23 to 34 kg received busulfan dose 4.8 mg/kg/day
- more than 34 kg received busulfan dose 3.2 mg/kg/day

Busulfan was administered intravenously on 4 consecutive days (Days -7, -6, -5, and -4) according to the respective hospital's standard with the following schedules: one portion per day over 3 hours; or 2 portions per day over 2 hours each; or 4 portions per day over 2 hours each.

Background conditioning regimen: This trial allowed administration of 2 different background conditioning regimens in addition to treosulfan or busulfan: one background conditioning regimen consisted of an intensified fludarabine containing regimen with additional thiotepa (Stratum A), whereas the other consisted of the standard regimen with fludarabine only (Stratum B).

- Fludarabine: recommended infusion time was 30 minutes, to be given after treosulfan. The total administered dose of fludarabine intravenously was 150 mg/m^2.
- Thiotepa: total dose for thiotepa intravenously was 10 mg/kg.

In the all subjects population, the majority of subjects in both treatment arms received the intensified regimen with thiotepa (84.6%, (44 of 52), treosulfan versus 83.3% (45 of 54), busulfan) compared with the 'standard regimen without thiotepa' (15.4% (8 of 52), treosulfan versus 16.7% (9 of 54), busulfan).

Randomisation and blinding

Central randomisation was performed by means of a computer generated randomisation list to either conditioning treatment with busulfan or treosulfan, in a 1:1 ratio, using a permuted block technique, and was stratified by the 2 pre-specified background conditioning regimens (Stratum A conditioning therapy with additional thiotepa; or Stratum B conditioning therapy without additional thiotepa). The use of thiotepa was at the discretion of individual investigators, and the majority of subjects in both treatment arms received thiotepa. The trial was not blinded.

Blinding was not considered to be feasible due to different treatment schedules of the test versus reference arm.

Statistical analysis

The trial was descriptive in nature and was not powered for confirmatory statistical testing of any pre-specified hypotheses. All subgroup analyses were explorative.

At EMA Paediatric Committee request, 100 or more evaluable paediatric patients (at least 40 subjects from 28 days to less than 4 years of age, and 40 or more subjects from 4 years to less than 12 years of age) were to be enrolled. The sample size was chosen mainly for feasibility reasons, and the fact that a vulnerable, orphan paediatric population was concerned. The trial complied with this request (with enrolment of 45 subjects aged 28 days to less than 4 years, 45 subjects aged 4 years to less than 12 years, and 16 subjects aged 12 to less than 18 years).

With the required sample size, an expected transplant-related mortality of 10% on visit Day 100 could be estimated with a precision of roughly ± 15% points within each treatment arm based on a power of 80% and a 2-sided Clopper-Pearson CI with a confidence coefficient of 90%; any toxicity occurring with at least a 4.5% probability within each treatment arm had a 90% chance of being seen at least once, whereas any toxicity occurring with at least 3.2% probability had an 80% chance of being seen at least once.

Participant flow

Study MC-FludT.16/NM randomised a total of 106 subjects; 101 subjects received the investigational medicinal product and were included in the efficacy and safety analyses. Of the 101 subject who received the investigational medicinal product, 86% (43 of 50) of subjects in the busulfan arm were alive and in ongoing long term follow compared with 91.2% (47 of 51) of subjects in the treosulfan arm. Premature termination occurred in 7 subjects in the busulfan arm (7 deaths) and 4 subjects in the treosulfan arm (2 deaths and 2 lost to follow-up). The clinical evaluation noted that important major deviations reported in this study were unlikely to adversely affect the validity of the efficacy analyses or exposed subjects to unnecessary risk.

Baseline data

The baseline demographic characteristics were generally comparable between the two treatment arms. There were more male (66.3%) than female (33.7%) subjects, and 83.2% of subjects were White; 27.7% of subjects were aged 28 days to 23 months, 56.4% were aged 2 to 11 years, and 15.8% were aged 12 to 17 years. The mean (standard deviation) BSA of subjects was 0.836 (0.396) m^2 in the busulfan arm and 0.746 (0.297) m^2 in the treosulfan arm.

Of the 101 subjects in the FAS population:

- 51 subjects (50.5%) had been diagnosed with primary immunodeficiency disease, comprising 28 (56.0%) subjects in the busulfan arm and 23 (45.1%) subjects in the treosulfan arm;
- 6 (5.9%) subjects had been diagnosed with inborn errors of metabolism, comprising 4 (8.0%) subjects in the busulfan arm and 2 (3.9%) subjects in the treosulfan arm;
- 34 (33.7%) subjects had been diagnosed with haemoglobinopathy, comprising 13 (26.0%) subjects in the busulfan arm and 21 (41.2%) subjects in the treosulfan arm;
- 10 (9.9%) subjects had been diagnosed with bone marrow failure comprising 5 (10.0%) subjects in the busulfan arm and 5 (9.8%) subjects in the treosulfan arm.

The majority of subjects in both treatment arms were matched unrelated donors rather than matched related donors.

Primary endpoint

The rate for freedom from transplant (treatment) related mortality until Day 100 was greater in the treosulfan arm than in the busulfan arm (100.0% versus 90.0%), and the 90% CI for the difference between the two treatment arms was -10.0% (90% CI: -19.3, -3.4), nominal p = 0.0528, adjusted for thiotepa and disease. The results for the subgroup analyses were consistent with the main analysis for all subgroups.

Secondary endpoints

Transplant-related mortality:

- At 12 months, transplant-related mortality was higher in the busulfan arm than in the treosulfan arm (12.0% versus 3.9%, hazard ratio = 0.29 (90% CI: 0.08, 1.09), nominal p = 0.1244).
- Based on Kaplan-Meier estimates, the transplant-related mortality at 36 months was 16.0% in the busulfan arm and 3.9% in the treosulfan arm.
- The exploratory subgroup analyses were generally consistent with the primary analysis, apart from higher transplant-related mortality rates at 12 months in the treosulfan arm than in the busulfan arm for subjects aged 12 to 17 years (33.3% versus 20.0%, respectively; hazard ratio = 1.84 (90% CI: 0.33, 10.08) in favour of busulfan).
- The Kaplan-Meier estimates for the transplant-related mortality at 12 months were 0% for both the 10 and 12 g/m^2 dose groups compared with 20% for the 14 g/m^2 dose group. There is an apparent dose dependency with treosulfan for transplant-related mortality at 12 months, which the study authors stated '*has to be seen in the context of PK data, which showed a comparable drug-exposure for all 3 dose groups*'.

Overall survival:

- Median duration of follow-up = 25.4 months (range: 11.7 to 63.3 months) in busulfan arm, versus 25.6 months (range: 10.7 to 60.9 months) in the treosulfan arm.
- Kaplan-Meier estimates of overall survival at 12 months were greater in the treosulfan arm than in the busulfan arm (96.1% versus 88.0%, hazard ratio = 0.29 (90% CI: 0.08, 1.09), nominal p = 0.1224).
- Based on Kaplan-Meier estimates, the overall survival at 36 months was 84.0% in the busulfan arm and 96.1% in the treosulfan arm.
- The exploratory subgroup analyses were generally consistent with the primary analysis, apart from overall survival at 12 months favouring the busulfan arm relative to the treosulfan arm in the 12 to 17 years subgroup (80.0% versus 66.7%, respectively; hazard ratio = 1.84 (90% CI: 0.33, 10.08) in favour of busulfan).
- There was an apparent treosulfan dose dependency, with overall survival at 12 months being lower in the highest dose group (14 g/m^2/day).

Graft failure:

- The cumulative incidence of graft failure at 12 months was significantly higher in subjects in the treosulfan arm than in the busulfan arm (15.8% versus 4.0%; hazard ratio = 5.48 (90% CI: 1.44, 20.91); nominal p = 0.0366).
- Primary graft failure was experienced by 2 (4.0%) subjects in the busulfan arm and 2 (3.9%) subjects in the treosulfan arm, while secondary graft failure was experienced by no (0%) subjects in the busulfan arm and 9 (18.4%) subjects in the arm group.
- An increased incidence of graft failure emerged in the treosulfan arm compared to the busulfan arm at about 3 months after conditioning, and the two cumulative incidence curves continued to separate during the remainder of the trial. Of particular concern, the

cumulative incidence of graft failure increased in subjects in the treosulfan arm from 12 months through to 36 months, while the cumulative incidence of graft failure in the busulfan arm remained stable from 12 months to 36 months.

- The subgroup analyses for graft failure at 12 months were generally comparable with the primary analysis. There was an apparent treosulfan dose dependency with treosulfan for graft failure at 12 months (failure rates higher with lower doses).

Engraftment:

- Reconstitution of granulopoiesis was greater in subjects in the treosulfan arm than in the busulfan arm (78.4% versus 72.0%).
  - The conditional cumulative incidence of reconstitution of granulopoiesis was lower in subjects in the treosulfan arm than in the busulfan arm at 14 and 28 days, while the maximum conditional cumulative incidence between the treatment arms was comparable
  - Neutropenia occurred in both treatment arms, and the mean duration of neutropenia was 4 days longer in the treosulfan arm than in the busulfan arm (19.9 versus 15.9 days, respectively).
- Reconstitution of leucopoiesis was greater in subjects in the treosulfan arm than in the busulfan arm (78.4% versus 72.0%).
  - The conditional cumulative incidence of reconstitution of granulopoiesis was lower in subjects in the treosulfan arm than in the busulfan arm at 14 days but comparable at 28 days. The maximum conditional cumulative incidence between the treatment arms was comparable.
  - Leukopenia occurred in both treatment arms, and the mean duration of leukopenia was approximately 3 days longer in the treosulfan arm than in the busulfan arm (19.0 versus 16.3 days, respectively).
- Reconstitution of thrombopoiesis:
  - A total of 35 subjects (70.0%) in the busulfan arm and 40 subjects (78.4%) in the treosulfan arm experienced reconstitution of thrombopoiesis defined as prophylactic platelet more than 20 x 10^9/L. The maximum conditional cumulative incidence was comparable in the two treatment arms.
  - A total of 35 subjects (70.0%) in the busulfan arm and 39 subjects (76.5%) in the treosulfan arm experienced reconstitution of thrombopoiesis defined as prophylactic platelet more than 50 x 10^9/L. The maximum conditional cumulative was comparable in the two treatment arms.

Complete donor chimerism:

- At Day 28 = 82.0% (busulfan) versus 84.3% (treosulfan)
- At Day 100 = 84.8% (busulfan) versus 66.7% (treosulfan)
- At month 12 = 76.7% (busulfan) versus 49.0% (treosulfan)
- The incidence of subjects with complete donor type chimerism decreased between visit Day 28 and visit Month 12 in both treatment arms, with the decrease being greater in the treosulfan arm than in the busulfan arm
- Complete donor type chimerism was comparable between the two treatment arms at the Day 28+ visit, but notably lower in the treosulfan arm than in the busulfan arm at both the Day 100 and the Month 12 visits. The notably lower incidence of complete donor type chimerism in subjects in the treosulfan arm compared to the busulfan arm at Month 12 accounts for the notably higher incidence of graft failure in the treosulfan arm at Month 12 compared with the busulfan arm.

Event-free survival:

- The incidence of event-free survival at Month 12 was higher in subjects in the busulfan arm than in the treosulfan arm (86.0% versus 80.3%, respectively, hazard ratio = 1.54 (90% CI: 0.74, 3.2), nominal p = 0.3343). As graft failure is included in the event definition, the lower event-free survival observed in the treosulfan arm reflects the higher number of secondary graft failures reported for treosulfan.
- The Kaplan-Meier curves for event-free survival began to separate in favour of the busulfan arm relative to the treosulfan arm at approximately 6 months after alloHSCT, and remained separated in favour of busulfan during the remainder of the trial.

Graft versus host disease-free survival:

- At the time of analysis, 15 subjects (30.0%) in the busulfan arm and 8 subjects (15.7%) in the treosulfan arm had experienced an event. GvHD events of death and moderate or severe chronic GvHD occurred more frequently in the busulfan arm than in the treosulfan arm, while acute GvHD occurred more frequently in the treosulfan arm than in the busulfan arm.
- Graft versus host disease-free survival at 12 months was higher in subjects in the treosulfan arm than in the busulfan arm (82.9% versus 69.4%, respectively; hazard ratio = 0.58 (90% CI: 0.28, 1.20) in favour of treosulfan; nominal p = 0.2178). The Kaplan-Meier estimates of GvHD remained unchanged in both treatment arms from Month 12 though Month 36.

Chronic graft versus host disease survival:

- At the time of analysis, 15 subjects (30.0%) in the busulfan arm and 5 subjects (9.8%) in the treosulfan arm had experienced chronic GvHD.
- Chronic GvHD-free survival at 12 months was significantly higher in subjects in the treosulfan arm than in the busulfan arm (89.3% versus 69.4%; hazard ratio = 0.32 (90% CI: 0.14, 0.76) in favour of treosulfan; nominal p = 0.0308). The Kaplan-Meier estimates of chronic GvHD remained unchanged in both treatment arms from Month 12 though Month 36.

Evaluation of rescue therapies:

- The incidence of the use of any rescue therapies was comparable in subjects in the busulfan and treosulfan arms (42.0% versus 41.2%, respectively), and there were no significant differences between the two treatment arms for the various rescue therapies.

Safety (adult population)

Evaluable safety data

Study MC-FludT.14/L Trial II is the pivotal study providing safety data for adult patients with AML or MDS, comparing the treosulfan based conditioning regimen being proposed for approval for the treatment of adult patients with malignant disease to a busulfan based reduced intensity conditioning regimen. The safety analysis set provided for the final analysis included 283 patients in the busulfan group and 270 patients in the treosulfan group. The clinical evaluation also reviewed safety data from the integrated safety summary which included data from a total of 613 adult patients exposed to treosulfan in five other Medac GmbH sponsored studies (Studies MC-FludT.6/L, MC-FludT.7/AML, MC-FludT.8/MDS, and MC-FludT.14/L Trial I).

Study MC-FludT.14/L Trial II (final analysis)

In Study MC-FludT.14/L Trial II, patients were randomised to intravenous infusions of treosulfan 10 g/m^2 given once daily on Days -4, -3 and -2 or intravenous infusions of busulfan 0.8 mg/kg given every 6 hours on Days -4 and -3 prior to alloHSCT on Day 0. There were no

significant differences between the two treatment groups as regards fludarabine, antithymocyte globulin, and calcium folinate exposure, while phenytoin was mandatory only for patients randomised to the busulfan group. The majority of patients in both treatment groups received stem cell transplants from the peripheral blood (97.5%, n = 276, busulfan versus 96.3%, n = 260, treosulfan).

The demographic data in Study MC-FludT.14/L Trial II (final analysis) was comparable for the two treatment groups.

Of the 551 patients in the full analysis set (FAS), 352 (63.9%) had been diagnosed with AML (168 patients treated with busulfan; 184 treated with treosulfan), and 199 (36.1%) had been diagnosed with MDS (115 patients treated with busulfan; 84 treated with treosulfan).

Treatment-emergent adverse events by high-level categories in the pivotal study are summarised below in Table 5 below.

Table 5: Study MC-FludT.14/L Trial II final analysis Overall summary of treatment-emergent adverse events (safety analysis set)

	Busulfan (N=283)	Treosulfan (N=270)	Total (N=553)
Any adverse event [n (%)]			
Patients with any adverse event	272 (96.1%)	250 (92.6%)	522 (94.4%)
Patients with AEs of at least CTCAE Grade III	151 (53.4%)	148 (54.8%)	299 (54.1%)
Drug related adverse events [n (%)]			
Patients with any drug related adverse event	192 (67.8%)	170 (63.0%)	362 (65.5%)
Patients with drug related AEs of at least CTCAE Grade III	82 (29.0%)	72 (26.7%)	154 (27.8%)
Serious adverse events [n (%)]			
Patients with any serious adverse event	20 (7.1%)	23 (8.5%)	43 (7.8%)
- Results in death	6 (2.1%)	8 (3.0%)	14 (2.5%)
- Life-threatening	8 (2.8%)	13 (4.8%)	21 (3.8%)
- Hospitalization or prolongation of hospitalization	9 (3.2%)	8 (3.0%)	17 (3.1%)
- Disability/incapacity	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug related serious adverse events [n (%)]			
Patients with any drug related serious adverse event	9 (3.2%)	9 (3.3%)	18 (3.3%)
Maximum CTCAE grade of adverse events [n (%)]			
Patients with AEs of a maximum CTCAE grade I	46 (16.3%)	41 (15.2%)	87 (15.7%)
Patients with AEs of a maximum CTCAE grade II	75 (26.5%)	61 (22.6%)	136 (24.6%)
Patients with AEs of a maximum CTCAE grade III	134 (47.3%)	123 (45.6%)	257 (46.5%)
Patients with AEs of a maximum CTCAE grade IV	14 (4.9%)	18 (6.7%)	32 (5.8%)
Patients with AEs of a maximum CTCAE grade V	3 (1.1%)	7 (2.6%)	10 (1.8%)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for adverse event; N = total number of subjects; n = number of subjects in category, which is followed-up by the study sponsor.

Grade refers to the severity of the adverse event, from Grade I (asymptomatic/mild) to Grade IV (life-threatening), or Grade V (where an adverse event leads to death).

Each of the treatment-emergent adverse events (TEAEs) categories were reported in a comparable proportion of patients in the treosulfan and busulfan groups. TEAEs in the overall population of the pooled data is shown below in Table 6 below.

Table 6: Pooled data (5 studies) Overall summary of treatment-emergent adverse events in adult patients treated with treosulfan based conditioning (safety analysis set)

	Adult trials (N=613)
Any adverse event [n (%)]	
Patients with any adverse event	593 (96.7%)
Patients with AEs of at least CTCAE v4.03 grade III	408 (66.6%)
Drug-related adverse events [n (%)]	
Patients with any drug-related AE	478 (78.0%)
Patients with drug-related AEs of at least CTCAE v4.03 grade III	219 (35.7%)
Serious adverse events [n (%)]	
Patients with any serious adverse event	83 (13.5%)
- Results in death	16 (2.6%)
- Life-threatening	22 (3.6%)
- Hospitalization or prolongation of hospitalization	11 (1.8%)
- Disability/incapacity	1 (0.2%)
- Congenital anomaly or birth defect	0 (0.0%)
- Missing reason for seriousness	41 (6.7%)
Drug-related serious adverse events [n (%)]	
Patients with any drug-related SAE	41 (6.7%)
Maximum CTCAE v4.03 grade of adverse events [n (%)]	
Patients with AEs of a maximum CTCAE grade I	62 (10.1%)
Patients with AEs of a maximum CTCAE grade II	123 (20.1%)
Patients with AEs of a maximum CTCAE grade III	329 (53.7%)
Patients with AEs of a maximum CTCAE grade IV	58 (9.5%)
Patients with AEs of a maximum CTCAE grade V	21 (3.4%)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for adverse event; v = version; N = total number of subjects; n = number of subjects in the subgroup.

Grade refers to the severity of the adverse event, from Grade I (asymptomatic/mild) to Grade IV (life-threatening), or Grade V (where an adverse event leads to death).

All five studies were sponsored by Medac GmbH, the marketing authorisation holder in the European Union.

In the pivotal study, the most frequently reported TEAEs occurring in 10% or more of patients in either treatment group (busulfan versus treosulfan, respectively), and by decreasing order of frequency in the busulfan group, were: oral mucositis (47.7 versus 37.8%); nausea (41.0% versus 33.0%); fever (35.7% versus 34.4%); hypertension (21.2% versus 14.1%); vomiting (19.4% versus 21.9%); diarrhoea (18.4% versus 15.9%); headache (18.4% versus 16.3%); oedema limbs (13.4% versus 22.6%); back pain (13.1% versus 14.8%); fatigue (12.4% versus 12.2%); gamma-glutamyl transferase (GGT) increased (12.0% versus 7.4%); constipation (11.7% versus 12.2%); febrile neutropenia (11.0% versus 14.8%); abdominal pain (9.9% versus 10.7%); bone pain (9.9% versus 13.7%); rash maculo-papular (8.8% versus 11.9%); and arthralgia (3.5% versus 10.0%).

There were a number of substantial differences in patient incidences (at least 5% difference) between the two treatment groups as regards some TEAEs. Substantially increased TEAEs in

patients in the busulfan group compared with the treosulfan group were observed for oral mucositis (47.7% versus 37.8%), nausea (41.0% versus 33.0%), and hypertension (21.2% versus 14.1%). Substantially increased TEAEs in patients in the treosulfan group compared with the busulfan group were observed for limb oedema (22.6% versus 13.4%), and arthralgia (10.0% versus 3.5%).

Adverse events of Grade 3 or higher

Common Terminology Criteria for adverse events (CTCAEs) of Grade III or higher were reported in a similar proportion of patients in the two treatment arms (53.4% of patients in the busulfan group versus 54.8% of patients in the treosulfan group) overall, however, a substantially greater proportion of patients in the treosulfan group than in the busulfan group (at least 5% more patients) reported infections and infestations (15.2% versus 9.2%, respectively).

Drug related treatment-emergent adverse events

In general, in the pivotal study, drug related TEAEs (any event) were reported more frequently in patients in the busulfan group (67.8%) than in the treosulfan group (63.0%). Substantially more patients in the busulfan group than in the treosulfan group (at least 5% difference) reported drug related TEAEs for oral mucositis (38.2% versus 32.2%), nausea (29.0% versus 21.5%), diarrhoea (11.0% versus 5.9%), and GGT increased (10.2% versus 5.2%); fever (11.7% versus 4.8%) and nervous system disorders (12.7% versus 7.4%).

Drug related CTCAEs Grade III or higher were reported in a similar proportion of patients in the two treatment groups (29.0% of patients in the busulfan group and 26.7% of patients in the treosulfan group).

Deaths

Deaths until Month 24 occurred more frequently in patients in the busulfan group than in treosulfan group (37.8% versus 26.7%, respectively). Transplantation related deaths occurred in 20.5% of patients in the busulfan group and 12.2% of patients in the treosulfan group, and disease relapse or progression deaths occurred in 16.6% of patients in the busulfan group and 12.6% of patients in the treosulfan group. The median time from transplantation to death in both treatment groups was similar (6.60 months, busulfan versus 5.90 months, treosulfan).

Of the 12.2% of patients in the treosulfan treatment group who died due to transplantation related causes, the most common causes (in 5% or more of patients) were infections (9.3%), predominantly bacterial infection (5.6%). Graft versus host disease (GvHD) occurred in 4.8% of patients in the treosulfan group.

There were 14 deaths in the post-trial surveillance period, 5 in the busulfan group and 9 in the treosulfan. The cause of death was not recorded during the post-trial surveillance period.

Serious adverse events

Treatment-emergent serious adverse events (SAEs) were reported in 7.1% of patients in the busulfan group and 8.5% of patients in the treosulfan group, including sepsis (1.8% versus 3.0%), lung infection (1.1% versus 2.2%), and acute kidney injury (0.4% versus 1.1%).

Drug-related SAEs (or serious adverse reactions (SARs)) were reported in a similar proportion of patients in the busulfan and treosulfan groups (3.2% versus 3.3%, respectively). The most common SARs reported in the two treatment groups (busulfan versus treosulfan, respectively) were infections or infestations (1.4% versus 2.2%): sepsis (0.4% versus 1.9%), lung infection (0.7% versus 0.7%), encephalitis (0.0% versus 0.4%), and other infection or infestation (0.4% versus 0.0%).

There were no clinically meaningful differences between the two treatment groups (busulfan versus treosulfan, respectively) as regards significant pre-defined CTCAEs Grade III/IV, that is mucositis (7.4% versus 5.9%); hepatic sinusoidal obstruction syndrome (0.4% versus 0%); seizures (0% versus 0.4%); and blood bilirubin increased (2.8% versus 3.3%).

Discontinuations due to adverse events

In the pivotal study, there were no events leading to premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy.

Hepatotoxicity

Hepatobiliary disorders by CTCAE System Organ Class were reported infrequently in patients in both the busulfan group (n = 6, 2.1%) and the treosulfan group (n = 4, 1.5%).

Relevant hepatic CTCAEs by term in patients in the busulfan group versus the treosulfan group were GGT increased (12.0% versus 7.4%), blood bilirubin increased (6.4% versus 9.3%), alanine transaminase (ALT) increased (6.4% versus 8.5%), aspartate transaminase increased (4.9% versus 8.5%), and serum alkaline phosphatase increased (0.4% versus 0.7%).

Liver function laboratory tests for aspartate transaminase, ALT, GGT, alkaline phosphatase, and bilirubin were analysed at Baseline, Days -3 to -1 before transplantation on Day 0, and Days 2 to 28 after transplantation, see Table 7 below.

Table 7: Study MC-FludT-14/L Trial II final analysis Liver function test parameters (median, 25th, 75th percentile)

Parameter (normal value)	Treatment group	Baseline	Day -1	Day +6	Day +28
AST, U/L (M: 10-50; F: 10-35)	TREO	22.0 (16.0, 30.0)	19.0 (13.0, 27.0)	27.0 (20.0, 43.2)	24.0 (17.0, 31.0)
	BU	22.0 (17.0, 31.0)	18.0 (13.0, 27.0)	23.0 (17.0, 32.0)	23.5 (17.7, 32.0)
ALT, U/L (M: 10-50; F: 10-35)	TREO	26.0 (17.0, 44.0)	31.0 (20.0, 56.0)	47.0 (27.0, 81.0)	24.0 (16.0, 36.0)
	BU	25.0 (17.0, 40.0)	27.0 (18.0, 46.0)	38.0 (23.0, 60.0)	21.0 (15.0, 32.1)
γGT, U/L (M: 12-64; F: 9-36)	TREO	31.0 (20.3, 54.0)	47.0 (29.0, 90.0)	54.0 (34.0, 104.0)	45.0 (27.0, 84.0)
	BU	29.0 (20.0, 54.0)	54.7 (35.0, 106.0)	85.4 (48.0, 169.0)	46.5 (30.0, 83.0)
AP, U/L (M/F: 30-120)	TREO	75.0 (59.0, 94.0)	63.0 (50.0, 81.8)	67.0 (55.0, 84.0)	79.0 (63.0, 106.0)
	BU	71.0 (58.0, 98.0)	55.0 (45.0, 73.0)	65.2 (53.0, 89.4)	75.0 (58.0, 101.5)
Bilirubin, µM (M/F: 2-21)	TREO	8.6 (6.8, 12.0)	17.1 (12.0, 23.9)	18.3 (12.1, 25.7)	12.0 (8.4, 17.0)
	BU	8.9 (6.8, 13.5)	15.7 (12.0, 22.5)	13.7 (10.3, 18.0)	12.0 (8.6, 15.4)

Abbreviations: ALT = alanine transaminases; AP = alkaline phosphatase; AST = aspartate transaminase; BU = busulfan; F = female; γGT = Gamma-glutamyl transferase; M = male; TREO = treosulfan.

Renal toxicity

Renal and urinary disorders by CTCAE System Organ Class were reported in a similar proportion of patients in both the busulfan group (9.2%) and the treosulfan group (11.1%), including acute kidney injury (n = 7, 2.5% versus n = 11, 4.1%), and other renal and urinary disorders (2.8% versus 2.6%).

Relevant renal function CTCAEs by term reported in patients in the busulfan group versus the treosulfan group were creatinine increased (4.2% versus 3.7%) and urine output decreased (0.4% versus 0.4%).

Other clinical chemistry

Median sodium and potassium levels at Baseline were similar in the two treatment groups, and did not significantly change over time in either treatment group.

Laboratory data for creatinine, lactate dehydrogenase, C-reactive protein, procalcitonin, and serum glucose were generally comparable in both treatment groups at Baseline. Serum creatinine levels at Baseline were higher in the busulfan group than in the treosulfan group. At Day 6, median serum creatinine had decreased from Baseline in both treatment groups but increased from Baseline thereafter in the two groups, stated by the sponsor to be probably due to concomitant treatment with cyclosporin. At Day 28 the median serum creatinine levels were higher than Baseline in both treatment groups, but the median levels were generally comparable in the two groups.

Median lactate dehydrogenase levels were generally comparable between the both treatment groups at all time-points.

Median C-reactive protein levels at Baseline were similar in both treatment groups, and were markedly higher in both groups at Day -1. At Day 6, the median C-reactive protein levels had fallen from the high levels observed at Day -1 but were still above baseline levels. At Day 28, median levels had fallen further from Day 6 in both treatment groups, but remained above baseline levels in the two groups.

Median procalcitonin levels at Baseline were similar in both treatment groups, and were markedly higher in both groups at Day -1. At Day 6, levels had fallen from the high levels observed at Day -1 but were still above baseline levels in both treatment groups. At Day 28, median levels had fallen further from Day 6 in both treatment groups and were generally comparable with baseline levels in the two groups.

Median glucose levels at Baseline were similar in both treatment groups, and there were no marked changes from Baseline in either treatment group through to Day 28.

Haematology

Blood and lymphatic system disorders by CTCAE System Organ Class were reported less frequently in patients in the busulfan group than in the treosulfan group (11.0% versus 14.8%, respectively). The only CTCAE by term reported in 2% or more of patients in either the busulfan group or the treosulfan group, respectively, was febrile neutropenia (11.0% versus 14.8%).

In the pivotal study, through to Day 28 post transplantation, 94.4% (n = 255) of patients in the treosulfan group and 91.9% (n = 260) of patients in the busulfan group received an erythrocyte transfusion, and 93.7% (n = 253) of patients in the treosulfan group and 68.6%% (n = 193) of patients in the busulfan group received a platelet transfusion. Growth factors (for example, G-CSF, GM-CSF)) from Day -6 pre-transplantation to Day 28 post-transplantation were administered to 34 (12.6%) patients in the treosulfan group and 39 (13.8%) patients in the busulfan group.

Electrocardiogram findings

No treatment-emergent CTCAEs categorised as electrocardiogram abnormalities were reported in the pivotal study. In the integrated safety summary, there was one report of 'electrocardiogram abnormal' as a preferred term AE in one male patient aged less than 50 years treated with treosulfan 12 g/m^2 in Study MC-FludT.6/L, with no other abnormalities being reported in the four other Medac GmbH studies in adults.

Cardiovascular safety

Cardiac disorders by CTCAE System Organ Class were reported less frequently in the busulfan group than in the treosulfan group (9.2% versus 15.2%). CTCAEs by terms reported in 2% or more of patient in either the busulfan or treosulfan groups, respectively, were atrial fibrillation (1.4% versus 4.1%), sinus tachycardia (1.8% versus 3.0%), and supraventricular tachycardia (1.8% versus 3.0%).

Immunological events

Immune disorders by CTCAE System Organ Class were reported in a similar proportion of patients in both the busulfan and treosulfan groups (7.8% versus 6.3%). The only CTCAE by term reported in 2% or more of patients in either the busulfan or treosulfan groups, respectively, was allergic reaction (7.8% versus 5.6%). Anaphylaxis and cytokine release syndrome were each reported in one (0.4%) patient in the treosulfan group and no patients in the busulfan group.

Skin reactions

Skin and subcutaneous tissue disorders by CTCAE System Organ Class were reported less frequently in patients in the busulfan group than in the treosulfan group (26.5% versus 29.3%, respectively). CTCAEs by term reported in 2% or more of patients in either the busulfan group or the treosulfan group, respectively, were rash maculo-papular (8.8% versus 11.9%), other specified skin and subcutaneous tissue disorders (7.8% versus 7.4%), pruritus (4.2% versus 5.9%), purpura (3.5% versus 5.2%), erythema multiforme (2.8% versus 3.0%), palmar-plantar erythrodysesthesia syndrome (3.5% versus 1.9%), and rash acneiform (1.8% versus 2.2%). There were no reports of toxic epidermolysis or Stevens-Johnson syndrome in either treatment group.

Safety (paediatric population)

Evaluable safety data

There are two clinical Phase II studies providing key safety data for 115 children and adolescents patients aged 28 days to 17 years with malignant and non-malignant disease treated with treosulfan based conditioning prior to alloHSCT (Studies MC-FludT.17/M and MC-FludT.16/NM). Initial submission of Study MC-FludT.16/NM also included interim safety data for 43 patients with non-malignant disease treated with busulfan based conditioning. These are also supplemented by safety data from two EBMT Registry studies (Peters 2011, Peters 2017) in a total of 1521 children and adolescents with malignant and non-malignant disease treated with various treosulfan based conditioning regimens prior to alloHSCT.

The approach to the evaluation of safety in the paediatric population in this submission has been to focus primarily on the pooled safety data in 115 patients treated with treosulfan based condition in Studies MC-FludT.17/M and MC-FludT.16/NM, supplemented where considered relevant by the data from the two EBMT Registry studies (Peters 2011, Peters 2017).

The final study report for Study MC-FludT.16/NM evaluating the safety and efficacy of paediatric patients aged one month and older with non-malignant diseases indicated for first alloHSCT was submitted with the sponsor's response to the RFI. The safety analysis presented for Study MC-FludT.16/NM was performed after the last subject had completed the Month 12 visit; as of data cut-off on 7 June 2021, most of the enrolled subjects had not completed the trial, with 84.9% of subjects ongoing with regard to long term follow-up. The interpretation of endpoints after the Month 12 visit is therefore limited to those who have already completed these visits.

Exposure

In Studies MC-FludT.17/M and MC-FludT.16/NM, all patients who were enrolled and received at least one dose of treatment were included in the safety analysis. As previously discussed, the proposed treosulfan dose in children and adolescents is based on the updated PopPK model (Venn Life Sciences 2020, PopPK). For both malignant and non-malignant disease, the sponsor proposes that treosulfan conditioning be given in combination with fludarabine either with thiotepa in the intensified regimen or without thiotepa in the standard regimen. The sponsor proposes that treosulfan be administered based on the body surface area (BSA). That is, less than 0.4, 0.4 to less than 0.9, or at least 0.9 m^2 at 10.0, 12.0, or 14.0 g/m^2, respectively, on Days -6, -5 and -4 before alloHSCT.

Overall, the total absolute median treosulfan dose with or without thiotepa was 31.7 g (range: 9 to 84 g), and the total absolute median dose of treosulfan / BSA with or without thiotepa was 36.18 g/m^2 (range: 26.3 to 42.6 g/m^2).

Adverse events

High level overviews of adverse events (AEs) in the two paediatric studies are summarised below in Table 8 below. A total of 93.9% of the 115 patients treated with treosulfan based conditioning experienced at least one treatment-emergent adverse event (TEAE). Overall, the high level AE categories in patients treated with treosulfan based conditioning were generally comparable for patients with malignant disease (Study MC-FludT.17/M) and non-malignant disease (MC-FludT.16/NM), apart from the higher incidence of adverse drug reaction (ADR) AEs in patients with malignant disease compared to non-malignant disease (90.0% versus 75.6%, respectively).

Table 8: Studies MC-FludT.17/M and MC-FludT.16/NM High level overview of treatment-emergent adverse events

Study	MC-FludT.16/NM		MC-FludT.17/M
Treatment arm	**TREO**	**BU**	**TREO**
Number of patients	45 (100%)	43 (100%)	70 (100%)
Any adverse event			
Patients with AEs of any CTCAE Grade	88.9%	86.0%	97.1%
Patients with AEs of at least CTCAE Grade III	71.1%	79.1%	75.7%
Drug-related adverse events			
Patients with ADRs of any CTCAE Grade	75.6%	65.1%	90.0%
Patients with ADRs of at least CTCAE Grade III	46.7%	48.8%	48.6%
Serious adverse events			
Patients with at least one serious AE	35.6%	34.9%	32.9%
Results in death	0	9.3%	1.4%
Life-threatening	6.7%	11.6%	8.6%
Hospitalisation or prolongation of hospitalisation	33.3%	16.3%	28.6%
Disability/Incapacity	0	2.3%	1.4
Congenital anomaly or birth defect	0	0	0
Drug-related serious adverse events			
Patients with drug related serious AEs	4.4%	7.0%	1.4%
Patients with maximum CTCAE Grade			
CTCAE Grade I	0	2.3%	4.3%
CTCAE Grade II	17.8%	4.7%	17.1%
CTCAE Grade III	55.6%	55.8%	60.0%
CTCAE Grade IV	15.6%	18.6%	15.7%
CTCAE Grade V	0	4.7%	0

Abbreviations: AE = adverse event; BU = busulfan; CTCAE = Common Terminology Criteria for adverse event; v = version; TREO = treosulfan.

Grade refers to the severity of the adverse event, from Grade I (asymptomatic/mild) to Grade IV (life-threatening), or Grade V (where an adverse event leads to death).

Treatment-emergent adverse events

The majority of patients in both studies treated with treosulfan based conditioning experienced at least one TEAE, with patients with malignant disease (Study MC-FludT.17/M) experiencing a higher incidence of TEAEs than patients with non-malignant disease (Study MC-FludT.16/NM; 97.1% versus 88.9%, respectively). The most frequently reported TEAEs by System Organ Class in both studies were gastrointestinal disorders.

The most frequently reported TEAEs by Preferred Term in patients overall treated with treosulfan based conditioning were (Study MC-FludT.16/NM versus Study MC-FludT.17/M versus overall, respectively), n (%):

- Stomatitis: 32 (71.1%) versus 54 (77.1%) versus 86 (74.8%)
- Pyrexia: 29 (64.4%) versus 51 (72.9%) versus 80 (69.6%)
- Vomiting: 29 (64.4%) versus 48 (68.6%) versus 77 (67.0%)
- Diarrhoea: 26 (57.8%) versus 46 (65.7%) versus 72 (62.6%)
- Nausea: 15 (33.3%) versus 32 (45.7%) versus 47 (40.9%)
- Hepatotoxicity: 22 (48.9%) versus 24 (34.3%) versus 46 (40.0%)
- Abdominal pain: 22 (48.9%) versus 22 (31.4%) versus 44 (38.3%)
- Hypertension:17 (37.8%) versus 22 (31.4%) versus 39 (33.9%)

Adverse event of Grade 3 or higher

A total of 73.8% of patients treated with treosulfan based conditioning experienced at least one CTCAE of Grade III or higher.

In the overall population, CTCAEs of Grade III or higher by Preferred Term reported in 5% or more of patients by descending order of frequency were: cytomegalovirus infection (35.7%), stomatitis (34.8%), diarrhoea (14.8%), nausea (13.0%), hypertension (12.2%), vomiting (11.3%), hypokalaemia (10.4%), device related infection (6.1%), rash maculo-papular (6.1%), febrile neutropenia (5.2%), sepsis (5.2%), and blood bilirubin increased (5.2%). CTCAEs of Grade III or higher in patients treated with treosulfan based conditioning occurred in a similar proportion of patients with non-malignant disease (71.1%, Study MC-FludT.16/NM) and malignant disease (75.7%, Study MC-FludT.17/M).

Drug-related treatment-emergent adverse events

A total of 84.3% of patients treated with treosulfan based conditioning experienced at least one drug related TEAE.

The most frequently reported drug related TEAEs by Preferred Term in 10% or more of patients overall treated with treosulfan based conditioning, by decreasing overall frequency (Study MC-FludT.16/NM versus Study MC-FludT.17/M versus overall, respectively) were n (%):

- Stomatitis: 29 (64.4%) versus 48 (68.6%) versus 77 (67.0%)
- Vomiting: 19 (42.2%) versus 29 (41.4%) versus 48 (41.7%)
- Diarrhoea: 20 (44.4%) versus 20 (28.6%) versus 40 (34.8%)
- Nausea: 9 (20.0%) versus 23 (32.9%) versus 32 (27.8%)

- Hepatotoxicity: 13 (28.9%) versus 17 (24.3%) versus 30 (26.1%)
- Abdominal pain: 12 (26.7%) versus 8 (11.4%) versus 20 (17.4%)
- Pyrexia: 4 (8.9%) versus 11 (15.7%) versus 15 (13.0%)
- Alanine transaminase increased: 6 (13.3%) versus 7 (10.0%) versus 13 (11.3%)
- Alopecia: 11 (24.4%) versus 1 (1.4%) versus 12 (10.4%)
- Pruritus: 7 (15.6%) versus 5 (7.1%) versus 12 (10.4%)

Drug related CTCAEs of Grade III or higher were reported in a similar proportion of patients with non-malignant (FludT.16/NM) disease and malignant disease study (Study MC-FludT.17/M) treated with treosulfan based conditioning (n = 21 46.7% versus n = 34, 48.6%, respectively). Overall, 55 (47.8%) patients treated with treosulfan based conditioning experienced at least one drug related CTCAE of Grade III or higher.

Deaths

In Study MC-FludT.17/M, death was reported in 12 patients (17.1%) treated with treosulfan through to the end of the longer term follow-up period (11.4% due to disease progression and 5.7% due to transplantation related causes).

In Study MC-FludT.16/NM, death was reported in 1.2% (one patient) treated with treosulfan (transplantation related) and 14.0% (6 patients) treated with busulfan based conditioning (all transplantation related). The one transplantation related death in the treosulfan group occurred in a female aged 13 years with primary immunodeficiency who had been treated with treosulfan 14 g/m^2 combined with fludarabine, time to death 4.0 months. The causes of death were GvHD, renal failure, multiple organ failure, infection, and gastrointestinal toxicity.

The 5 transplantation related deaths in the treosulfan groups in the two paediatric clinical studies (Studies MC-FludT.16/NM and MC-FludT.17/M) occurred in patients aged 10 to 16 years. All patients had received treosulfan 14 g/m^2 combined with fludarabine and the time to death ranged from 0.5 to 46.7 months.

Data in paediatric patients with non-malignant diseases were also available from the 2017 EBMT Registry study (Peters 2017).

Serious adverse events

Serious adverse events (SAEs) were reported in 33.9% of patients overall treated with treosulfan based conditioning (Studies MC-FludT.16/NM and MC-FludT.17/M), and 34.9% of patients with non-malignant disease treated with busulfan based conditioning (Study MC-FludT.16/NM).

In Study MC-FludT.17/M, SAEs in patients with malignant disease treated with treosulfan based conditioning were reported in 23 (32.9%) patients. SAEs reported in 2 or more patients were infections and infestations other in 6 (8.6%) patients, febrile neutropenia in 3 (4.3%) patients, and sepsis and fever in 2 (2.9%) patients each.

In Study MC-FludT.16/NM, SAEs in patients with non-malignant disease were reported 16 (35.6%) patients treated with treosulfan based conditioning and 15 (34.9%) patients treated with busulfan based conditioning. SAEs reported in 2 or more patients overall (busulfan versus treosulfan) were fever (n = 0, 0% versus n = 7, 8.0%), infections and infestations other (n = 0, 0% versus n = 4, 8.9%), lung infection (n = 4, 9.3% versus n = 0.0%), blood and lymphatic disorders other (n = 2, 4.7% versus n = 1, 2.2%), sepsis (n = 2, 4.7% versus n = 1, 2.2%), encephalopathy (n = 1, 2.3% versus n = 1, 2.2%), enterocolitis (n = 1, 2.3% versus n = 1, 2.2%),

vomiting (n = 0, 0% versus n = 2, 4.4%), and hepatobiliary disorders other (n = 2, 4.7% versus n = 0, 0%).

Drug-related SAEs (serious adverse reactions (SARs)) were reported in 2.6% of patients treated with treosulfan (2 patients, 4.4%, Study MC-FludT.16/NM versus one patient, 2.6%, Study MC-FludT.17/M). In Study MC-FludT.16/NM, the 2 SARs reported in the 2 patients were MDS and transplant failure in one patient each. In Study MC-FludT.17/M, the one SAR reported in the one patient was stomatitis.

Pre-defined significant selected toxicities

Pre-defined significant selected toxicities reported in the two paediatric studies in patients treated with treosulfan based conditioning are summarised in Table 9 below.

Table 9: Studies MC-FludT.17/M and MC-FludT.16/NM Incidence of selected toxicities in patients treated with treosulfan based conditioning (safety set)

	Trial number		
	MC-FludT. 16/NM (N=45)	MC-FludT. 17/M (N=70)	Overall (N=115)
HSOS according to Jones (1987)			
Patients with event	1 (2.2%)	1 (1.4%)	2 (1.7%)
Patients without event	44 (97.8%)	69 (98.6%)	113 (98.3%)
Incidence of event [%] (95% CI)	2.2 (0.1, 11.8)	1.4 (0.0, 7.7)	1.7 (0.2, 6.1)
Early toxicity defined as any AE occurring until day +28			
Patients with event	39 (86.7%)	68 (97.1%)	107 (93.0%)
Patients without event	6 (13.3%)	2 (2.9%)	8 (7.0%)
Incidence of event [%] (95% CI)	86.7 (73.2, 94.9)	97.1 (90.1, 99.7)	93.0 (86.8, 96.9)
Hepatic toxicity according to Bearman (1988)			
Patients with event	22 (48.9%)	24 (34.3%)	46 (40.0%)
Patients without event	23 (51.1%)	46 (65.7%)	69 (60.0%)
Incidence of event [%] (95% CI)	48.9 (33.7, 64.2)	34.3 (23.3, 46.6)	40.0 (31.0, 49.6)
Lung toxicity (CTCAE term Pulmonary fibrosis)			
Patients with event	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients without event	45 (100.0%)	70 (100.0%)	115 (100.0%)
Incidence of event [%] (95% CI)	0.0 (0.0, 7.9)	0.0 (0.0, 5.1)	0.0 (0.0, 3.2)
Infections (SOC Infections and infestations)			
Patients with event	25 (55.6%)	50 (71.4%)	75 (65.2%)
Patients without event	20 (44.4%)	20 (28.6%)	40 (34.8%)
Incidence of event [%] (95% CI)	55.6 (40.0, 70.4)	71.4 (59.4, 81.6)	65.2 (55.8, 73.9)

Abbreviations: AE = adverse event; CI = confidence interval; CTCAE = Common Terminology Criteria for adverse event; HSOS = hepatic sinusoidal obstruction syndrome; N = total number of subjects; SOC = System Organ Class.

Graft versus host disease

The incidence of acute GvHD and chronic GvHD from the two paediatric studies are shown in the Table 10 and Table 11, respectively.

Table 10: Studies MC-FludT.17/M and MC-FludT.16/NM Incidence of acute graft versus host disease

Study	MC-FludT.16/NM		MC-FludT.17/M
Treatment arm	**TREO**	**BU**	**TREO**
Number of patients	45	43	70
Cumulative incidence aGvHD, all grades			
At Day 14; % (90% CI)	11.9 (3.7, 20.1)	2.4 (0.0, 6.4)	7.2 (2.1, 12.4)
At Day 28; % (90% CI)	35.7 (23.6, 47.9)	34.1 (22.0, 46.3)	37.7 (28.1, 47.3)
At Day 100; % (90% CI)	54.8 (42.1, 67.4)	46.3 (33.5, 59.2)	43.5 (33.7, 53.3)
Cumulative incidence aGvHD, grade III/IV			
At Day 14; % (90% CI)	2.4 (0.0, 6.3)	2.4 (0.0, 6.4)	0.0 (0.0, 0.0)
At Day 28; % (90% CI)	2.4 (0.0, 6.3)	4.9 (0.0, 10.4)	5.8 (1.2, 10.4)
At Day 100; % (90% CI)	14.3 (5.4, 23.2)	9.8 (2.1, 17.4)	8.7 (3.1, 14.3)

Abbreviations: aGVHD = acute graft versus host disease; BU = busulfan; CI = confidence interval; TREO = treosulfan.

Table 11: Studies MC-FludT.17/M and MC-FludT.16/NM Incidence of chronic graft versus host disease

Study	MC-FludT.16/NM		MC-FludT.17/M
Treatment arm	**TREO**	**BU**	**TREO**
Number of patients	45	43	70
Cumulative incidence of cGvHD			
At 6 months; % (90% CI)	13.9 (4.4, 23.4)	30.1 (17.0, 43.2)	NR
At 12 months; % (90% CI)	17.4 (6.7, 28.1)	44.3 (29.5, 59.1)	23.9 (15.3, 32.4)
At 24 months; % (90% CI)	17.4 (6.7, 28.1)	44.3 (29.5, 59.1)	25.4 (16.6, 34.1)
At 36 months; % (90% CI)	NR	NR	25.4 (16.6, 34.1)
Cumulative incidence of moderate/severe cGvHD			
At 6 months; % (90% CI)	11.1 (2.5, 19.7)	21.0 (9.4, 32.6)	NR
At 12 months; % (90% CI)	14.6 (4.6, 24.5)	24.4 (12.0, 36.9)	17.9 (10.2, 25.6)
At 24 months; % (90% CI)	14.6 (4.6, 24.5)	24.4 (12.0, 36.9)	19.4 (11.5, 27.4)
At 36 months; % (90% CI)	NR	NR	19.4 (11.5, 27.4)

Abbreviations: cGVHD = chronic graft versus host disease; BU = busulfan; CI = confidence interval; TREO = treosulfan.

Liver toxicity

Hepatotoxicity was reported in 40.0% of patients (total 115 patients) treated with treosulfan based conditioning.

Table 12: Studies MC-FludT.17/M and MC-FludT.16/NM Hepatobiliary disorders by System Organ Class and Preferred Term in patients treated with treosulfan based conditioning

	Trial number		
Primary System Organ Class Preferred Term	**MC-FludT. 16/NM (N=45)**	**MC-FludT. 17/M (N=70)**	**Overall (N=115)**
Hepatobiliary disorders			
Any event	23 (51.1%)	25 (35.7%)	48 (41.7%)
Hepatotoxicity	22 (48.9%)	24 (34.3%)	46 (40.0%)
Hepatomegaly	1 (2.2%)	2 (2.9%)	3 (2.6%)
Venoocclusive liver disease	1 (2.2%)	1 (1.4%)	2 (1.7%)
Hepatic lesion	1 (2.2%)	0 (0.0%)	1 (0.9%)
Hepatic pain	1 (2.2%)	0 (0.0%)	1 (0.9%)
Liver disorder	1 (2.2%)	0 (0.0%)	1 (0.9%)

Abbreviation: N = total number of subjects.

Renal toxicity

Renal and urinary disorders occurred frequently overall in patients treated with treosulfan based conditioning (see Table 13 below); renal or urinary disorder CTCAEs of Grade III or higher were reported in 6.1% of patients treated with treosulfan, and renal or urinary disorder SAEs were reported in 0.9% of patients treated with treosulfan.

Table 13: Studies MC-FludT.17/M and MC-FludT.16/NM Renal and urinary disorders by System Organ Class and Preferred Term reported in at least one patient overall in the pooled data in patients treated with treosulfan based conditioning

	Age group			
Primary System Organ Class Preferred Term	28 days to 23 months (N=22)	2 to 11 years (N=54)	12 to 17 years (N=39)	Overall (N=115)
Renal and urinary disorders				
Any event	2 (9.1%)	16 (29.6%)	10 (25.6%)	28 (24.3%)
Haematuria	0 (0.0%)	7 (13.0%)	3 (7.7%)	10 (8.7%)
Acute kidney injury	0 (0.0%)	2 (3.7%)	3 (7.7%)	5 (4.3%)
Pollakiuria	1 (4.5%)	2 (3.7%)	1 (2.6%)	4 (3.5%)
Urinary tract pain	0 (0.0%)	2 (3.7%)	2 (5.1%)	4 (3.5%)
Cystitis noninfective	0 (0.0%)	1 (1.9%)	1 (2.6%)	2 (1.7%)

Abbreviation: N = total number of subjects.

Haematology

The most frequent blood or lymphatic system disorder TEAE overall was febrile neutropenia.

Of patients treated with treosulfan based conditioning in both paediatric studies, with the most frequent TEAE overall being febrile neutropenia.

Blood or lymphatic system disorder CTCAE of Grade III or higher were reported in 10.4% of patients treated with treosulfan based conditioning, and blood or lymphatic system disorder SAEs were reported in 4.3% of patients treated with treosulfan based conditioning. The only SAE (Preferred Term) reported in at least one patient was febrile neutropenia, which was reported in 3 (2.6%) patients in Study MC-FludT.17/M.

Electrocardiogram findings and cardiovascular safety

Cardiac disorders (System Organ Class) were reported in a similar proportion of patients treated with treosulfan based conditioning in the two paediatric studies, with the most frequent TEAE in both studies being sinus tachycardia. Electrocardiogram data were not routinely monitored in the two paediatric studies.

Immunological events

Immune system disorders (System Organ Class) were reported notably more frequently in patients with malignant disease treated with treosulfan based conditioning than in patients with non-malignant disease. This difference was driven by the notably higher incidence of hypersensitivity in patients with malignant disease compared to non-malignant disease.

Immune system disorders CTCAEs of Grade III or higher in patients treated with treosulfan based conditioning were reported in 2 (2.9%) patients in Study MC-FludT.17/M (both events being hypersensitivity) and no patients in Study MC-FludT.16/NM. SAEs in patients treated with treosulfan based conditioning were reported in one (1.4%) patient in Study MC-FludT.17/M (hypersensitivity) and no patients in Study MC-FludT.16/NM.

Skin toxicity

Skin and subcutaneous tissue disorders (System Organ Class) in patients treated with treosulfan based conditioning were reported in a similar proportion of patients in the two paediatric studies (27 patients, 60.0%, in Study MC-FludT.16/NM versus 41 patients, 58.6%, in Study MC-FludT.17/M).

Skin and subcutaneous tissue disorders CTCAEs of Grade III or higher in patients treated with treosulfan based conditioning were reported more frequently in Study MC-FludT.17/M (11.4%) than in Study MC-FludT.16/NM (6.7%).

Common Terminology Criteria for adverse events (CTCAEs) of Grade III or higher in at least one patient treated with treosulfan based conditioning in at least one of the two studies (Study MC-FludT.16/NM versus Study MC-FludT.17/M, respectively) were: rash maculo-papular (4.4% versus 7.1%), dermatitis exfoliative (2.2% versus 2.9%), erythema in (0.0% versus 1.4%), and pruritus in (0.0% versus 1.4%).

Other safety issues in the paediatric population

Safety in paediatric populations as stratified per age, gender, and dose was reviewed, and as summarised below:

- In general, TEAEs in the key high level categories increased with age in the paediatric population treated with treosulfan based conditioning in the pooled data from the two paediatric Studies MC-FludT.16/NM and MC-FludT.17/M (86.4% versus 92.6% versus 100.0% for 28 days to 23 months, 2 to 11 years, and 12 to 17 years, respectively). The exceptions were SAEs and SARs.
- The most noticeable differences between the two genders in patients treated with treosulfan based conditioning in the pooled data from the two paediatric studies related to the higher incidence of TEAEs (any events) and CTCAEs of Grade III or higher, irrespective of causality, in female compared to male patients. The proportion of patients with other high level TEAEs were generally comparable in males and females apart from deaths, which occurred more frequently in female than in male patients.
- In patients treated with treosulfan based conditioning in the pooled data from the two paediatric studies, the incidence of TEAEs in each of the high-level categories was notably higher in the 14 g/m^2 group than in the 10 g/m^2 group, apart from SAEs and SARs.
  - TEAEs were reported more frequently in the 14 g/m^2 than in the 10 g/m^2 dose group (97.9% versus 80.0%), as were CTCAEs of Grade III or higher (87.5% versus 60.0%), drug related TEAEs (87.5% versus 73.3%) and drug related CTCAEs of Grade III or higher (62.5% versus 20.0%).
  - In addition, pre-defined significant TEAEs of early toxicity, defined as any AE occurring until Day 28, occurred more frequently in the 14 g/m^2 group than in the 10 g/m^2 group (95.8% versus 80.0%), as did hepatoxicity (45.8% versus 33.3%) and infections (70.8% versus 53.3%).
  - Death at the end of the trials (integrated safety summary data) was also reported more commonly in the 14 g/m^2 group than in the 10 g/m^2 group (7 patients (14.6%) versus 0%).
  - However, SAEs were reported in a similar proportion of patients in the two dose groups (37.5%, 14 g/m^2 versus 40.0%, 10 g/m^2), while SARs were reported infrequently in paediatric patients.
  - The cumulative incidence of acute GvHD Grade III-IV at 100 days after transplantation was similar in the 14 g/m^2 and 10 g/m^2 dose groups (12.8% versus 14.3%, respectively), while the cumulative incidence of moderate or severe chronic GvHD at 12 months after

transplantation was greater in the 10 g/m^2 dose group than in the 14 g/m^2 dose group (25.0% versus 17.3%, respectively).

Safety data from Study MC-FludT.16/NM

It is noted that the BSA groups for the treosulfan based dosing scheme were updated as of 17 April 2019. Overall, 15.7% of subjects received treosulfan according to the modified BSA groups: 11.1% in the 10 g/m^2/day group, 18.8% in the 12 g/m^2/day group, and 10.0% in the 14 g/m^2/day group. Two subjects were affected by the treosulfan dose modifications in that they were allocated to a different dose group: one subject with BSA 0.48 m^2 received 12 g/m^2/day and one subject with BSA 0.85 m^2 received 14 g/m^2/day according to the modified BSA groups. The administration of fludarabine and thiotepa was comparable between the 2 treatment arms.

Overall, adverse events, drug related AEs, SAEs, deaths, and drug related serious AEs are as presented in Table 14 below:

Table 14: Study MC-FludT.16/NM High level overview of treatment-emergent adverse events

	Busulfan (N=50)	Treosulfan (N=51)	Total (N=101)
Any adverse event [n (%)]			
Subjects with any adverse event	48 (96.0%)	49 (96.1%)	97 (96.0%)
Subjects with AEs of at least CTCAE grade III	41 (82.0%)	41 (80.4%)	82 (81.2%)
Drug-related adverse events [n (%)]			
Subjects with any drug-related adverse event	37 (74.0%)	41 (80.4%)	78 (77.2%)
Subjects with drug-related AEs of at least CTCAE grade III	25 (50.0%)	26 (51.0%)	51 (50.5%)
Serious adverse events [n (%)]			
Subjects with any serious adverse event	16 (32.0%)	18 (35.3%)	34 (33.7%)
- Results in death	4 (8.0%)	0 (0.0%)	4 (4.0%)
- Life-threatening	4 (8.0%)	3 (5.9%)	7 (6.9%)
- Hospitalization or prolongation of hospitalization	8 (16.0%)	16 (31.4%)	24 (23.8%)
- Disability/incapacity	1 (2.0%)	0 (0.0%)	1 (1.0%)
- Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0 (0.0%)
Drug-related serious adverse events [n (%)]			
Subjects with any drug-related serious adverse event	3 (6.0%)	2 (3.9%)	5 (5.0%)
Maximum CTCAE grade of adverse events [n (%)]			
Subjects with AEs of a maximum CTCAE grade I	1 (2.0%)	0 (0.0%)	1 (1.0%)
Subjects with AEs of a maximum CTCAE grade II	6 (12.0%)	8 (15.7%)	14 (13.9%)
Subjects with AEs of a maximum CTCAE grade III	30 (60.0%)	34 (66.7%)	64 (63.4%)
Subjects with AEs of a maximum CTCAE grade IV	8 (16.0%)	7 (13.7%)	15 (14.9%)
Subjects with AEs of a maximum CTCAE grade V	3 (6.0%)	0 (0.0%)	3 (3.0%)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for adverse event; N = total number of subjects; n = number of subjects in each category.

In general, the safety profile of the two treatment arms were shown to be comparable. High level AEs with a 5% or more difference in subject incidence between the two treatment arms were drug related AEs (74.0%, busulfan versus 80.4%, treosulfan), SAEs resulting in death (8.0%, busulfan versus 0%, treosulfan), SAEs resulting in hospitalisation or prolonged hospitalisation (16.0%, busulfan versus 31.4%, treosulfan), maximum CTCAEs Grade III (60.0%, busulfan versus 66.7%, treosulfan), and maximum CTCAEs Grade V (6.0%, busulfan versus 0%, treosulfan). The incidence of CTCAEs of Grade III or higher was similar in the two treatment arms (82.0%, busulfan versus 80.4%, treosulfan).

In addition, safety data from these patients (n = 101) are summarised as follows:

- TEAEs: 96.0% subjects in the busulfan arm versus 96.1% of subjects in the treosulfan arm.
- Grade III or above AEs: 82.0% (busulfan) versus 80.4% (treosulfan).
- Drug related TEAEs: 74.0% (busulfan) versus 80.4% (treosulfan); the following were more common in the treosulfan arm (occurring in at least 2% more subjects than in the busulfan arm): oral mucositis (62.7% versus 58.0%), vomiting (43.1% versus 38.0%), diarrhoea (39.% versus 22.0% and abdominal pain (23.5% versus 12.0%). Nausea was more common in subjects in the busulfan arm (30.0% versus 17.6%).
- Drug related Grade III or above AEs: similar in both arms (50% busulfan versus 51% treosulfan).
- Deaths: 8.9% of subjects (14.0% in the busulfan arm versus 3.9% in the treosulfan arm); all were transplantation related, and multiple causes of death were usually reported per subject.
- SAEs: similar in both arms (32.0% of subjects in busulfan arm versus 35.3% of subjects in treosulfan arm).
- Drug related SAEs: 6.0% (busulfan) versus 3.9% (treosulfan).
- Other significant pre-defined TEAEs: hepatic sinusoidal obstruction syndrome (10.0% busulfan versus 2.0% treosulfan); infections (70.0% busulfan versus 60.8% treosulfan). Rates of hepatic toxicity and lung toxicity were similar in the two arms.
- Acute GvHD Grade I-IV up until Day 100 was greater in the treosulfan arm than in the busulfan arm (54.9% versus 42.0%, respectively, nominal p = 0.0889).
- Acute GvHD Grade III-IV up until Day 100 was greater in the treosulfan arm than in the busulfan arm (13.7% versus 8.0%, respectively; nominal p = 0.4598).
- Acute GvHD Grade II-IV was similar in the two treatment arms (26.0%, busulfan versus 27.5%, treosulfan; nominal p = 0.6407).
- Chronic GvHD at 12 months was significantly greater in subjects in the busulfan arm than in the treosulfan arm (38.6% versus 12.8%, respectively).

Post-marketing experience

The submission included post-marketing data available for Trecondi: periodic safety update report (PSUR) dated 1 September 2012 to 31 August 2017; cumulative Interval tabulation from post-marketing data sources dated 1 September 2017 to 17 March 2020, PSUR dated 20 June 2019 to 19 December 2019, and PSUR dated 20 June 2020 to 19 December 2020.

It was stated in the most recent PSUR in the submission dated 20 June 2020 to 19 December 2020 that the estimated interval exposure and cumulative exposure from marketing experience for treosulfan in combination with fludarabine for conditioning prior alloHSCT since first approved in the EU in 2019 is 2575 adult patients and 644 paediatric patients. The post-marketing data have not identified safety signals beyond those observed in the clinical trial program for adults and children.

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.3 (6 November 2018; data lock point (DLP) 13 October 2017), Global RMP version 0.4 (30 December 2020; DLP 19 June 2020) and Australia specific annex (ASA) version 0.1 (April 2021) in support of this application.

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 15. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 15: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Treatment related second malignancy	ü	–	ü	–
Important potential risks	Seizures in small infants	ü	–	ü	–
Missing information	Effect on fertility	ü	–	ü	–
	Use in patients with prior allogeneic haematopoietic stem cell transplantation (alloHSCT)	ü	–	ü	–

- The summary of safety concerns is considered acceptable from an RMP perspective. At the time of the second round of RMP evaluation, the nonclinical evaluation report was not yet available. The sponsor has been requested to assess any safety concerns raised by the nonclinical evaluation for inclusion in RMP or ASA updates.
- The sponsor has proposed routine pharmacovigilance activities only for all safety concerns. The pharmacovigilance plan is considered acceptable.
- The sponsor has proposed routine risk minimisation activities only for all safety concerns. At the second round of evaluation, requested amendments were made to the Product Information and Consumer Medicines Information (CMI). The risk minimisation plan is considered acceptable.

Risk-benefit analysis

Delegate's considerations

Background

Allogeneic haematopoietic stem cell transplantation (alloHSCT) is potentially curative for leukaemias, myelodysplastic syndromes (MDS), lymphomas and multiple myeloma. It is also used in non-malignant diseases such as primary immunodeficiency, inborn errors of metabolism, haemoglobinopathies and bone marrow failure syndromes. Patients undergoing an alloHSCT are prepared with chemotherapy alone or chemotherapy combined with radiotherapy, the so-called conditioning or preparative regimen. The conditioning regimen has three aims: reduction of the tumour burden when the disease is neoplastic; elimination of the self-renewing capacity of the recipient's own haematopoiesis; and suppression of the recipient's immune system in order to allow engraftment of donor stem cells. Reducing the toxicity of the preparative regimen is critical to improving the safety of transplantation.

Proposed indication

Following the first round of clinical evaluation, the indications now being proposed by the sponsor differ from those proposed in the original application. The sponsor now proposes to register treosulfan, a new therapeutic entity, for the following indications;

In the adult population:

> *Trecondi (treosulfan) is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with AML or MDS at increased risk for standard conditioning therapies.*

In the paediatric population:

> *Trecondi (treosulfan) is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with malignant and non-malignant diseases.*

Adult population

Evaluation of the evidence

The sponsor has provided adequate evidence of effectiveness to support approval of Trecondi (treosulfan) in combination with fludarabine as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukaemia (AML) or myelodysplastic syndromes (MDS) at increased risk for standard conditioning therapies.

Approval of treosulfan is supported by results from the pivotal Phase III study, Study MC-FludT.14/L Trial II, a randomised, controlled, open label, multicentre, international, group sequential Phase III non-inferiority trial comparing treosulfan to busulfan as part of a conditioning regimen containing fludarabine prior to alloHSCT in adults with AML or MDS who were considered at increased risk for standard conditioning therapies (that is ineligible for standard conditioning regimen).

Completion of the second (confirmatory) interim analysis (n = 476 patients) showed non-inferiority of treosulfan compared to busulfan for event-free survival at 24 months. The final (last) analysis of Study MC-FludT.14/L Trial II included a total of 551 patients (full analysis set (FAS); n = 283 in the busulfan group and n = 268 in the treosulfan group), including 352 (63.9%) patients with AML and 199 (36.1%) patients with MDS.

The event-free survival at 24 months after alloHSCT (primary endpoint) in the treosulfan group was statistically significantly non-inferior to the busulfan group. In the final analysis (per-protocol set (PPS)), 48.7% of patients in the busulfan group and 36.6% of patients in the treosulfan treatment group experienced an event. Kaplan-Meier estimates of event-free survival at 24 months were 51.1% (95% confidence interval (CI): 44.8%, 57.0%) in the busulfan group, and 65.3% (95% CI: 59.0%, 70.9%) in the treosulfan group, with the one-sided p-value for non-inferiority of treosulfan compared to busulfan being 0.0000001. The results for non-inferiority testing in the FAS were similar to the results in the PPS population.

In addition, statistically significant superiority of the treosulfan group compared to the busulfan group for event-free survival at 24 months was demonstrated in the FAS. (event-free survival (superiority)) at Month 24 in the FAS: 51.2% (busulfan) versus 65.7% (treosulfan); hazard ratio = 0.64 (95% CI: 0.49, 0.84) in favour of the treosulfan group; adjusted p = 0.0005787). The median follow-up time was 29.7 months in the treosulfan treatment group and 29.4 months in the busulfan treatment group.

The pre-specified exploratory subgroup analyses of event-free survival at 24 months (FAS) were consistent with the results in the total population. For AML patients, event-free survival at 24 months was 53.3% in the busulfan group and 64.7% in the treosulfan group (hazard ratio = 0.72 (95%: 0.52, 0.99) in favour of treosulfan). For MDS patients, event-free survival at 24 months was 48.2% in the busulfan group and 68.1% in the treosulfan group (hazard ratio = 0.66 (95%: 0.42, 1.02) in favour of treosulfan).

The secondary efficacy analyses demonstrated that the outcomes were generally comparable for the two treatment groups or superior in the treosulfan group compared to the busulfan group. As all secondary endpoint analyses were exploratory and no statistical adjustment was made for multiplicity of pairwise testing, p-values presented for the analyses in the study report are considered to be nominal rather than confirmatory.

Two registry studies, EBMT (2019) and CIBMTR (2019) were also submitted, providing supportive efficacy data for the proposed treosulfan (10 g/m^2)/fludarabine conditioning regimen. Two additional Phase II studies investigating the efficacy and safety of treosulfan (14 g/m^2) based conditioning in patients with AML and MDS (Studies MC-FludT.7/AML and MC-FludT.8/MDS, respectively) at either increased or standard risk for alloHSCT with respect to toxicity were evaluated. The results of these two studies are not directly relevant to the proposed usage of treosulfan in adult patients with malignant disease as the treosulfan dose of 14 g/m^2 used in these studies for the treatment of adult patients with AML or MDS is more than the dose (10 g/m^2) being proposed for the treatment of adult patients with malignant disease.

Uncertainties

It is noted that there were no pivotal clinical studies investigating the efficacy of treosulfan (10 g/m^2) combined with cytotoxic or chemotherapeutic agents, other than fludarabine, as part of a conditioning regimen for the treatment of adult patients with malignant disease. Observational data from the two registry studies of treosulfan (10 g/m^2) combined with fludarabine (EBMT 2019; CIBMTR 2019) suggests that this regimen might be more effective than some other conditioning therapies (for example busulfan and cyclophosphamide; fludarabine and melphalan).

Risks and unfavourable effects

The primary safety population included adult patients who received the proposed treosulfan conditioning regimen prior to alloHSCT for AML or MDS in Study MC-FludT.14/L Clinical Trial II. This study included a total of 553 patients in the final analysis safety set (283 patients in the busulfan group and 270 patients in the treosulfan group). In general, the safety profiles of the two busulfan and treosulfan groups were comparable.

- In the treosulfan group, the commonest (occurring in 10% or more of patients) treatment-emergent adverse events (TEAEs) were oral mucositis (37.8%), fever (34.4%), nausea (33.0%), vomiting (21.9%), limb oedema (22.6%), headache (16.3%), diarrhoea (15.9%), back pain (14.8%), febrile neutropenia (14.8%), hypertension (14.1%), bone pain (13.7%), constipation (12.2%), fatigue (12.2%), maculopapular rash (11.9%), abdominal pain (10.7%), and arthralgia (10.0%).
- Limb oedema was reported more frequently in the treosulfan group than in the busulfan group (22.6% versus 13.4% respectively), and arthralgia (10.0% versus 3.5% respectively). Oral mucositis (47.7% versus 37.8%), nausea (41.0% versus 33.0%), and hypertension (21.2% versus 14.1%) were reported more frequently in the busulfan group than in the treosulfan group, respectively.
- The proportion of patients experiencing at least one Grade III or above AE was similar in both treatment groups (53.4% busulfan versus 54.8%, treosulfan).

- Drug related TEAEs were reported in 67.8% of patients in the busulfan group and 63.0% of patients in the treosulfan group.
- The proportion of patients experiencing at least one drug related Grade III or above AE was similar in both treatment groups (29.0% busulfan versus 26.7% treosulfan).
- In the treosulfan group, the commonest Grade III or above AEs reported (in 5% or more of patients) were febrile neutropenia (14.8%), hypertension (7.8%), oral mucositis (5.9%), and ALT increased (5.2%).
- Serious adverse events (SAEs) were reported in 7.1% of patients in the busulfan group and 8.5% of patients in the treosulfan group. SAEs reported in 1% or more of patients in either treatment group (busulfan versus treosulfan, respectively) were sepsis (1.8% versus 3.0%), lung infection (1.1% versus 2.2%), and acute kidney injury (0.4% versus 1.1%).
- Deaths (until Month 24) occurred more frequently in patients in the busulfan group than in treosulfan group (37.8% versus 26.7%, respectively). Transplantation related deaths occurred in 20.5% of patients in the busulfan group and 12.2% of patients in the treosulfan group, and disease relapse or progression deaths occurred in 16.6% of patients in the busulfan group and 12.6% of patients in the treosulfan group. Of the 12.2% of patients in the treosulfan treatment group who died due to transplantation related causes, the most common causes (5% or more of patients) were infections (9.3%), predominantly bacterial infection (5.6%). Graft versus host disease (GvHD) occurred in 4.8% of patients in the treosulfan group.
- No clinically meaningful differences between the two treatment groups (busulfan versus treosulfan, respectively) as regards significant pre-defined Common Terminology Criteria for adverse events Grade III/IV, that is mucositis (7.4% versus 5.9%); hepatic sinusoidal obstruction syndrome (0.4% versus 0%), seizures (0% versus 0.4%), and blood bilirubin increased (2.8% versus 3.3%).
- No significant hepatic, renal, skin, or cardiovascular safety concerns were identified; clinical chemistry and haematological laboratory parameters were generally comparable in both treatment groups.
- Acute GvHD Grades I to IV: 57.2% busulfan versus 52.6% treosulfan; Grade III/IV: 8.1% busulfan versus 6.3% treosulfan. Chronic GvHD: 59.5% busulfan versus 60.3% treosulfan; extensive chronic GvHD: 26.7% busulfan versus 19.7 % treosulfan. GvHD related deaths: 7.4% busulfan versus 4.8% treosulfan.

The pattern of risks of treatment with treosulfan based conditioning identified in the pivotal study are consistent with the pattern of risks observed in the pooled data from the five Medac GmbH studies. However, the risks of treatment were increased with higher dose treosulfan (14 g/m^2) combined with fludarabine conditioning compared with lower dose treosulfan (10 g/m^2) combined with fludarabine conditioning.

Missing information

There were no clinical studies in adults in the submission providing safety data on special groups relating to race, hepatic impairment or renal impairment.

Paediatric population with malignant disease

Evaluation of the data

The application to register treosulfan based conditioning prior to alloHSCT in paediatric patients with malignant haematological disease was supported by one Phase II study, Study MC-FludT.17/M. This was a multinational, multicentre, prospective, non-randomised,

non-controlled, Phase II study in children and adolescents with haematological malignant disease requiring myeloablative conditioning prior to alloHSCT. The study was designed to assess the safety and efficacy of treosulfan combined with fludarabine, administered as a 'standard regimen' without thiotepa or an 'intensified regimen' with thiotepa. Efficacy was evaluated in 70 patients (ages ranging from 28 days to 17 years; median age of 9.5 years) with malignant disease; these included patients with acute lymphoblastic leukaemia (ALL; 38.5%), AML (41.4%), or MDS (14.3%), or juvenile myelomonocytic leukaemia (JMML; 5.7%). Nearly all of the ALL and AML patients were in first or second complete remission and had received their first haematopoietic stem cell transplantation (HSCT). 92.9% of patients received treosulfan combined with fludarabine and thiotepa as conditioning regimen prior to alloHSCT, compared to 7.1% without thiotepa. These data suggest that the efficacy and safety results reported for the study are being primarily driven by treosulfan and fludarabine with thiotepa.

The trial was descriptive in nature and was not intended to test any pre-specified hypotheses. A primary efficacy endpoint was not defined in this study because the primary trial endpoint is the safety parameter of freedom from transplant (treatment) related mortality until 100 days after transplant.

The median follow-up for the 70 patients was 41.8 months, with the range for those surviving being 24.2 to 57.5 months. The treosulfan dose was adapted individually based on the body surface area (BSA). That is, no more than 0.5 m^2, more than 0.5 to 1 m^2, and more than 1 m^2 received treosulfan 10 g/m^2 (6 patients, 8.6%), 12 g/m^2 (26 patients, 37.1%) or 14 g/m^2 (38 patients, 54.3%), respectively.

The rate for freedom from transplant (treatment) related mortality until 100 days after alloHSCT was 98.6% (90% CI: 93.4, 99.9). There was only one transplant (treatment) related death through to Day 100 after alloHSCT, which was considered to be a transplant related death. The results for the secondary efficacy endpoints provide support for the benefits of treosulfan based conditioning prior to alloHSCT for paediatric patients with malignant disease.

Risks and uncertainties

The limitations of this single arm, Phase II study include the absence of a randomised control group and the small number of patients with haematological malignant conditions other than ALL or AML. Given that nearly all patients received conditioning treatment with the 'intensified regimen' rather than the 'standard regimen', it can be reasonably inferred that the efficacy results are being primarily driven by this regimen in patients with ALL and AML. The absence of a control group is mitigated to some extent by the clinically meaningful response rates based on objectively determined endpoints for treosulfan based conditioning (for example, death, engraftment, complete donor type chimerism, relapse). The submission also included a pre-specified report comparing engraftment and overall survival in paediatric patients from Study MC-FludT.17/M with data from published historical studies (in paediatric patients with malignant disease) and with data from Study MC-FludT.14/L Trials I and II (in adult patients with malignant disease). This showed that the treosulfan based conditioning regimen used in Study MC-FludT.17/M was more effective than the treosulfan based conditioning regimens used in the published historical studies and in Study MC-FludT.14/L Trials I and II, however, limitations to interpretation are noted relating to biases arising from the non-randomised patient groups and the differences in the treosulfan based conditioning regimens.

Despite these limitations, it is considered that the results for the primary endpoint and secondary efficacy endpoints of this study provide adequate evidence to support the efficacy of treosulfan combined with fludarabine conditioning prior to alloHSCT in paediatric patients with malignant disease, particularly for the intensified regimen with thiotepa. Reassurance regarding the generalisability of the efficacy results for treosulfan based conditioning from

Study MC-FludT.17/M in paediatric patients with malignant disease (AML, ALL, MDS and JMML) to all paediatric haematological malignancies is supported by the clinically meaningful engraftment rates (granulopoiesis, leukopoiesis, and thrombopoiesis), the high rates of complete donor type chimerism, the absence of primary graft failure, and the negligible number patients experiencing secondary graft failure. Supportive data for the efficacy of treosulfan based conditioning prior to alloHSCT in children and adolescents with malignant disease is provided by the EBMT Registry study (Peters, 2011).

Other uncertainties: with respect to dosing, as previously highlighted, the BSA dependent treosulfan dose used in Studies MC-FludT.17/M and MC-FludT.16/NM was different from the BSA dependent treosulfan dose being proposed for registration. The BSA dependent treosulfan dose being proposed for registration is based on updated population pharmacokinetic (PopPK) modelling using data in paediatric patients from Studies MC-FludT.16/NM (24 patients) and MC-FludT.17/M (59 patients) to update the initial PopPK model based on PK data from 7 different historical studies, which included mostly adults and only a limited number of children.

Paediatric population with non-malignant disease

Evaluation of the evidence

Study MC-FludT.16/NM is the key clinical trial submitted to support the treosulfan conditioning regimen for the proposed indication in the paediatric population (aged 28 days to 17 years) with non-malignant disease indicated for first alloHSCT. This study was a prospective, randomised (1:1), open label, multicentre, active controlled, parallel group Phase II clinical trial designed to describe the safety and efficacy of a treosulfan based conditioning regimen (FT_{10-14} with or without thiotepa)[1] compared with a standard busulfan based myeloablative regimen (FB4 with or without thiotepa)[1] in a paediatric population age 28 days to less than 18 years with non-malignant diseases indicated for first myeloablative alloHSCT. Both treosulfan and busulfan were administered as part of a standardised fludarabine containing conditioning regimen with or without thiotepa.

The submitted results focused on analyses of data for a follow-up period of 12 months, but also contained longer term follow-up data available as of the data cut-off date, with a median duration of follow-up of 25.4 months (range: 11.7 to 63.3 months) in the busulfan arm and 25.6 months (range: 10.7 to 60.9 months) in the treosulfan arm. 101 subjects were included in both the FAS and safety sets: 50 subjects in the busulfan arm and 51 subjects in the treosulfan arm. The trial aims to follow-up subjects until 36 months after transplantation of the last randomised subject, including planned longer term follow-up evaluation for secondary graft failure, chronic GvHD, overall survival, and transplant-related mortality until the year 2023. At the time of the analysis, 90 subjects were ongoing in the trial (43 on busulfan; 47 on treosulfan).

Randomisation was stratified by the two pre-specified conditioning regimens, with or without additional thiotepa. The majority of subjects received thiotepa, including 83.3% in the busulfan arm and 84.6% in the treosulfan arm. Other than stratification based on the background conditioning regimens with or without thiotepa, no other factors were considered for stratification. Therefore, some imbalances in disease type between the two treatment arms were observed. There were more subjects in the FAS with primary immunodeficiency disease in the busulfan arm (56.0%) than in the treosulfan arm (45.1%), and more subjects with haemoglobinopathies in the treosulfan arm (41.2%) than in the busulfan arm (26.0%). The numbers of subjects with inborn errors of metabolism or with bone marrow failure were small in both treatment arms (that is, inborn errors of metabolism = 8.0%, busulfan, 3.9%, treosulfan; bone marrow failure = 10.0%, busulfan versus 9.8%, treosulfan).

The study was descriptive in nature, and no formal confirmatory testing of efficacy or safety was planned. No primary efficacy variable was defined for the trial, although some, but not all secondary outcomes were described as efficacy parameters. The primary endpoint was freedom from transplantation (treatment) related mortality at Day 100 in the FAS; this was reported in 100% (90% CI: 94.3%, 100.0%) of subjects in the treosulfan arm (no events in 51 subjects) and 90% (90% CI: 80.1% versus 96.0%) of subjects in the treosulfan arm (5 events in 50 subjects).

Key secondary endpoints of overall survival, transplant-related mortality, GvHD-free survival and chronic GvHD-free survival favoured treosulfan compared with busulfan. Apart from chronic GvHD-free survival at 12 months, the differences between the two treatment arms for these four outcomes were not statistically significant (nominal $p > 0.05$).

- Overall survival at 12 months was 88.0% (90% CI: 77.9, 93.7) in the busulfan arm and 96.1% (90% CI: 88.0, 98.8) in the treosulfan arm: hazard ratio = 0.29 (90% CI: 0.08, 1.09), nominal p = 0.1244.
- the incidence of transplant-related mortality at 12 months was lower in the treosulfan arm (3.9% (90% CI: 1.2, 12.0)) compared with the busulfan arm (12.0% (90% CI: 6.3, 22.1)): hazard ratio = 0.29 (90% CI: 0.08, 1.09), nominal p = 0.1244
- The incidence of the composite endpoint GvHD-free survival at 12 months was 69.4% (90% CI: 57.1, 78.8) in the busulfan arm and 82.9% (90% CI: 71.5, 90.1) in the treosulfan arm: hazard ratio = 0.58 (90% CI: 0.28, 1.20), nominal p = 0.2178.
- The incidence of the composite endpoint chronic GvHD-free survival at 12 months was 69.4% (90% CI: 57.1, 78.8) in the busulfan arm and 89.3% (90% CI: 79.0, 94.7): hazard ratio = 0.32 (90% CI: 0.14, 0.76), nominal p = 0.0308

Of particular note, graft failure at 12 months occurred more frequently in subjects in the treosulfan arm (15.8% (90% CI: 7.4, 24.3)) than in subjects in the busulfan arm (4.0% (90% CI: 0.0, 8.6)), with the difference between the two arms being nominally statistically significant (p = 0.0366, adjusted for thiotepa and disease). This difference was due to a higher number of secondary graft failures in the treosulfan arm than in the busulfan arm (9 subjects, 18.4% versus 0 subjects, 0%, respectively), while the number of primary graft failures was the same in the two treatment arms (2 subjects, 4.0% versus 2 subjects, 3.9%, respectively).

The difference in graft failure at 12 months between the two treatment arms reflects the lower rate of complete donor chimerism at 12 months in the treosulfan arm compared with the busulfan arm (49.0% versus 76.7%, respectively, nominal p = 0.2445, adjusted for thiotepa and disease). The higher rate of graft failure at 12 months in the treosulfan arm translated into reduced event-free survival at 12 months based on lower Kaplan-Meier estimates in this arm compared with the busulfan arm (80.3% versus 86.0%, respectively, nominal p = 0.3343, adjusted for thiotepa and disease as factors).

Of particular concern in this trial was the increasing cumulative incidence of graft failure over time from alloHSCT in the treosulfan arm. In contrast to increasing graft failures in subjects in the treosulfan arm from 12 months through 36 months, graft failures in subjects in the busulfan arm remained stable. The cumulative incidence of graft failures in the two treatment arms (busulfan versus treosulfan, respectively) were 4.0% versus 15.8% at 12 months, 4.0% versus 21.0% at 24 months, and 4.0% versus 24.8% at 36 months. In addition, the incidence of event-free survival in the treosulfan arm declined from 12 months through 36 months in a notably greater number of subjects than in the busulfan arm. The Kaplan-Meier estimates for event-free survival for subjects in the busulfan versus treosulfan arms, respectively, were 86.0% versus 83.0% at 12 months, 86.0% versus 75.3% at 24 months and 81.9% versus 71.9% at 36 months.

The results suggest that, over time, increased morbidity due to secondary graft failure is likely to occur in paediatric subjects treated with treosulfan conditioning prior to first alloHSCT compared with busulfan conditioning.

Of note, in the single arm study in paediatric subjects with malignant disease (Study MC-FludT.17/M) exploring the efficacy and safety of treosulfan (FT_{10-14} with or without thiotepa),[1] none of the 70 treated subjects experienced a primary graft failure and 1.4% (1 of 69) treated subjects experienced a secondary graft failure. In addition, complete donor type chimerism at Day 28, Day 100 and 12 months was 94.2%, 91.3%, and 91.2%, respectively. These results suggest that the FT_{10-14} with or without thiotepa regimen is more myeloablative in paediatric patients aged 28 days to 17 years with malignant disease compared with non-malignant disease.

On balance, it is considered that the greater risks of secondary graft failure outweigh the smaller survival benefits (freedom from transplantation (treatment) related mortality at Day 100; transplant-related mortality; overall survival; GvHD-free survival and chronic GvHD-free survival) associated with the proposed treosulfan based conditioning regimen in children and adolescents with non-malignant disease indicated for first alloHSCT. At 36 months, the risk of graft failure was 24.8% in the treosulfan arm and 4.0% in the busulfan arm.

Risks and uncertainties

The risk assessment for the proposed treosulfan based conditioning regimen prior to alloHSCT for the treatment of paediatric patients older than one month is primarily based on the pooled data from 115 patients from the two clinical studies in patients with malignant disease (Study MC-FludT.17/M) and non-malignant disease (Study MC-FludT.16/NM). The median age of the 115 patients in the pooled data set was 7.0 years (range: 28 days to 17 years); 89.6% of patients received the intensified regimen of treosulfan / fludarabine with thiotepa and 10.4% of patients received the standard regimen of treosulfan / fludarabine without thiotepa.

Pooled data from these patients (n = 115) are as follows:

- Treatment-emergent adverse events occurred in 93.9% of patients.
- Grade III or above AEs occurred in 73.9% of patients.
- Drug related TEAEs occurred in 84.3% of patients. The commonest by Preferred Term occurring in 10% or more patients included stomatitis (67.0%), vomiting (41.7%), diarrhoea (34.8%), nausea (27.8%), hepatotoxicity (26.1%), abdominal pain (17.4%), pyrexia (13.0%), ALT increased (11.3%), alopecia (10.4%), and pruritus (10.4%).
- Drug related Grade III or above AEs occurred in 47.8% of patients. The commonest occurring in 5% or more of patients included stomatitis (31.3%), nausea (8.7%), and diarrhoea (7.8%).
- In Study MC-FludT.17/M, death had occurred in 17.1% of patients treated with treosulfan based conditioning. Of which, 11.4% were due to disease progression and 5.7% were due to transplantation related causes.
- In Study MC-FludT.16/NM, death was reported in 1.2% (one patient) treated with treosulfan based conditioning (transplantation related) and 14.0% (6 patients) treated with busulfan based conditioning (all transplantation related).
- Serious adverse events occurred in 33.9% of patients. SAEs reported in 2 (1.7%) or more patients were pyrexia (7.8%), cytomegalovirus (5.2%), upper respiratory tract infection (3.5%), sepsis (2.6%), febrile neutropenia (2.6%), encephalitis (1.7%), encephalopathy (1.7%), and vomiting (1.7%). Drug related SAEs occurred in 2.6%.

- Other significant pre-defined TEAEs included: hepatic sinusoidal obstruction syndrome (1.7%); hepatotoxicity (40.0%); and infections or infestations (65.2%). No patients experienced pre-defined significant lung toxicity (pulmonary fibrosis).
- Acute GvHD Grade I-IV were found in 46.1% of patients. Of which, 55.1% had non-malignant disease versus 42.9% had malignant disease.
- Chronic GvHD were found in 22.3% of patients. Of which, 16.7% had non-malignant disease versus 25.4% had malignant disease.

In general, the overall safety profile of treosulfan was worse in patients with malignant disease (Study MC-FludT.17/M) compared to patients with non-malignant disease (Study MC-FludT.16/NM). In patients with non-malignant disease, the overall safety profiles were generally comparable for patients treated with treosulfan based conditioning and patients treated with busulfan based conditioning (Study MC-FludT.16/NM).

The acceptable safety profile of treosulfan based conditioning observed in the pooled data from paediatric patients with malignant disease (Study MC-FludT.7/L) and non-malignant disease (Study MC-FludT.16/NM), supported by the extensive safety data from the EBMT Registry studies (Peters 2011, Peters 2017) for treosulfan based conditioning regimens for various paediatric malignant and non-malignant diseases, provide reassurance as regards the safety of treosulfan based conditioning prior to alloHSCT in all paediatric haematological malignancies.

Paediatric population (pooled data)

In the pooled population, AEs in patients treated with treosulfan based conditioning increased with increasing age and treosulfan dose. The results give rise to uncertainty relating to the proposed treosulfan BSA dependent dose regimen for the paediatric population, particularly for adolescent patients aged 12 to 17 years who are likely to be treated with the adult treosulfan 14 g/m^2 dose.

As highlighted by the clinical evaluation, the proposed recommended BSA adapted dose of treosulfan for the treatment of the paediatric population with malignant disease differs from that administered in Study MC-FludT.17/M. The proposed BSA dependent treosulfan dose for treatment of children and adolescents is based on updated PopPK modelling using historical data and data derived from the two paediatric Studies MC-FludT.16/NM and MC-FludT.17/M (Venn Life Sciences 2020, PopPK). In Study MC-FludT.17/M, the majority of patients received a treosulfan dose of 14 g/m^2/day (n = 38, 54.3%), while treosulfan doses of 10 g/m^2/day and 12 g/m^2/day were administered to 8.6% (n = 6) and 37.1% (n = 30) of patients, respectively.

Overall, the paediatric safety data based on the pooled population for 115 patients from the two paediatric studies (Studies MC-FludT.17/M and FludT.16/NM) are generally supportive of the treosulfan BSA dependent dose regimen being proposed for the paediatric population with malignant disease. However, the safety data from the pooled paediatric population suggested that the safety profile in patients treated with the treosulfan 10 g/m^2 regimen was better than patients treated with the treosulfan 14 g/m^2 regimen. In addition, as age was correlated with treosulfan dose adverse events increased with age.

Consequently, there are uncertainties relating to the safety of the 14 g/m^2 regimen, particularly when administered to adolescent patients aged 12 to 17 years. Based on the treosulfan BSA adapted dose being proposed by the sponsor for the paediatric population, it is likely that most adolescent patients aged 12 to 17 years with malignant disease will be treated with 14 g/m^2. This gives rise to concern, given the notably increased toxicity of the treosulfan 14 g/m^2 dose compared to the treosulfan 10 g/m^2 dose in adult patients with AML or MDS.

It is noted that the Canadian monograph for treosulfan recommends the same dosage regimen for the treatment of AML or MDS in paediatric patients older than one year and in adults (that is, treosulfan 10 g/m^2 in combination with fludarabine as part of conditioning treatment prior to alloHSCT). In addition, the clinical evaluation notes that based on the additional reference (Burroughs et al, 2014)[21] submitted by the sponsor it appears that the US Food and Drug Administration (FDA) is also recommending treosulfan at a dose of 10 g/m^2 on Days -4, -3, and -2 for both paediatric patients aged more than one year and adult patients with MDS or AML. Burroughs' and Nemecek's letter to the FDA commented that the regulatory agencies recommendation relating to dosage is based on data from 'a randomised, adult only, Phase III trial published by Beelen et al (2019)[22] in a cohort of patients with a median age of 61 years and more than 90% aged over 50 years. Burroughs and Nemecek concluded that the FDA's recommendation fails to consider data obtained with different dosage regimens in paediatric and younger adult patients and expressed concern that the FDA's dose recommendation 'will result in poor patient outcomes (in paediatric and younger adults) due to higher rates of disease relapse and/or graft rejection.

Additional comments and references regarding dosing were provided by the sponsor, with their comments noted as follows:

- A mandatory reduction of the treosulfan dose or exposure to 10 g/m^2 in the paediatric population would bear the risk to increase the relapse and graft failure rate, resulting in decreased progression-free survival and, eventually, overall survival.
- Only 4 out of 121 children (3.3%) in Studies MC-FludT.16/NM and MC-FludT.17/M who were older than one year and had been treated with the dose of 10 g/m^2 treosulfan.
- The proposed BSA adapted dose of 10 to 14 g/m^2 treosulfan in children is also consistent with current clinical practice worldwide, and the BSA adapted dose calculation for the FT$_{10\text{-}14}$ regimen with or without thiotepa;[1] regime is universally used by all paediatric transplant centres; numerous publications and registry data analyses have confirmed the excellent efficacy and safety of this regimen. The BSA adapted dose of 10 to 14 g/m^2 treosulfan in the paediatric population was registered by the European Medicines Agency, with FT$_{10\text{-}14}$ with or without thiotepa, authorised for paediatric patients older than one month with malignant diseases.

Therefore, overall, paediatric data in patients older than one month with haematological malignancies appear to support approval of treosulfan 10 to 14 g/m^2 (BSA dose adapted) intravenously per day on three consecutive days (Days -6, -5, -4) in combination with fludarabine 30 mg/m^2 BSA intravenously on five consecutive days (Days -7, -6, -5, -4, -3), either with thiotepa intravenously (5 mg/kg) twice a day (Day -2) or without thiotepa, prior to alloHSCT. However, the Delegate will seek further advice and input from the Advisory Committee on Medicines (ACM) regarding this dosing issue.

Overall benefit-risk assessment

Adult population

The benefit-risk assessment for treosulfan in combination with fludarabine as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with AML or MDS at increased risk for standard conditioning therapies is

[21] Burroughs, L.M et al. Treosulfan-Based Conditioning and Hematopoietic Cell Transplantation for Nonmalignant Diseases: A Prospective Multi-Center Trial, *Biol Blood Marrow Transplant*, 2014; 20(12): 1996-2003.

[22] Beelen, D.W. et al. Treosulfan or Busulfan Plus Fludarabine as Conditioning Treatment before Allogeneic Haemopoietic Stem Cell Transplantation for Older Patients with Acute Myeloid Leukaemia or Myelodysplastic Syndrome (MC-FludT.14/L): a Randomised, Non-inferiority, Phase 3 trial, *Lancet Haematol*, 2019; 19:30157-30157.

considered to be favourable. The pivotal Phase III Study MC-FludT.14/L Trial II has demonstrated a statistically significant non-inferiority of treosulfan compared to busulfan (in both the FAS and PPS populations) for event-free survival at 24 months. In general, the safety profiles of the two busulfan and treosulfan groups were comparable.

All patients in the study had risks for standard conditioning therapies (that is, aged 50 years or older and/or haematopoietic cell transplantation co-morbidity index scores more than 2), and patients who had received a previous alloHSCT were excluded from the study. There were no clinical studies submitted on the use of treosulfan in combination with other chemotherapeutic agents for conditioning prior to alloHSCT. Therefore, there are uncertainties about the benefit-risk balance for conditioning using treosulfan in combination with chemotherapeutic agents other than fludarabine. The safety profile of treosulfan as shown in the pivotal study is considered acceptable in the context of life-threatening diseases such as AML and MDS, where patients are not suitable for standard conditioning therapies.

Paediatric population with malignant disease

The benefit-risk assessment of Trecondi (treosulfan) in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to alloHSCT in paediatric patients (aged one month and older) with haematological malignancies is considered to be favourable. Treosulfan based conditioning prior to alloHSCT in paediatric patients with malignant haematological disease was supported by one Phase II study, Study MC-FludT.17/M. A primary efficacy endpoint was not defined in this study; the primary trial endpoint was the safety parameter of freedom from transplant (treatment) related mortality until 100 days after alloHSCT, which was demonstrated to be 98.6% (90% confidence interval: 93.4, 99.9). The results for the secondary efficacy endpoints provide support for the benefits of treosulfan based conditioning prior to alloHSCT for paediatric patients with malignant disease. In addition, the cross-study comparison relating to engraftment (reconstitution of granulopoiesis) and overall survival between patients in Study MC-FludT.17/M and historical data from the literature in paediatric patients with haematological disease support treosulfan based conditioning, as does the comparison between paediatric patients from Study MC-FludT.17/M and the adult patients from Study MC-FludT.14/L Trials I and II.

The acceptable safety profile of treosulfan based conditioning observed in the pooled data from paediatric patients with malignant disease (Study MC-FludT.7/L) and non-malignant disease (Study MC-FludT.16/NM), supported by the extensive safety data from the EBMT Registry studies (Peters 2011, Peters 2017) for treosulfan based conditioning regimens for various paediatric malignant and non-malignant diseases, provide reassurance as regards the safety of treosulfan based conditioning prior to alloHSCT in all paediatric haematological malignancies.

Overall, paediatric data in patients older than one month with haematological malignancies appear to support approval of treosulfan 10 to 14 g/m^2 (BSA dose adapted) as per proposed dosing recommendation. However, uncertainties remain relating to the safety of the 14 g/m^2 regimen, particularly when administered to adolescent patients aged 12 to 17 years, given the notably increased toxicity of the treosulfan 14 g/m^2 dose compared to the treosulfan 10 g/m^2 dose in adult patients with AML or MDS. The Delegate will seek further advice and input from the ACM regarding recommended dosing.

Paediatric population with non-malignant disease

The benefit-risk assessment of Trecondi (treosulfan) in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to alloHSCT in paediatric patients (aged one month and older) with non-malignant disease is considered to be unfavourable.

In the paediatric population with non-malignant disease indicated for first alloHSCT, freedom from transplantation (treatment) related mortality at Day 100 (primary analysis) favoured subjects in the treosulfan arm compared with the busulfan arm (100%, no events versus 90%, 5 events). In addition, the secondary endpoints of overall survival, transplant-related mortality, GvHD-free survival and chronic GvHD-free survival at 12 months all favoured the treosulfan arm compared with the busulfan arm. However, it is considered these benefits were outweighed by a significant increase in the incidence of graft failure at 12 months in the treosulfan arm compared with the busulfan arm. The difference in the graft failure rates at 12 months between the two arms reflects the reduction in the complete donor chimerism rate at 12 months in the treosulfan arm compared with the busulfan arm.

Of particular concern in this trial was the increasing cumulative incidence of graft failure from 12 months through to 36 months in subjects in the treosulfan arm compared with the busulfan arm. The cumulative incidence of graft failure in the two treatment arms (busulfan versus treosulfan, respectively) was 4.0% versus 15.8% at 12 months, 4.0% versus 21.0% at 24 months, and 4.0% versus 24.8% at 36 months. In addition, the incidence of event-free survival in the treosulfan arm declined from 12 months through to 36 months in a notably greater number of subjects than in the busulfan arm (80.3% versus 86.0% at 12 months; 75.3% versus 86.0% at 24 months; and 71.9% versus 81.9% at 36 months). The results suggest that, over time, increased morbidity due to secondary graft failure is likely to occur in paediatric subjects treated with treosulfan conditioning prior to first alloHSCT compared with busulfan conditioning. There were no data on the number of subjects who received a second HSCT due to graft failure or on the effectiveness of the treosulfan conditioning regimen administered for graft failure in the paediatric population with non-malignant disease.

On balance, it is considered that the greater risks of secondary graft failure observed with treosulfan compared with busulfan in paediatric subjects aged 28 days to 17 years with non-malignant disease indicated for first alloHSCT outweigh the smaller benefits of treosulfan compared with busulfan relating to freedom from transplantation (treatment) related mortality at Day 100, transplant-related mortality, overall survival, GvHD-free survival and chronic GvHD-free survival.

Proposed action

Approval for the following indication is not recommended as the benefit risk assessment for treosulfan is considered to be unfavourable in this population:

> *Trecondi (treosulfan) is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with non-malignant diseases*

Once all outstanding issues are resolved, approval is supported for the following indications:

> *Trecondi (treosulfan) is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with AML or MDS at increased risk for standard conditioning therapies*
>
> *Trecondi (treosulfan) is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with malignant diseases*

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Does ACM have any clinical concerns regarding the administration and use of this product if the lower pH limit of the reconstituted solution (for the duration of the in-use period) is set at a pH of 3.0?

The ACM considered the main concern with administration of low pH intravenous infusions to be phlebitis. However, the ACM noted that treosulfan, along with other chemotherapy agents in conditioning regimens, are administered via central venous access in clinical practice, and as a result advised phlebitis is not a clinical concern. The ACM also highlighted that administration of treosulfan via a central venous line is not specified in the provided Product Information (PI).

The proposed PI lists acidosis as an adverse effect of unknown incidence, which the ACM considered to be a theoretical concern. The ACM also noted the regular use of treosulfan in clinical practice. The ACM was of the view that a pH of 3.0 would be reasonable.

2. Does ACM support the proposed body surface area dependent treosulfan dose regimen for use in the paediatric population?

The ACM advised the proposed body surface area (BSA) dependent treosulfan dose in the paediatric population was supported. The variation between the proposed dosing in the PI and the dosing utilised in paediatric Studies MC-FludT.17/M and MC-FludT.16/NM was considered utilising population pharmacokinetic modelling, and the ACM was of the view that minimal differences in the mean and range of exposures are to be expected between the various BSA categories.

The ACM also noted the EBMT Registry study (Peters 2011) demonstrated no statistically significant association between treosulfan dose and transplant related mortality in patients below 18 years who received an alloHSCT for both malignant and non-malignant disease, and that 14 g/m^2 is widely used for paediatric patients greater than one year of age with BSA greater than 1 m^2 in current Australian clinical practice.

The ACM considered that the described treatment-emergent adverse events (TEAEs) are anticipated across all alloHSCT conditioning regimens, and the duration of neutropenia described in the provided paediatric studies to be consistent with other conditioning regimens in current practice.

3. Does the available data from the Phase II Study MC-FludT.16/NM support the use of treosulfan based conditioning therapy prior to alloHSCT in paediatric patients with non-malignant disease?

The ACM considered that the Study MC-FludT.16/NM data was limited due to insufficient study power, Phase II design and low study numbers but was of the view that treosulfan is likely to provide a similar overall survival benefit compared to busulfan in conditioning therapy prior to alloHSCT in paediatric patients with non-malignant disease. The ACM also noted that approximately one third of paediatric patients are being treated for non-malignant disease.

The ACM discussed the increased graft failure rate in the treosulfan arm of the study and noted that there was no information provided on patients' prior treatment to correlate to the increased graft failure rate. The ACM was of the view that additional information about the patients prior to the failure would be important to better understand the reason for the increased graft failure rate.

The ACM noted the paediatrics cohort is heterogenous, and transplant-associated issues vary depending on the individual patient disease, co-morbidities and age. The ACM was of the view that there is a continued need for a range of conditioning agents to be available to support individualised treatment and positive outcomes for all patients in a highly underserved population.

It was considered that infants with non-malignant diseases requiring alloHSCT are at higher risk of hepatic sinusoidal obstruction syndrome, and the ACM considered treosulfan to demonstrate a reduced risk of this potentially life-threatening complication over busulfan. Additionally, the ACM was of the view that the statistically significant reduction in chronic graft versus host disease (GvHD) demonstrated in Study MC-FludT.16/NM through use of treosulfan over busulfan was of clinical importance in this cohort.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Trecondi is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with AML [acute myeloid leukaemia] or MDS [myelodysplastic syndrome] at increased risk for standard conditioning therapies.*
>
> *Trecondi is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with malignant and non-malignant diseases.*

Outcome

Based on a review of quality, safety, and efficacy, the TGA approved the registration of Trecondi (treosulfan) 1 g and 5 g, powder for solution, vial, indicated for:

> ***Adults with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS)***
>
> *Trecondi (treosulfan) is indicated in combination with fludarabine as part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult patients with AML or MDS at increased risk for standard conditioning therapies.*
>
> ***Paediatric patients aged 1 month and older with malignant and non-malignant haematological diseases***
>
> *Trecondi (treosulfan) is indicated in combination with fludarabine, with or without thiotepa, as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in paediatric patients older than one month with malignant and non-malignant diseases.*

Specific conditions of registration applying to these goods

- Trecondi (treosulfan) is to be included in the Black Triangle Scheme. The PI and CMI for Trecondi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Trecondi Global risk management plan (RMP) (version 0.4, dated 30 December 2020, data lock point 19 June 2020), with Australian specific annex (version 0.1, dated April 2021),

included with Submission PM-2021-02707-1-6, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Trecondi approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

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Reference/Publication #