Summary Report of Benefit-Risk Assessment

TRECONDI POWDER FOR SOLUTION FOR INFUSION 5 G PER VIAL
TRECONDI POWDER FOR SOLUTION FOR INFUSION 1 G PER VIAL

NEW DRUG APPLICATION

Active Ingredient(s)	Treosulfan
Product Registrant	Link Healthcare Singapore Pte Ltd
Product Registration Number	SIN16922P, SIN16923P
Application Route	Abridged evaluation
Date of Approval	26 December 2023

Table of Contents

A INTRODUCTION

Trecondi is indicated for use 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 syndrome (MDS) at increased risk of toxicity with standard conditioning therapies, and in paediatric patients older than one month with malignant diseases.

The active substance, treosulfan, is a prodrug of a bifunctional alkylating agent with cytotoxic activity against haematopoietic precursor cells. The activity of treosulfan is due to the spontaneous conversion into a mono-epoxide intermediate and L-diepoxybutan. These epoxides alkylate nucleophilic centres of deoxyribonucleic acid (DNA) and induce DNA cross-links which are considered responsible for the stem cell depleting and antineoplastic effects.

Trecondi is available as a powder for solution for injection containing 5 g or 1 g of treosulfan per vial. There are no excipients added in the drug product.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, treosulfan, is manufactured at [redacted] The drug product, Trecondi Powder for Solution for Infusion, is manufactured at Oncotec Pharma Produktion GmbH, Sachsen-Anhalt, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications were established in accordance with ICH Q6A guidelines and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is double polyethylene bags placed within a plastic container. The stability data presented was adequate to support the storage of the drug substance at 25ºC.

Drug product:

The manufacturing process utilises aseptic filling followed by lyophilisation.

The manufacturing site is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6A guidelines and impurity limits were adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is a colourless type I glass vial, with chlorobutyl rubber stopper and aluminium seal including a flip-off cap for both the 5 g/vial and 1 g/vial strengths. The stability data submitted was adequate to support the approved shelf-life of 48 months when stored at or below 30ºC. The in-use period after reconstitution in 0.45% sodium chloride solution is 48 hours when stored at 25ºC.

C ASSESSMENT OF CLINICAL EFFICACY

Adults

The clinical efficacy of treosulfan in combination with fludarabine as part of conditioning treatment prior to alloHSCT in adult patients with AML and MDS was based primarily on one pivotal Phase III study, MC-FludT.14/L Trial II.

Study MC-FludT.14/L Trial II was a Phase III, randomised, parallel-group, open-label, multicentre, group-sequential, non-inferiority trial to evaluate the efficacy and safety of treosulfan-based conditioning versus a busulfan-based reduced-intensity conditioning (RIC) treatment prior to alloHSCT in patients with AML or MDS at increased risk of toxicity with standard conditioning regimens due to age ≥ 50 years at transplant and/or HSCT-Comorbidity Index (HCT-CI) score > 2. The use of busulfan-based RIC as the active comparator for patients considered ineligible for standard conditioning regimens was appropriate and in accordance with clinical practice guidelines.

Patients were randomised to receive treosulfan 10 g/m^2/day as a 2-hour intravenous (IV) infusion on 3 consecutive days (Day -4, -3 and -2) combined with fludarabine or busulfan 3.2 mg/kg/day (0.8 mg/kg every 6 hours) as a 2-hour IV infusion on Day -4 and -3 (total dose 6.4 mg/kg) combined with fludarabine, followed by allogeneic HSCT on Day 0. Both treatment groups used the same fludarabine dosing (30 mg/m^2/day as a 0.5-hour IV infusion on 5 consecutive days from Days -6 to -2). Randomisation was stratified by cytogenetic and/or molecular risk group for AML or Revised International Prognostic Scoring System (IPSS-R) for MDS, and by donor type and transplantation centre.

The primary efficacy endpoint was event-free survival (EFS) within 2 years after transplantation. Events were defined as relapse of disease, graft failure or death (whichever occurred first). The secondary efficacy endpoints were overall survival (OS), relapse/progression incidence, rates of primary graft failure and secondary graft failure, non-relapse mortality (NRM), transplantation-related mortality (TRM), engraftment, complete donor-type chimerism, graft-versus-host disease (GvHD)-free and relapse/progression-free survival (GRFS), and chronic GvHD-free and relapse/progression-free survival (CRFS).

The primary objective of the study was to demonstrate the non-inferiority of treosulfan to busulfan, with the pre-specified non-inferiority margin of 1.3 on the hazard ratio (HR) scale. If significant non-inferiority within the Per Protocol Set (PPS) could be shown, a sequential

testing was to be applied by testing the non-inferiority within the Full Analysis Set (FAS)[1], followed by superiority within the FAS with respect to the primary endpoint.

The study was planned as a group-sequential study with 3 interim analyses, using the O'Brien-Fleming α-spending function to ensure that the experiment-wise one-sided type-I-error of 2.5% did not exceed the pre-specified significance level α. The primary endpoint was met at the second pre-planned interim analysis, hence recruitment for the study was stopped. At this point, 476 of the total 570 randomised patients had been analysed. Of the 476 patients, 460 patients who qualified for the FAS constituted the confirmatory analysis of the study. The information fraction based on the number of events at the second interim analysis was 34.9%, corresponding to an alpha level of 0.000149 according to the O'Brien-Fleming α-spending function. A subsequent final analysis was conducted on 551 out of 570 randomised patients who qualified for the FAS. The final analysis was considered exploratory in nature.

The patient demographics were comparable across the groups. The mean (standard deviation [SD]) age of the total population in the FAS (N=551) was 59.6 (6.3) years (median 60 years; range 31 to 70 years). There were more male (60.8%) than female (39.2%) patients in the study. More than half (63.9%) of the patients had AML, and the remaining 36.1% of the patients had MDS. The AML and MDS disease characteristics were generally balanced across the groups.

At the second interim analysis (confirmatory analysis), treosulfan was demonstrated to be non-inferior to busulfan for the primary endpoint, EFS at 24 months in the PPS (63.5% vs 51.1%; HR 0.67, 99.9702% CI: 0.37, 1.23; adjusted p=0.0000424), as the upper limit of the confidence interval (CI) was below the protocol-defined non-inferiority margin of 1.3. Non-inferiority was also demonstrated in the FAS (64.0% vs 50.4%; HR 0.65, 99.9702% CI: 0.36, 1.19; adjusted p=0.0000164). The p-value for the test of superiority (0.0051268) did not meet the significance level (0.000149). The results from the final analysis were consistent with that observed in the second interim analysis. For the PPS, the HR was 0.64 (95% CI: 0.48, 0.84) in favour of the treosulfan treatment group. Comparable results were obtained for the FAS, where the HR was 0.64 (95% CI: 0.49, 0.84).

The results of the subgroup analyses of EFS by prognostic factors were generally consistent across subgroups by donor type, risk group, combination of donor type and risk group, disease (AML vs MDS), age group, HCT-CI score, remission status in AML and disease status in MDS, except for the subgroup of MRD risk group II (HR 1.18, 95% CI: 0.61, 2.26). Nonetheless, it was noted that the 95% CI was wide which could be attributed to the relatively small sample size of the subgroup (n ≤ 30 in each treatment group). For AML patients, EFS at 24 months was 64.7% in the treosulfan group and 53.3% in the busulfan group (HR 0.72, 95% CI: 0.52, 0.99). For MDS patients, EFS at 24 months was 68.1% in the treosulfan group and 48.2% in the busulfan group (HR 0.66, 95% CI: 0.42, 1.02).

The secondary endpoints analyses were considered exploratory in nature as there were no multiplicity adjustments for the secondary endpoints. In the FAS at the final analysis, OS at 24 months was observed to be higher in the treosulfan group compared to the busulfan group (72.7% vs 60.2%; HR 0.64, 95% CI: 0.48, 0.87; adjusted p=0.0037). The incidence of relapse/progression at 24 months was similar between treosulfan and busulfan groups (22.0% vs 25.2%; HR 0.82, 95% CI: 0.59, 1.16; adjusted p=0.2631). The proportions of patients with primary or secondary graft failure were lower in the treosulfan group compared to the busulfan

[1] The FAS included all randomised patients who were treated with at least one dose of study treatment and had at least one efficacy parameter documented after baseline.

group. There was 1 primary graft failure and no secondary graft failures in the treosulfan treatment group, while there was a total of 9 graft failures (1 primary, 8 secondary) in the busulfan treatment group.

The cumulative incidence of NRM (i.e., death without previous occurrence of a relapse or progression) at 24 months was lower in the treosulfan group compared to the busulfan group (12.0% vs 20.4%; HR 0.63, 95% CI: 0.41, 0.97; adjusted p=0.0343). The incidence of TRM at 24 months was also lower in the treosulfan group compared to the busulfan group (12.8% vs 24.1%, HR 0.52, 95% CI: 0.34, 0.82; adjusted p=0.0043). TRM with infections as cause of death was lower in the treosulfan treatment group than busulfan treatment group (HR 0.57, 95% CI: 0.34, 0.97; adjusted p=0.0371). This was also the case for causes of death other than infections (HR 0.42, 95% CI: 0.18, 0.97; adjusted p=0.0423).

Engraftment was assessed by reconstitution of granulopoiesis (i.e., first 3 consecutive days with absolute neutrophilic granulocyte count > 0.5 x 10^9/L in the peripheral blood), leukopoiesis (i.e., first 3 consecutive days with total white blood cell count > 1 x 10^9/L in the peripheral blood), and thrombopoiesis (i.e., first 3 consecutive days with platelet count > 20 x 10^9/L and > 50 x 10^9/L, in the absence of platelet transfusion). Reconstitution of granulopoiesis and leukopoiesis at 28 days after HSCT was similar in the treatment groups. In terms of reconstitution of thrombopoiesis > 50 x 10^9/L, the conditional cumulative incidence at 28 days after HSCT was lower in the treosulfan group compared to the busulfan group (89.4% vs 95.0%), but the maximal conditional cumulative incidence reached was similar between the groups (98.9% vs 98.8%, respectively). The median duration of neutropenia and leukopenia was longer in the treosulfan group than the busulfan group (neutropenia: 14.0 days vs 12.0 days, p<0.0001; leukopenia: 14.0 days vs 13.0 days, p=0.0007).

The incidence of complete donor-type chimerism was higher in the treosulfan treatment group compared to busulfan treatment group at both Day +28 visit (93.2% vs 83.3%; adjusted p=0.0159) and Day +100 visit (86.1% vs 80.2%; adjusted p=0.0381). GRFS at 24 months was higher in the treosulfan group compared to the busulfan group (50.3% vs 37.1%; HR 0.73, 95% CI: 0.57, 0.92; adjusted p=0.0087). CRFS at 24 months was also higher in the treosulfan group compared to the busulfan group (51.4% vs 37.2%; HR 0.70, 95% CI: 0.55, 0.88; adjusted p=0.0030).

Summary of Key Efficacy Results (Study MC-FludT.14/L Trial II)

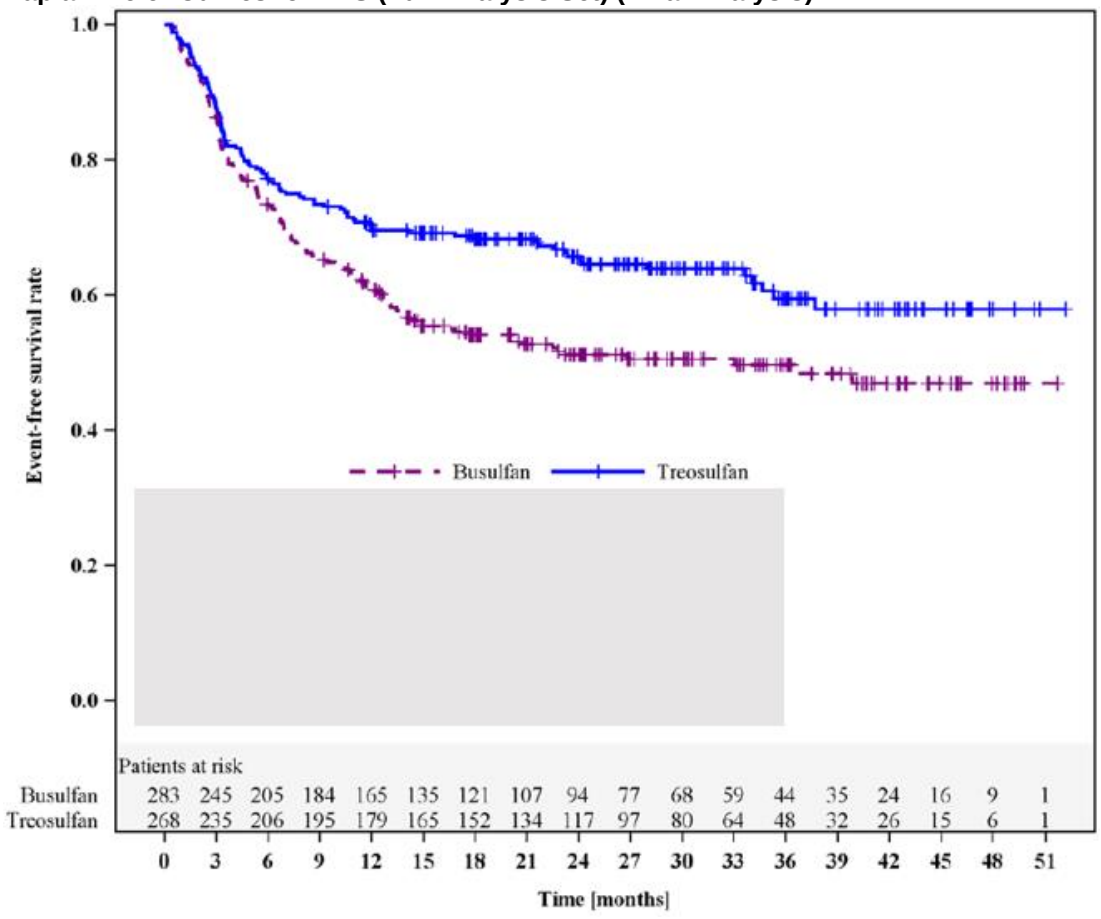
	Treosulfan	Busulfan
Primary efficacy endpoint		
Event-free survival, N (Per Protocol Set) (second interim analysis)	215	234
EFS events, n (%)	67 (31.2)	97 (41.5)
EFS at 24 months, % (95% CI)	63.5 (55.4, 70.5)	51.1 (43.4, 58.2)
HR[a] (99.9702% CI)	0.67 (0.37, 1.23)	
p-value[a] for testing non-inferiority of treosulfan compared to busulfan	0.0000424	
Event-free survival, N (Full Analysis Set) (second interim analysis)	220	240
EFS events, n (%)	68 (30.9)	100 (41.7)
EFS at 24 months, % (95% CI)	64.0 (56.0, 70.9)	50.4 (42.8, 57.5)
HR[a] (99.9702% CI)	0.65 (0.36, 1.19)	
p-value[a] for testing non-inferiority of treosulfan compared to busulfan	0.0000164	
p-value[a] for testing superiority of treosulfan compared to busulfan	0.0051268	
Event-free survival, N (Full Analysis Set) (final analysis)	268	283

EFS events, n (%)	97 (36.2)	137 (48.4)
EFS at 24 months, % (95% CI)	65.7 (59.5, 71.2)	51.2 (45.0, 57.0)
EFS at 36 months, % (95% CI)	59.5 (52.2, 66.1)	49.7 (43.3, 55.7)
HR[a] (95% CI)	0.64 (0.49, 0.84)	
Secondary efficacy endpoints (Full Analysis Set) (final analysis)		
Overall survival, N	268	283
OS events, n (%)	81 (30.2)	112 (39.6)
OS at 24 months, % (95% CI)	72.7 (66.8, 77.8)	60.2 (54.0, 65.8)
HR[a] (95% CI)	0.64 (0.48, 0.87)	
Adjusted p-value[a]	0.0037	
Relapse/progression incidence, N	268	283
Patients with event, n (%)	61 (22.8)	72 (25.4)
Cumulative incidence at 24 months, % (95% CI)	22.0 (16.9, 27.1)	25.2 (20.0, 30.3)
HR[b] (95% CI)	0.82 (0.59, 1.16)	
Adjusted p-value[b]	0.2631	
Graft failure, N	268	283
Primary graft failure, n (%)	1 (0.4)	1 (0.4)
Secondary graft failure, n (%)	0 (0)	8 (2.9)
Non-relapse mortality, N	268	283
Patients with event, n (%)	35 (13.1)	56 (19.8)
Cumulative incidence at 24 months, % (95% CI)	12.0 (8.0, 15.9)	20.4 (15.5, 25.2)
HR[b] (95% CI)	0.63 (0.41, 0.97)	
Adjusted p-value[b]	0.0343	
Transplantation-related mortality, N	268	283
Patients with event, n (%)	33 (12.3)	58 (20.5)
TRM at 24 months, % (95% CI)	12.8 (9.2, 17.7)	24.1 (19.1, 30.2)
HR[a] (95% CI)	0.52 (0.34, 0.82)	
Adjusted p-value[a]	0.0043	
Reconstitution of granulopoiesis, N	268	283
Conditional cumulative incidence at 28 days, % (95% CI)	96.2 (93.4, 99.1)	96.8 (94.6, 99.1)
Maximum conditional cumulative incidence reached, % (95% CI)	100.0 (99.1, 100.0)	100.0 (99.4, 100.0)
HR[b] (95% CI)	1.06 (0.91, 1.24)	
Adjusted p-value[b]	0.4235	
Reconstitution of leukopoiesis, N	268	283
Conditional cumulative incidence at 28 days, % (95% CI)	98.5 (96.1, 100.0)	97.2 (95.2, 99.1)
Maximum conditional cumulative incidence reached, % (95% CI)	100.0 (99.0, 100.0)	100.0 (99.3, 100.0)
HR[b] (95% CI)	1.10 (0.94, 1.27)	
Adjusted p-value[b]	0.2307	
Reconstitution of thrombopoiesis > 20 x 10^9/L, N	268	283
Conditional cumulative incidence at 28 days, % (95% CI)	94.7 (92.0, 97.4)	97.8 (96.3, 99.4)
Maximum conditional cumulative incidence reached, % (95% CI)	99.2 (97.6, 100.0)	99.6 (98.0, 100.0)
HR[b] (95% CI)	0.80 (0.68, 0.93)	
Adjusted p-value[b]	0.0038	
Reconstitution of thrombopoiesis > 50 x 10^9/L, N	268	283
Conditional cumulative incidence at 28 days, % (95% CI)	89.4 (85.3, 93.5)	95.0 (92.3, 97.7)
Maximum conditional cumulative incidence reached, % (95% CI)	98.9 (96.9, 100.0)	98.8 (97.1, 100.0)
HR[b] (95% CI)	0.79 (0.67, 0.92)	
Adjusted p-value[b]	0.0036	
Complete donor-type chimerism		

Patients at risk at Day +28 visit	263	282
Incidence of complete chimerism at Day +28 visit, % (95% CI)	93.2 (89.4, 95.9)	83.3 (78.5, 87.5)
Odds ratio (95% CI)[c]	2.81 (1.58, 5.01)	
Adjusted p-value[d]	0.0159	
Patients at risk at Day +100 visit	252	263
Incidence of complete chimerism at Day +100 visit, % (95% CI)	86.1 (81.2, 90.1)	80.2 (74.9, 84.9)
Odds ratio (95% CI)[c]	1.59 (0.99, 2.56)	
Adjusted p-value[d]	0.0381	
GvHD-free and relapse/progression-free survival, N	268	283
Patients with event, n (%)	130 (48.5)	169 (59.7)
GRFS at 24 months, % (95% CI)	50.3 (43.9, 56.3)	37.1 (31.1, 43.1)
HR[a] (95% CI)	0.73 (0.57, 0.92)	
Adjusted p-value[a]	0.0087	
Chronic GvHD-free and relapse/ progression-free survival, N	268	283
Patients with event, n (%)	128 (47.8)	168 (59.4)
CRFS at 24 months, % (95% CI)	51.4 (45.0, 57.4)	37.2 (31.3, 43.2)
HR[a] (95% CI)	0.70 (0.55, 0.88)	
Adjusted p-value[a]	0.0030	

[a] Adjusted for donor type as factor, and risk group and centre as strata using Cox regression model
[b] Adjusted for donor type as factor and risk group as stratum using Fine and Gray model
[c] Adjusted for donor type and risk group
[d] Stratified Cochran-Mantel-Haenszel test adjusted for donor type and risk group

Kaplan-Meier Curves for EFS (Full Analysis Set) (Final Analysis)



Overall, the efficacy of treosulfan-based conditioning regimen in adults was adequately demonstrated based on the pivotal study, which showed that treosulfan-based regimen was non-inferior in terms of EFS at 24 months compared to busulfan-based regimen prior to alloHSCT in adult patients with AML or MDS at increased risk of toxicity with standard conditioning regimens, and supported by the results of the secondary endpoints.

Paediatrics

The clinical efficacy in paediatric patients was based primarily on one pivotal Phase II study, MC-FludT.17/M, and supported by comparison of data with historical data and data from the adult Phase III study, MC-FludT.14/L. A meta-analysis of data from the European Society for Blood and Marrow Transplant (EBMT) registry on treosulfan-based conditioning in paediatric patients was also presented.

Study MC-FludT.17/M was a Phase II, multicentre, open-label, single-arm, non-controlled study to describe the safety and efficacy of treosulfan administered as part of a standardised fludarabine-containing conditioning regimen in paediatric patients from 28 days to < 18 years of age with haematological malignant diseases, including acute lymphoblastic leukaemia (ALL), AML, MDS and juvenile myelomonocytic leukaemia (JMML). The study investigated the body surface area (BSA)-adapted treosulfan doses of 10, 12, or 14 g/m^2 for patients with a BSA of ≤ 0.5 m^2, > 0.5 to 1 m^2, and > 1 m^2, respectively. Patients were administered treosulfan IV over 2 hours on 3 consecutive days (Days -6, -5 and -4), before allogeneic HSCT on Day 0. In addition, all patients received fludarabine 30 mg/m^2/day on Days -7 to -3. On investigator's discretion, for additional immunosuppression, patients could receive thiotepa IV in 2 single doses of 5 mg/kg on Day -2 (intensified regimen).

The primary endpoint was a safety endpoint which measured freedom from transplant (treatment)-related mortality, defined as death from any transplant-related cause from the day of first administration of study medication until day +100 after HSCT. The secondary efficacy endpoints included TRM, OS, incidence of relapse/progression, graft failures, NRM, engraftment, donor-type chimerism, EFS, GRFS and CRFS. The study was descriptive in nature and not intended to test any pre-specified hypotheses.

The study included a total of 70 patients. There were more male (62.9%) than female (37.1%) subjects, and all subjects were white. The mean (SD) age was 9.1 (5.8) years. There were 9 subjects (12.9%) who were aged 28 days to 23 months, 28 subjects (40.0%) aged 2 to 11 years and 33 subjects (47.1%) aged 12 to 17 years. Of the 70 subjects, 29 (41.4%) had been diagnosed with AML, 27 (38.6%) with ALL, 10 (14.3%) with MDS, and 4 (5.7%) with JMML. Most of the subjects (54.3%) received the 14 g/m^2/day dose, 37.1% received the 12 g/m^2/day dose, and 8.6% received the 10 g/m^2/day dose. The majority of subjects (92.9%) received an intensified treatment with thiotepa.

The rate of freedom from transplant (treatment)-related mortality until 100 days after HSCT was 98.6% (90% CI: 93.4, 99.9). There was 1 event of transplant (treatment)-related death until day +100 after HSCT.

No subject experienced a primary graft failure, and only 1 subject (1.4%) experienced a secondary graft failure. Conditional cumulative incidences of reconstitution of granulopoiesis and leukopoiesis at 28 days after HSCT was 86.9% (90% CI: 79.8, 93.9) and 95.6% (90% CI: 90.9, 100.0), respectively, with maximal conditional cumulative incidence of 100%. Conditional cumulative incidences of reconstitution of thrombopoiesis of > 20 x 10^9/L and > 50 x 10^9/L at

28 days after HSCT was 78.0% (90% CI: 69.5, 86.5) and 62.2% (90% CI: 52.5, 71.9), respectively, with maximal conditional cumulative incidence of > 90%. The maximum cumulative incidence of engraftment of 100.0% (90% CI: 100.0, 100.0) was consistent with that reported for treosulfan- or busulfan-based conditioning regimens in historical trials (89% to 100%) and the adult studies (95.7% to 99.3%). The incidence of complete donor-type chimerism was 94.2% (90% CI: 87.2, 98.0) at Day +28 visit, 91.3% (90% CI: 83.6, 96.1) at Day +100 visit and 91.2% (90% CI: 82.4, 96.5) at Month 12 visit.

OS rate at 12 months was 91.4% (90% CI: 83.9, 95.5). It was above the range reported for treosulfan- or busulfan-based conditioning regimens in the literature (78% to 88%) and the adult studies (72% to 78%).

The results were supported by the other secondary efficacy endpoints, including EFS, incidence of relapse/progression, NRM, TRM, GRFS and CRFS, which generally demonstrated more favourable outcomes compared to the adult study MC-FludT.14/L Trial II.

Summary of Key Efficacy Results (Study MC-FludT.17/M)

	Treosulfan (N=70)
Primary endpoint	
Freedom from transplant (treatment)-related mortality	
Freedom from transplant (treatment)-related mortality until 100 days, % (90% CI)	98.6 (93.4, 99.9)
Secondary efficacy endpoints	
Transplant-related mortality	
Patients with event, n (%)	4 (5.7)
TRM at 100 days, % (90% CI)	1.4 (0.3, 7.2)
TRM at 12 months, % (90% CI)	1.4 (0.3, 7.2)
TRM at 24 months, % (90% CI)	4.6 (1.8, 11.4)
TRM at 36 months, % (90% CI)	4.6 (1.8, 11.4)
Overall survival	
Patients with event, n (%)	12 (17.1)
OS at 12 months, % (90% CI)	91.4 (83.9, 95.5)
OS at 24 months, % (90% CI)	85.7 (77.1, 91.2)
OS at 36 months, % (90% CI)	84.3 (75.5, 90.1)
Incidence of relapse/progression	
Patients with event, n (%)	16 (22.9)
Cumulative incidence of relapse/progression at 12 months, % (90% CI)	15.7 (8.6, 22.9)
Cumulative incidence of relapse/progression at 24 months, % (90% CI)	23.0 (14.7, 31.3)
Cumulative incidence of relapse/progression at 36 months, % (90% CI)	23.0 (14.7, 31.3)
Relapse-free/progression-free survival	
Patients with event, n (%)	19 (27.1)
Relapse-free/progression-free survival at 12 months, % (90% CI)	82.9 (73.9, 89.0)
Relapse-free/progression-free survival at 24 months, % (90% CI)	72.7 (62.7, 80.4)
Relapse-free/progression-free survival at 36 months, % (90% CI)	72.7 (62.7, 80.4)
Graft failures	
Primary graft failure, n (%)	0/70 (0.0)
Secondary graft failure, n (%)	1/69 (1.4)
Non-relapse mortality	
Patients with event, n (%)	2 (2.9)
Cumulative incidence of NRM at 12 months, % (90% CI)	1.4 (0.0, 3.8)
Cumulative incidence of NRM at 24 months, % (90% CI)	2.9 (0.0, 6.1)
Cumulative incidence of NRM at 36 months, % (90% CI)	2.9 (0.0, 6.1)
Reconstitution of granulopoiesis	
Conditional cumulative incidence at 28 days, % (90% CI)	86.9 (79.8, 93.9)
Maximum conditional cumulative incidence reached, % (90% CI)	100.0 (97.7, 100.0)
Reconstitution of leukopoiesis	
Conditional cumulative incidence at 28 days, % (90% CI)	95.6 (90.9, 100.0)

Maximum conditional cumulative incidence reached, % (90% CI)	100.0 (97.7, 100.0)
Reconstitution of thrombopoiesis of > 20 x 10^9/L	
Conditional cumulative incidence at 28 days, % (90% CI)	78.0 (69.5, 86.5)
Maximum conditional cumulative incidence reached, % (90% CI)	94.1 (88.4, 99.9)
Reconstitution of thrombopoiesis of > 50 x 10^9/L	
Conditional cumulative incidence at 28 days, % (90% CI)	62.2 (52.5, 71.9)
Maximum conditional cumulative incidence reached, % (90% CI)	91.9 (84.9, 98.8)
Incidence of complete donor-type chimerism	
Incidence of complete chimerism at Day +28 visit, % (90% CI)	94.2 (87.2, 98.0)
Incidence of complete chimerism at Day +100 visit, % (90% CI)	91.3 (83.6, 96.1)
Incidence of complete chimerism at Month 12 visit, % (90% CI)	91.2 (82.4, 96.5)
Event-free survival	
Patients with event, n (%)	19 (27.1)
EFS at 12 months, % (90% CI)	81.4 (72.3, 87.8)
EFS at 24 months, % (90% CI)	72.7 (62.8, 80.4)
EFS at 36 months, % (90% CI)	72.7 (62.8, 80.4)
GvHD-free and relapse/progression-free survival	
Patients with event, n (%)	31 (44.3)
GRFS at 12 months, % (90% CI)	65.7 (55.5, 74.1)
GRFS at 24 months, % (90% CI)	55.5 (45.2, 64.6)
GRFS at 36 months, % (90% CI)	55.5 (45.2, 64.6)
Chronic GvHD-free and relapse/progression-free survival	
Patients with event, n (%)	30 (42.9)
CRFS at 12 months, % (90% CI)	67.1 (57.0, 75.4)
CRFS at 24 months, % (90% CI)	56.9 (46.6, 66.0)
CRFS at 36 months, % (90% CI)	56.9 (46.6, 66.0)
Use of rescue therapies	
Any rescue therapies, n (%)	11 (15.7)

Supportive data was available from a meta-analysis from the EBMT registry. The meta-analysis included a total of 165 paediatric patients who received alloHSCT for a malignant disease indication, including ALL (n=71), AML (n=57), other leukaemia/lymphoma (n=25) and other solid tumours (n=12). Treosulfan-based conditioning treatment prior to alloHSCT resulted in high engraftment rate (96%), irrespective of the underlying malignancy (range: 92% to 100%). The EFS and OS rates were consistently lower in patients with solid tumours compared to those with haematological malignancies (3-year OS rate: 13% vs 46-68%; 3-year EFS rate: 17% vs 39-56%). Nevertheless, considering that the engraftment rate was compelling (92%) despite the small sample size, and in the context of the indication sought for conditioning treatment, the data was supportive of the efficacy of treosulfan-based conditioning regimen.

Overall, taking into consideration the clinically meaningful efficacy results in the pivotal study, supportive evidence from the EBMT registry analyses and subgroup analyses results, the data was considered adequate and supported the efficacy of treosulfan-conditioning regimen in paediatric patients with malignant diseases. The limited availability of data for patients with solid tumours has been highlighted in the package insert.

D ASSESSMENT OF CLINICAL SAFETY

Adults

The clinical safety of treosulfan in adult patients was evaluated based on safety data from the pivotal study MC-FludT.14/L Trial II, which included 270 patients who received treosulfan-

based regimen and 283 patients who received busulfan-based regimen in the Safety Analysis Set.

Overview of Safety Profile (Study MC-FludT.14/L Trial II)

	Treosulfan (N=270)	Busulfan (N=283)
Any TEAE	250 (92.6%)	272 (96.1%)
Grade ≥3 TEAE	148 (54.8%)	151 (53.4%)
Drug-related TEAE	170 (63.0%)	192 (67.8%)
SAE	23 (8.5%)	20 (7.1%)
Drug-related SAE	9 (3.3%)	9 (3.2%)
Discontinuation of study drug due to AE	0	0
Deaths	72 (26.7%)	107 (37.8%)
Transplantation-related deaths	33 (12.2%)	58 (20.5%)
Death due to relapse/progression	34 (12.6%)	47 (16.6%)
Secondary malignancy	1 (0.4%)	1 (0.4%)
Unknown/other	4 (1.5%)	1 (0.4%)

Treatment-emergent adverse events (TEAEs) were reported by 92.6% of patients in the treosulfan group and 96.1% of patients in the busulfan group. The most frequently reported TEAEs (>10% in either group) included oral mucositis (37.8% in treosulfan group vs 47.7% in busulfan group), nausea (33.0% vs 41.0%), fever (34.4% vs 35.7%), vomiting (21.9% vs 19.4%), limb oedema (22.6% vs 13.4%), hypertension (14.1% vs 21.2%), headache (16.3% vs 18.4%), diarrhoea (15.9% vs 18.4%), back pain (14.8% vs 13.1%), febrile neutropenia (14.8% vs 11.0%), fatigue (12.2% vs 12.4%), constipation (12.2% vs 11.7%), bone pain (13.7% vs 9.9%), abdominal pain (10.7% vs 9.9%), maculopapular rash (11.9% vs 8.8%), gamma-glutamyl transferase (GGT) increased (7.4% vs 12.0%) and arthralgia (10.0% vs 3.5%). There were higher incidences of TEAEs (>5% difference) reported in the treosulfan group compared to the busulfan group for limb oedema and arthralgia, while higher incidences of TEAEs were reported in the busulfan group compared to the treosulfan group for oral mucositis, nausea and hypertension.

Grade ≥3 TEAEs were reported in a similar proportion of patients in the treosulfan and busulfan groups (54.8% vs 53.4%). However, infections/infestations were reported with higher incidence (>5% difference) in the busulfan group compared to the treosulfan group (15.2% vs 9.2%).

Drug-related TEAEs were reported by 63.0% of patients in the treosulfan group and 67.8% of patients in the busulfan group. Higher incidences of drug-related TEAEs (>5% difference) were reported in the busulfan group compared to the treosulfan group for oral mucositis (38.2% vs 32.2%), nausea (29.0% vs 21.5%), diarrhoea (11.0% vs 5.9%), fever (11.7% vs 4.8%) and GGT increased (10.2% vs 5.2%). There were no drug-related TEAEs reported with higher incidence (>5% difference) in the treosulfan group compared to the busulfan group.

Serious adverse events (SAEs) were reported by 8.5% of patients in the treosulfan group and 7.1% of patients in the busulfan group. The most common SAEs were sepsis (3.0% in treosulfan group vs 1.8% in busulfan group) and lung infection (2.2% vs 1.1%). Drug-related SAEs were reported by similar proportion of patients in the treosulfan group and busulfan group (3.3% vs 3.2%). The most common drug-related SAEs reported with treosulfan and busulfan were sepsis (1.9% vs 0.4%, respectively) and lung infection (0.7% vs 0.7%, respectively). No patients discontinued study drugs due to AEs.

Deaths until Month 24 occurred in a lower proportion of patients in the treosulfan group than in the busulfan group (26.7% vs 37.8%). Both transplantation-related deaths and deaths due to relapse/progression occurred at lower incidences in the treosulfan group compared to the

busulfan group (12.2% vs 20.5% and 12.6% vs 16.6%, respectively). The most common causes of transplantation-related deaths in the treosulfan and busulfan groups were infections (9.3% vs 14.1%) followed by GvHD (4.8% vs 7.4%).

The incidences of adverse events of special interest (AESIs) were generally similar between the treosulfan and busulfan groups: grade III/IV mucositis (5.9% vs 7.4%), grade III/IV hepatic sinusoidal obstruction syndrome (HSOS) (n=0 vs n=1), grade III/IV seizure (n=1 vs n=0) and grade III/IV blood bilirubin increased (3.3% vs 2.8%).

In terms of GvHD, the incidences of acute GvHD (52.6% vs 57.2%), grade III-IV acute GvHD (6.3% vs 8.1%), chronic GvHD (60.3% vs 59.5%) and extensive chronic GvHD (19.7% vs 26.7%) were similar or numerically lower in the treosulfan group compared to the busulfan group.

Overall, the safety profile of treosulfan in adult patients was considered acceptable in the context of AML and MDS patients who require conditioning treatment prior to alloHSCT but are not suitable for standard conditioning therapies due to increased risk of toxicity. The package insert has included appropriate warnings and precautions to address the identified safety risks.

Paediatrics

The safety data of treosulfan in paediatric patients were derived from 2 clinical studies, MC-FludT.17/M and MC-FludT.16/NM[2], comprising a total of 88 paediatric patients. Supportive safety data was also available from the EBMT registry study which included 626 paediatric patients.

Overview of Safety Profile (Studies MC-FludT.17/M and MC-FludT.16/NM)*

	MC-FludT.17/M (N=70)	MC-FludT.16/NM (N=18)	Total (N=88)
Any TEAE	67 (95.7%)	16 (88.9%)	83 (94.3%)
Grade ≥3 TEAE	52 (74.3%)	13 (72.2%)	65 (73.9%)
Drug-related TEAE	59 (84.3%)	14 (77.8%)	73 (83.0%)
SAE	22 (31.4%)	4 (22.2%)	26 (29.5%)
Drug-related SAE	1 (1.4%)	0	1 (1.1%)
Discontinuation of study drug due to AE	0	0	0
Deaths	6 (8.6%)	1 (5.6%)	7 (8.0%)
Deaths due to relapse/progression	4 (5.7%)	0	4 (4.5%)
Transplantation-related deaths	2 (2.9%)	1 (5.6%)	3 (3.4%)

* Based on data until the interim database lock on 16 May 2017

TEAEs were reported by 94.3% of the patients in both clinical studies. The most common TEAEs (>10%) included stomatitis (78.4%), pyrexia (71.6%), vomiting (68.2%), diarrhoea (63.6%), nausea (45.5%), hypertension (35.2%), abdominal pain (34.1%), headache (29.5%), maculopapular rash (29.5%), pruritus (23.9%), cough (18.2%), pain in extremity (18.2%), viraemia (15.9%), cytomegalovirus infection (13.6%), sinus tachycardia (12.5%), hypersensitivity (12.5%), constipation (12.5%), pain of skin (11.4%), haematoma (10.2%), ALT increased (10.2%), device-related infection (10.2%) and infusion-related reaction (10.2%).

[2] A Phase II study comparing treosulfan-based conditioning therapy with busulfan-based conditioning prior to allogenic HSCT in paediatric patients with non-malignant disease.

Grade ≥3 TEAEs were reported by 73.9% of the patients. The most common Grade ≥3 TEAEs (>10%) included stomatitis (38.6%), nausea (15.9%), diarrhoea (14.8%), vomiting (13.6%) and hypertension (12.5%).

Drug-related TEAEs were reported by 83.0% of the patients. The most common drug-related TEAEs (>10%) included stomatitis (69.3%), vomiting (43.2%), diarrhoea (33.0%), nausea (30.7%), abdominal pain (15.9%), pyrexia (14.8%) and pruritus (11.4%).

The proportion of patients with SAEs was 29.5%. The most common SAEs occurred in the System Organ Class (SOC) of infections and infestation (19.3%), followed by general disorders and administration site conditions (6.8%), all due to pyrexia. No patients discontinued study drugs due to AEs.

In Study MC-FludT.17/M, 6 deaths were reported – 4 due to relapse/progression and 2 due to transplantation-related causes. In Study MC-FludT.16/NM, 1 transplant-related death was reported.

With regard to AESIs, grade III/IV mucositis was reported in 38.6% of patients. Grade II HSOS occurred in 2 patients (2.3%), and grade III/IV blood bilirubin increased occurred in 4 patients (4.5%). Acute GvHD grade I-IV was reported by 44.3% of patients and acute GvHD grade III-IV by 11.4% of patients. There was no report of cases of grade III/IV seizures.

The incidences of several TEAEs were noted to be higher in the paediatric patients compared to the adult patients, including infection AEs (59.1% vs 27.0%), gastrointestinal AEs such as stomatitis/mucositis (78.4% vs 37.8%), vomiting (68.2% vs 21.9%), diarrhoea (63.6% vs 15.9%) and abdominal pain (34.1% vs 10.7%), as well as skin-related AEs such as maculopapular rash (29.5% vs 11.9%) and pruritus (23.9% vs 5.9%). The observed increased toxicities might be contributed by the additive toxicity of thiotepa resulting from the intensified conditioning regimen. Although higher frequencies of some adverse events (AEs) were observed in the paediatric population compared to the adult population, none of the events led premature discontinuation of study or dose reduction. In addition, the higher frequencies of AEs did not lead to an increased NRM or TRM in paediatric as compared to adults (NRM at 24 months: 2.9% vs 12.0%; TRM at 24 months: 4.6% vs 12.8%).

Dose-related increase in TEAEs were also observed for gastrointestinal AEs, skin-related AEs, as well as infections. These AEs are generally manageable in clinical practice, with the use of mucositis prophylaxis as well as prophylactic or empiric anti-infective treatment.

Longer-term safety follow-up from Study MC-FludT.17/M up to 3 years after HSCT showed generally consistent results with those observed in the interim analysis. The safety profile observed in the EMBT registry was also consistent with the findings from the clinical studies.

Overall, the safety profile of treosulfan in paediatric patients was considered acceptable for the intended population given the severity of the indication, i.e., patients with malignant diseases who require conditioning treatment prior to alloHSCT. The warnings and precautions included in the package insert are considered adequate.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Patients receiving alloHSCT are required to undergo conditioning regimen in order to reduce the tumour burden, eliminate the self-renewing capacity of the patient's own haematopoiesis, and suppress the recipient's immune system to allow engraftment of stem cells. Availability of conditioning regimens with improved toxicities profiles without increasing the risk for relapse would provide additional options for better management of the safety of alloHSCT.

In adult patients with AML or MDS at increased risk of toxicity with standard conditioning regimens, treosulfan-based regimens had been demonstrated to be non-inferior to busulfan-based regimens for the primary endpoint, EFS at 24 months in the PPS (63.5% vs 51.1%; HR 0.67, 99.9702% CI: 0.37, 1.23; adjusted p=0.0000424) in the pivotal study, MC-FludT.14/L Trial II. The results of the secondary efficacy endpoints, including OS, relapse/progression incidence, primary and secondary graft failure rates, NRM, TRM, engraftment, complete donor-type chimerism, GRFS and CRFS generally demonstrated comparable or better results in the treosulfan group compared to the busulfan group.

In paediatric patients with malignant diseases, the overall data based on the pivotal study, MC-FludT.17/M, which showed a high rate of freedom from transplant (treatment)-related mortality until 100 days after HSCT at 98.6% (90% CI: 93.4, 99.9), with no primary graft failure, and only 1 subject (1.4%) experienced a secondary graft failure provided favourable evidence on safety. Furthermore, the incidence of complete donor-type chimerism was high across different time points, ranging from 91.2% to 94.2% between Day +28 and Month 12. The maximum cumulative incidence of engraftment was 100.0% (90% CI: 100.0, 100.0), which was comparable to the historical data for treosulfan- or busulfan-based regimens (89% to 100%) and the adult studies (95.7% to 99.3%). The OS rate at 12 months was 91.4% (90% CI: 83.9, 95.5), which was higher than that reported for treosulfan- or busulfan-based regimens in the literature (78% to 88%) and adult studies (68.0% to 75.3%). Consistent results were observed with the other secondary efficacy endpoints, including EFS, incidence of relapse/progression, NRM, TRM, GRFS and CRFS. These results also corroborated with the EBMT registry study, which demonstrated a high engraftment rate across various underlying malignancies (92% to 100%). Although patients with solid tumours showed lower EFS and OS rates than those with haematological malignancies (3-year OS rate: 13% vs 46-68%; 3-year EFS rate: 17% vs 39-56%), a comparable engraftment rate of 92% was observed in this subgroup. In the context of the indication sought for conditioning treatment, the data supported the efficacy of treosulfan-based conditioning regimen in paediatric patients with malignant diseases.

The safety profile of treosulfan was considered acceptable for the intended population given the severity of the indication. The most notable safety concerns with treosulfan were infections and gastrointestinal disorders including nausea, stomatitis, vomiting and diarrhoea. These toxicities have been highlighted in the package insert.

Overall, the benefits of treosulfan in combination with fludarabine outweighed the risks when used as part of conditioning treatment prior to alloHSCT in adult patients with AML or MDS at increased risk of toxicity with standard conditioning therapies, and in paediatric patients older than one month with malignant diseases.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Trecondi in combination with fludarabine as part of conditioning treatment prior to alloHSCT in adult patients with AML or MDS at increased risk of toxicity with standard conditioning therapies,

and in paediatric patients older than one month with malignant diseases, was deemed favourable and approval of the product registration was granted on 26 December 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trecondi 1 g powder for solution for infusion
Trecondi 5 g powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trecondi 1 g powder for solution for infusion
One vial contains 1 g of treosulfan.

Trecondi 5 g powder for solution for infusion
One vial contains 5 g of treosulfan.

When reconstituted according to section 6.6, 1 mL of the solution for infusion contains 50 mg treosulfan.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) at increased risk of toxicity with standard conditioning therapies, and in paediatric patients older than one month with malignant diseases.

4.2 Posology and method of administration

Administration of treosulfan should be supervised by a physician experienced in conditioning treatment followed by alloHSCT.

Posology

Adults with AML and MDS

Treosulfan is given in combination with fludarabine.
The recommended dose and schedule of administration is:

- Treosulfan 10 g/m² 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/m²;
- Fludarabine 30 mg/m² 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/m²;
- Treosulfan should be administered before fludarabine on days -4, -3, -2 (FT_{10} regimen).

Elderly

No dose adjustment is necessary in any subset of the elderly population.

Renal and hepatic impairment

No dose adjustment is necessary for mild or moderate impairment, but treosulfan is contraindicated in patients with severe impairment (see section 4.3).

Paediatric population

Treosulfan is given in combination with fludarabine, with thiotepa (intensified regimen; $FT_{10-14}TT$ regimen) or without thiotepa (FT_{10-14} regimen).
The recommended dose and schedule of administration is:

- Treosulfan 10-14 g/m² body surface area (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 30-42 g/m²;
  The dose of treosulfan should be adapted to the patient's BSA as follows (see section 5.2):

Body surface area (m²)	**Treosulfan dose (g/m²)**
≤ 0.5	10.0
> 0.5 – 1.0	12.0
> 1.0	14.0

- Fludarabine 30 mg/m² 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/m²;
- Treosulfan should be administered before fludarabine;
- Thiotepa (intensified regimen 5 mg/kg twice a day), given as two intravenous infusions over 2–4 hours on day -2 before stem cell infusion (day 0).

The safety and efficacy of treosulfan in children less than 1 month of age has not yet been established.

Method of administration

Treosulfan is for intravenous use as a two-hour infusion.

Precautions to be taken before handling or administering the medicinal product

When handling treosulfan, inhalation, skin contact or contact with mucous membranes should be avoided. Pregnant personnel should be excluded from handling cytotoxics.

Intravenous administration should be performed using a safe technique to avoid extravasation (see section 4.4).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance
- Active non-controlled infectious disease
- Severe concomitant cardiac, lung, liver, and renal impairment

- Fanconi anaemia and other DNA breakage repair disorders
- Pregnancy (see section 4.6)
- Administration of live vaccine

4.4 Special warnings and precautions for use

Myelosuppression

Profound myelosuppression with pancytopenia is the desired therapeutic effect of treosulfan-based conditioning treatment, occurring in all patients. It is therefore recommended to monitor blood cell counts frequently until recovery of the haematopoietic system.
During phases of severe neutropenia (median duration of neutropenic period is 14-17.5 days in adults and 21-24 days in paediatric patients) the risk of infection is increased. Prophylactic or empiric anti-infective treatment (bacterial, viral, fungal) should therefore be considered. Growth factors (G-CSF, GM-CSF), platelet and/or red blood cell support should be given as indicated.

Secondary malignancies

Secondary malignancies are well-established complications in long-term survivors after alloHSCT. How much treosulfan contributes to their occurrence is unknown. The possible risk of a second malignancy should be explained to the patient. On the basis of human data, treosulfan has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen.

Mucositis

Oral mucositis (including high-grade severity) is a very common undesirable effect of treosulfan-based conditioning followed by alloHSCT (see section 4.8). Use of mucositis prophylaxis (e.g. topical antimicrobials, barrier protectants, ice and adequate oral hygiene) is recommended.

Vaccines

Concomitant use of live attenuated vaccines is not recommended.

Fertility

Treosulfan can impair fertility. Therefore, men treated with treosulfan are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with treosulfan.
Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients (see section 4.6).

Paediatric population

Seizures

There have been isolated reports of seizures in infants (≤ 4 months of age) with primary immunodeficiencies after conditioning treatment with treosulfan in combination with fludarabine or cyclophosphamide. Therefore, infants ≤ 4 months of age should be monitored for signs of neurological adverse reactions.

Respiratory, thoracic and mediastinal disorders

There was a significant association between age and respiratory toxicity in paediatric patients treated with treosulfan-based conditioning.

Children younger than one year (mainly non-malignant diseases, especially immunodeficiencies) experienced more respiratory grade III/IV toxicity, possibly due to pulmonary infections already existing before the start of conditioning treatment.

Dermatitis diaper

Dermatitis diaper may occur in small children because of excretion of treosulfan in the urine. Therefore, nappies should be changed frequently up to 6–8 hours after each infusion of treosulfan.

Extravasation

Treosulfan is considered an irritant. Intravenous application should be performed using a safe technique. If extravasation is suspected, general safety measures should be implemented. No specific measure has been proven to be recommendable.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction of treosulfan was observed in high-dose chemotherapy.

Detailed *in vitro* studies did not completely exclude potential interactions between high plasma concentrations of treosulfan and CYP3A4, CYP2C19, or P-gp substrates. Therefore, medicinal products with a narrow therapeutic index (e.g. digoxin) that are substrates for CYP3A4, CYP2C19 or P-gp should not be given during treatment with treosulfan.

The effect of treosulfan on the pharmacokinetics of fludarabine is not known.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Both sexually active men and women of childbearing potential have to use effective contraception during and up to 6 months after treatment.

Pregnancy

There are no data from the use of treosulfan in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Treosulfan is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether treosulfan is excreted in human milk. Breast-feeding should be discontinued during treatment with treosulfan.

Fertility

Treosulfan might impair fertility in men and women. Men should seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility.

As known for other alkylating conditioning agents treosulfan can cause ovarian suppression and amenorrhoea with menopausal symptoms in pre-menopausal women.

4.7 Effects on ability to drive and use machines

Treosulfan has moderate influence on the ability to drive and use machines. It is likely that certain adverse reactions of treosulfan like nausea, vomiting or dizziness could affect these functions.

4.8 Undesirable effects

Summary of the safety profile

Profound myelosuppression/pancytopenia is the desired therapeutic effect of conditioning therapy and occurs in all patients. Blood cell counts usually recover after HSCT.

The most commonly observed adverse reactions (adults/paediatric patients) after treosulfan-based conditioning followed by alloHSCT include infections (13.1% /11.4%), gastrointestinal disorders (nausea [39.5%/30.7%], stomatitis [36.0%/69.3%], vomiting [22.5%/43.2%], diarrhoea [15.6%/33.0%], abdominal pain [10.4%/17%]), fatigue (15.1%/2.3%), febrile neutropenia (11.3%/1.1%), oedema (7.8%/0%), rash (7.2%/12.5%), and increases of alanine transaminase (ALT [5.1%/9.1%]), aspartate transaminase (AST [4.4%/8.0%]), gamma-glutamyl transferase (γGT [3.7%/2.3%]), and bilirubin (18.8%/5.7%).

Adults

Tabulated list of adverse reactions

The frequencies of adverse reactions reported in the table below are derived from 5 clinical trials (including a total of 564 patients) where treosulfan combined with fludarabine was investigated as conditioning treatment prior to alloHSCT in adult patients. Treosulfan was administered in a dose range of 10-14 g/m² BSA on 3 consecutive days.

Adverse reactions are listed below, by system organ class and by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Infections and infestations*	**Very common** Infections (bacterial, viral, fungal) **Common** Sepsis[a] **Not known** Septic shock[c]	**Common** Infections (bacterial, viral, fungal), sepsis[a] **Not known** Septic shock[c]
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	**Not known** Treatment-related second malignancy	**Not known** Treatment-related second malignancy
Blood and lymphatic system disorders*	**Very common** Myelosuppression, pancytopenia, febrile neutropenia	**Very common** Myelosuppression, pancytopenia, febrile neutropenia
Immune system disorders*	**Common** Hypersensitivity	

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Metabolism and nutrition disorders	**Common** Decreased appetite **Uncommon** Hyperglycaemia **Not known** Acidosis[b], glucose tolerance impaired, electrolyte imbalance	**Common** Decreased appetite **Uncommon** Hyperglycaemia **Not known** Acidosis[b], glucose tolerance impaired, electrolyte imbalance
Psychiatric disorders	**Common** Insomnia **Uncommon** Confusional state **Not known** Agitation	**Rare** Confusional state
Nervous system disorders	**Common** Headache, dizziness **Uncommon** Peripheral sensory neuropathy **Not known** Encephalopathy, intracranial haemorrhage, extrapyramidal disorder, syncope, paraesthesia	**Rare** Headache, peripheral sensory neuropathy **Not known** Encephalopathy, intracranial haemorrhage, syncope
Eye disorders	**Not known** Dry eye	
Cardiac disorders*	**Common** Cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia) **Not known** Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion	**Uncommon** Cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia) **Not known** Cardiac arrest, myocardial infarction
Vascular disorders	**Common** Hypertension, flushing **Uncommon** Haematoma, hypotension **Not known** Embolism, haemorrhage	**Uncommon** Hypertension **Not known** Embolism, haemorrhage

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Respiratory, thoracic and mediastinal disorders	**Common** Dyspnoea, epistaxis **Uncommon** Pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, cough, laryngeal pain, hiccups **Not known** Oropharyngeal pain, hypoxia, dysphonia	**Uncommon** Dyspnoea, pleural effusion, pharyngeal or laryngeal inflammation **Rare** Epistaxis, pneumonitis **Not known** Hypoxia
Gastrointestinal disorders*	**Very common** Stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain **Common** Oral pain, gastritis, dyspepsia, constipation, dysphagia **Uncommon** Mouth haemorrhage, abdominal distension, oesophageal or gastrointestinal pain, dry mouth **Not known** Gastrointestinal haemorrhage, neutropenic colitis, oesophagitis, anal inflammation, mouth ulceration	**Common** Stomatitis/mucositis, diarrhoea, nausea, abdominal pain **Uncommon** Vomiting, oral pain, dysphagia, mouth haemorrhage, oesophageal or gastrointestinal pain **Not known** Gastrointestinal haemorrhage, neutropenic colitis
Hepatobiliary disorders*	**Uncommon** Veno-occlusive liver disease, hepatotoxicity **Not known** Hepatic failure, hepatomegaly, hepatic pain	**Rare** Veno-occlusive liver disease, hepatotoxicity **Not known** Hepatic failure
Skin and subcutaneous tissue disorders	**Common** Maculo-papular rash, purpura, erythema, palmar-plantar erythrodysaesthesia syndrome, pruritus, alopecia **Uncommon** Erythema multiforme, dermatitis acneiform, rash, hyperhidrosis **Not known** Generalised erythema, dermatitis, skin necrosis or ulcer, skin hyperpigmentation[d], dry skin	**Uncommon** Maculo-papular rash, purpura, erythema **Not known** Skin necrosis

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Musculoskeletal and connective tissue disorders	**Common** Pain in extremities, back pain, bone pain, arthralgia, myalgia **Not known** Muscular weakness	**Rare** Pain in extremities, bone pain
Renal and urinary disorders	**Common** Acute kidney injury, haematuria **Not known** Renal failure, cystitis[c], dysuria	**Uncommon** Acute kidney injury, haematuria
General disorders and administration site conditions	**Very common** Asthenic conditions (fatigue, asthenia, lethargy) **Common** Oedema, pyrexia[e], chills **Uncommon** Non-cardiac chest pain, pain **Not known** Injection site reaction, feeling cold	**Common** Fatigue **Rare** Non-cardiac chest pain, oedema pyrexia[e]
Investigations	**Very common** Bilirubin increased **Common** Transaminases (ALT/AST) increased, γGT increased, blood alkaline phosphatase increased, C-reactive protein increased, weight decreased, weight increased **Not known** Blood creatinine increased, blood lactate dehydrogenase (LDH) increased	**Common** Bilirubin increased, transaminases (ALT/AST) increased, γGT increased **Uncommon** Blood alkaline phosphatase increased, C-reactive protein increased **Not known** Blood LDH increased

* See detailed sections below

[a] Clinically or microbiologically documented infection with grade 3 or 4 neutropenia (absolute neutrophil count [ANC] < 1.0 x 10^9/L) and sepsis

[b] Acidosis might be a consequence of the release of methanesulfonic acid through treosulfan activation/cleavage in the plasma

[c] Case reports (> 2) after treosulfan-based conditioning obtained from other sources

[d] Bronze pigmentation

[e] Fever in the absence of neutropenia where neutropenia is defined as ANC < 1.0 x 10^9/L

Description of selected adverse reactions

Infections

The overall incidence of infections was 13.1% (74/564). The most frequent type was lung infection (12/74 [16.2%]). Pathogens included bacteria (e.g. *Staphylococcus*, *Enterococcus*, *Corynebacterium*), viruses (e.g. cytomegalovirus [CMV], Epstein-Barr virus [EBV], herpes) as well as fungi (e.g. candida). The infection rate was lowest in patients treated with the dose regimen of 10 g/m² of treosulfan per day, from day -4 to -2 (7.7%).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

One of 564 adult patients (0.2%) developed a second malignancy (breast cancer). A few further cases of second malignancies after treosulfan-based conditioning have been reported by other investigators. After long-term therapy with conventional doses of oral treosulfan in patients with solid tumours acute myeloid leukaemia was observed in 1.4% of 553 patients.

Blood and lymphatic system disorders

Blood disorders were observed in 67 of 564 adult patients (11.9%). The most frequent adverse reaction was febrile neutropenia (11.3%). The lowest incidence was noted with the dose regimen of 10 g/m²/day, day -4 to -2 (4.1%).
The median (25%/75% percentiles) duration of neutropenia was 14 (12, 20) days with the 10 g/m² treosulfan dose and 17.5 (14, 21) days with the 14 g/m² treosulfan dose.

Cardiac disorders

Cardiac disorders were observed in 25 patients (4.4%). The most frequent adverse reactions were cardiac arrhythmias, e.g. atrial fibrillation (1.2%), sinus tachycardia (0.9%), supraventricular tachycardia (0.4%), and ventricular extrasystole (0.4%). Isolated cases of cardiac arrest, cardiac failure, and myocardial infarction occurred. The lowest frequency of cardiac disorders was seen with the dose regimen of 10 g/m²/day, day -4 to -2 (2.7%).

Gastrointestinal disorders

Gastrointestinal disorders were observed in 357 patients (63.3%). The most frequent adverse reactions reported were nausea (39.5%), stomatitis (36%), vomiting (22.5%), diarrhoea (15.6%), and abdominal pain (10.4%). The lowest frequencies of these adverse reactions were seen with the dose regimen of 10 g/m² per day, day -4 to -2 (20.4%, 30.3%, 13.1%, 5.0%, and 5.5% respectively).

Hepatobiliary disorders

The overall incidence of veno-occlusive liver disease (VOD) was 0.9% (5/564). VOD occurred only with the dose regimen of 14 g/m²/day treosulfan. None of these cases were fatal or life-threatening.

Paediatric population

Tabulated list of adverse reactions

The adverse reactions reported in the table below are derived from two clinical trials (including a total of 88 patients; median age 8 years [range 0–17 years]) where treosulfan combined with fludarabine (and mostly with additional thiotepa) was administered as conditioning treatment prior to alloHSCT in paediatric patients with malignant or non-malignant diseases. Treosulfan was administered in a dose range of 10-14 g/m² BSA on three consecutive days.

Adverse reactions are listed below, by system organ class and by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Infections and infestations*	**Very common** Infections (bacterial, viral, fungal)	**Common** Infections (bacterial, viral, fungal)
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	**Not known** Treatment-related second malignancy[a]	**Not known** Treatment-related second malignancy[a]
Blood and lymphatic system disorders*	**Very common** Myelosuppression, pancytopenia **Not known** Febrile neutropenia	**Very common** Myelosuppression, pancytopenia **Not known** Febrile neutropenia
Metabolism and nutrition disorders	**Not known** Alkalosis, electrolyte imbalance, hypomagnesaemia	**Not known** Alkalosis
Nervous system disorders*	**Not known** Headache, paraesthesia, seizure	**Not known** Paraesthesia
Eye disorders	**Not known** Conjunctival haemorrhage, dry eye	
Vascular disorders	**Not known** Capillary leak syndrome, hypertension, hypotension	**Not known** Capillary leak syndrome, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	**Common** Oropharyngeal pain, epistaxis **Not known** Hypoxia	**Not known** Hypoxia
Gastrointestinal disorders*	**Very common** Stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain **Common** Dysphagia, oral pain **Not known** Neutropenic colitis, anal inflammation, dyspepsia, proctitis, gastrointestinal pain, constipation	**Very common** Stomatitis/mucositis, nausea **Common** Dysphagia, diarrhoea, vomiting, abdominal pain **Not known** Neutropenic colitis
Hepatobiliary disorders	**Not known** Veno-occlusive liver disease, hepatomegaly, hepatotoxicity	**Not known** Veno-occlusive liver disease

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Skin and subcutaneous tissue disorders	**Very common** Pruritus **Common** Dermatitis exfoliative, maculo-papular rash, rash, erythema, pain of skin, skin hyperpigmentation[b], alopecia **Not known** Skin ulcer, erythema multiforme, urticaria, dermatitis bullous, dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, dermatitis diaper[a]	**Common** Dermatitis exfoliative, maculo-papular rash, erythema
Musculoskeletal and connective tissue disorders	**Not known** Pain in extremities	
Renal and urinary disorders	**Not known** Acute kidney injury, renal failure, noninfective cystitis	**Not known** Acute kidney injury, renal failure
Reproductive system and breast disorders	**Not known** Scrotal erythema	
General disorders and administration site conditions	**Very common** Pyrexia[c] **Not known** Chills, fatigue, pain	
Investigations	**Common** Transaminases (ALT/AST) increased, bilirubin increased **Not known** γGT increased	**Common** Bilirubin increased **Uncommon** Transaminases (ALT/AST) increase **Not known** γGT increased

* See detailed sections below

[a] Case reports (> 1) after treosulfan-based conditioning obtained from other sources

[b] Bronze pigmentation

[c] Fever in the absence of neutropenia where neutropenia is defined as ANC < 1.0 x 10^9/L

Description of selected adverse reactions

Infections

The overall incidence of infections in 88 paediatric patients was 11.4% (10/88) and thus comparable to that seen in adults. The frequency was higher in the paediatric age group 12–17 years (6/35 [17.1%]) compared to younger children (4/53 [7.5%]).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Five cases of a second malignancy (myelodysplastic syndrome, acute lymphoblastic leukaemia, Ewing's sarcoma) were reported by other investigators after treosulfan-based conditioning. All five paediatric patients received alloHSCT for primary immunodeficiencies, i.e. diseases with an increased risk for neoplasias per se.

Blood and lymphatic system disorders

The median (25%/75% percentiles) duration of neutropenia was 21 (16, 26) days in paediatric patients with malignant diseases and 24 (17, 26) days in patients with non-malignant disorders.

Nervous system disorders

Seizure in the context of an encephalitis infection was reported in one of 88 paediatric patients. A report from an investigator-initiated trial performed in children with primary immunodeficiencies lists four cases of seizures occurring after other treosulfan-based conditioning regimens (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the HSA.

4.9 Overdose

The principal toxic effect of treosulfan is profound myeloablation and pancytopenia. In addition, acidosis, skin toxicity, nausea, vomiting and gastritis may occur. In the absence of haematopoietic stem cell transplantation, the recommended dose of treosulfan would constitute an overdose. No specific antidote of treosulfan overdose is known. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, ATC code: L01AB02

Mechanism of action

Treosulfan is a prodrug of a bifunctional alkylating agent with cytotoxic activity to haematopoietic precursor cells. The activity of treosulfan is due to the spontaneous conversion into a mono-epoxide intermediate and L-diepoxybutan (see section 5.2).
The epoxides formed alkylate nucleophilic centres of deoxyribonucleic acid (DNA) and are able to induce DNA cross-links which are considered responsible for the stem cell depleting and antineoplastic effects.

Pharmacodynamic effects

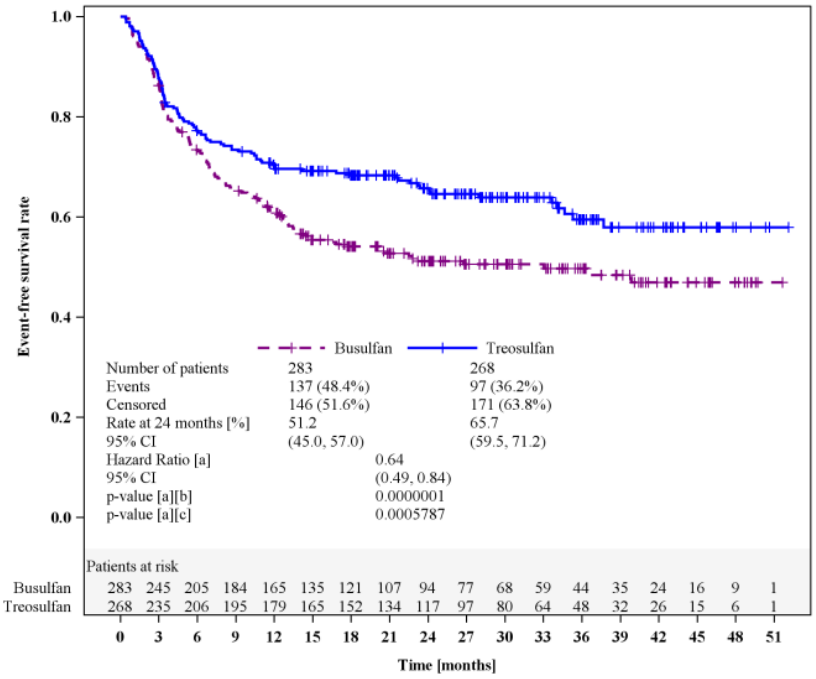
Treosulfan has a broad antineoplastic and antileukaemic activity. This was demonstrated against transplanted mouse and rat lymphomas/leukaemias, sarcomas and hepatomas, human tumour xenografts, human tumour biopsies and cell lines.
The immunosuppressive effects of treosulfan are attributed to its toxicity against primitive and committed progenitor cells, T and NK cells, reduction of cellularity of primary and secondary

lymphatic organs and a preclusive effect on the 'cytokine storm' that precedes the development of Graft-versus-Host-Disease (GvHD) and is involved in the pathogenesis of veno-occlusive disease.

Clinical efficacy and safety

In the pivotal phase III trial, adult patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) and increased risk for standard conditioning therapies because of higher age (≥ 50 years) or comorbidities (haematopoietic cell transplantation comorbidity index [HCT-CI] score > 2) were randomised to receive a conditioning regimen with 3 × 10 g/m² treosulfan combined with fludarabine (FT_{10}; n = 268) or a regimen of intravenous busulfan (total dose 6.4 mg/kg) combined with fludarabine (FB2; n = 283), followed by alloHSCT. 64% of patients had AML and 36% MDS. The median age of patients was 60 years (range 31–70 years); 25% of patients were older than 65 years. The primary endpoint of this study was event-free survival (EFS) after 2 years. Events were defined as relapse of disease, graft failure or death (whatever occurred first). Non-inferiority of FT_{10} *versus* the reference FB2 was statistically proven (Figure 1).

Figure 1: Kaplan-Meier estimates of event-free survival (Full Analysis Set)



[a] Adjusted for donor type as factor, and risk group and centre as strata using Cox regression model.
[b] For testing non-inferiority of treosulfan compared to busulfan.
[c] For testing superiority of treosulfan compared to busulfan.

Analyses of EFS at 2 years for various pre-defined subgroups (donor type, risk group, disease, age group, HCT-CI score, remission status at study entry, and various combinations of these parameters) were always in favour of the treosulfan regimen (hazard ratio [HR] of FT_{10} *vs*. FB2 < 1), with only one exception (risk group II of matched related donor [MRD] patients; HR 1.18 [95% CI 0.61, 2.26]). Further results are shown in Table 1.

Table 1: Treatment results at 24 months (Full analysis set)

Parameter	**Treosulfan**	**Busulfan**	**Hazard ratio[b] (95% CI)**	**P value[b]**
Number of patients	268	283		
Overall survival[a]; % (95% CI)	72.7 (66.8, 77.8)	60.2 (54.0, 65.8)	0.64 (0.48, 0.87)	0.0037
Cumulative incidence of relapse/progression; % (95% CI)	22.0 (16.9, 27.1)	25.2 (20.0, 30.3)	0.82 (0.59, 1.16)	0.2631
Cumulative incidence of transplant-related mortality; % (95% CI)	12.8 (9.2, 17.7)	24.1 (19.1, 30.2)	0.52 (0.34, 0.82)	0.0043
[a] Based on Kaplan-Meier estimates; [b] adjusted for donor type, risk group and centre using Cox regression model				

Results of GvHD are shown in Table 2.

Table 2: Cumulative incidence of GvHD (Full analysis set)

Parameter	**Treosulfan**	**Busulfan**	**P value**
Number of patients	268	283	
Acute GvHD, all Grades; % (95% CI)	52.8 (46.8, 58.8)	57.2 (51.5, 63.0)	0.2038
Acute GvHD, Grades III/IV; % (95% CI)	6.4 (3.4, 9.3)	8.1 (4.9, 11.3)	0.4267
Chronic GvHD[a]; % (95% CI)	61.7 (55.1, 68.3)	60.3 (53.8, 66.7)	0.9964
Extensive chronic GvHD[a]; % (95% CI)	19.8 (14.5, 25.1)	28.6 (22.5, 34.7)	0.0750
[a] Up to 2 years after alloHSCT			

Paediatric population

The efficacy and safety of treosulfan-based conditioning was evaluated in 70 patients with acute lymphoblastic leukaemia (ALL), AML, MDS, or juvenile myelomonocytic leukaemia (JMML) who received a conditioning regimen with treosulfan and fludarabine with (n = 65) or without (n = 5) thiotepa (see section 4.2). A total of 37 patients (52.9%) were younger than 12 years.
No patient experienced a primary graft failure but one patient with ALL experienced a secondary graft failure. The incidence of complete donor-type chimerism was 94.2% (90% CI 87.2-98.0%) at day +28 visit, 91.3% (90% CI 83.6-96.1%) at day +100 visit and 91.2% (90% CI 82.4-96.5%) at month 12 visit.
The overall survival at 24 months is 85.7% (90% CI 77.1-91.2%). A total of 12 of the 70 patients (17.1%) died, 8 patients because of relapse/progression and 4 patients transplant-related. Freedom from transplant-related mortality until day +100 after HSCT (primary endpoint) is 98.6% (90% CI 93.4–99.9%) because one of the 70 patients died due to transplantation/treatment-related cause until day +100 after HSCT. Transplant-related mortality at 24 months is 4.6% (90% CI 1.8 – 11.4%). Sixteen patients had a relapse/progression. The cumulative incidence of relapse/progression is 23.0% (90% CI 14.7-31.3%) at month +24.

A European Group for Blood and Marrow Transplantation (EBMT) registry study from 2011 analysed the efficacy and safety of treosulfan-based conditioning in paediatric patients with malignant and non-malignant diseases. Overall, 165 patients with malignant diseases were included; 71 had ALL, 57 AML, 25 haematological malignancies other than ALL and AML, and 12 patients had solid tumours. Treosulfan-based conditioning treatment prior to alloHSCT resulted in excellent engraftment (92–

100%) in paediatric patients with malignant diseases, irrespective of the specific underlying malignancy. The OS at 3 years was 51% for ALL, 46% for AML, 68% for haematological malignancies other than ALL and AML (68%), and 13% for solid tumours.
Data for paediatric patients with solid tumours receiving treosulfan-based conditioning treatment prior to alloHSCT is limited.

5.2 Pharmacokinetic properties

Treosulfan is a prodrug that is spontaneously converted under physiological conditions (pH 7.4; 37 °C) into a monoepoxide intermediate and L-diepoxybutane with a half-life of 2.2 hours.

Absorption

After intravenous administration, peak plasma levels are reached at the end of the infusion time. Maximum plasma levels (mean ± SD) in adult patients after a 2-hour intravenous infusion of 10, 12, or 14 g/m² treosulfan were 306 ± 94 µg/mL, 461 ± 102 µg/mL, and 494 ± 126 µg/mL, respectively.

Distribution

Treosulfan is rapidly distributed in the body; however, its penetration through the blood-brain-barrier is quite limited (see section 5.3). The volume of distribution in adult patients is about 20–30 litres. No dose accumulation with the recommended daily treatment on three consecutive days was observed. Treosulfan does not bind to plasma proteins.

Biotransformation

Under physiological conditions (pH 7.4, temperature 37 °C), the pharmacologically inactive treosulfan is converted spontaneously (non-enzymatically) into the active monoepoxide intermediate (S,S-EBDM = (2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate) and finally to L-diepoxibutane (S,S-DEB = (2S,3S)-1,2:3,4-diepoxybutane).
At concentrations up to 100 µM, treosulfan has no unequivocal effect on CYP1A2, 2C9, 2C19, 2D6, or 3A4 activities *in vitro*. Therefore, treosulfan is unlikely to participate in, or contribute to, potential CYP450-mediated interactions *in vivo*.

Elimination

Plasma concentrations of treosulfan decline exponentially and are best described by a first order elimination process fitted by a two-compartment model.
The terminal half-life ($T_{1/2ß}$) of intravenously administered treosulfan (up to 47 g/m²) is approximately 2 hours. Approximately 25–40% of the treosulfan dose is excreted unchanged with the urine within 24 hours, nearly 90% of which within the first 6 hours after administration.

Linearity/non-linearity

Regression analysis of the area under the curve ($AUC_{0-\infty}$) *versus* treosulfan dose indicated a linear correlation.

Renal and hepatic impairment

No pharmacokinetic studies with treosulfan were done in patients with severe renal or hepatic impairment, because such patients are generally excluded from alloHSCT. About 25–40% of treosulfan is excreted in urine; however, an influence of renal function on renal clearance of treosulfan was not observed.

Paediatric population

Conventional dose calculation simply based on BSA results in a significantly higher exposure (AUC) of smaller children and infants with low BSA compared to adolescents or adults. Therefore, dosing of treosulfan in paediatric patients has to be adapted to the BSA (see section 4.2).
Mean apparent terminal half-life of treosulfan was comparable between the different age groups and ranged between 1.3 and 1.6 hours.

5.3 Preclinical safety data

Due to its alkylating mechanism of action treosulfan is characterised as a genotoxic compound with carcinogenic potential. Specific reproductive and developmental toxicity studies on treosulfan in animals were not conducted. However, during chronic toxicity tests in rats spermatogenesis and ovarian function were significantly affected. Published literature data report on gonadotoxicity of treosulfan in pre-pubertal and pubertal male and female mice.
Published data concerning treatment of mice and rats with L-diepoxibutane (the alkylating transformation product of treosulfan) revealed impairment of fertility, uterine-ovarian and sperm development.

Juvenile animal studies

In juvenile rat toxicity studies treosulfan induced slight retardation of physical development and a slightly delayed time-point of vaginal opening in females. A very low penetration of blood-brain-barrier by treosulfan was observed in rats. The treosulfan concentrations in brain tissue were 95%–98% lower than in plasma. However, an approximately 3-fold higher exposure in brain tissue of juvenile rats in comparison to young adults was found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial
4 years

Reconstituted solution for infusion
After reconstitution with sodium chloride 4.5 mg/mL (0.45%) solution, chemical and physical stability has been demonstrated for 2 days at 25 °C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.
Do not store in a refrigerator (2 °C-8 °C) as this might cause precipitation.

6.4 Special precautions for storage

Store at or below 30 °C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Trecondi 1 g powder for solution for infusion
Colourless type I glass vial, with rubber stopper and aluminium cap containing 1 g of treosulfan.

Trecondi 5 g powder for solution for infusion
Colourless type I glass vial, with rubber stopper and aluminium cap containing 5 g of treosulfan.

Trecondi is available in single vial packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

As with all cytotoxic substances, appropriate precautions should be taken when handling treosulfan.

Trained personnel should reconstitute the medicinal product. When handling treosulfan, inhalation, skin contact or contact with mucous membranes should be avoided (the use of adequate protective disposable gloves, goggles, gown and mask is recommended). Contaminated body parts should be carefully rinsed with water and soap, the eyes should be rinsed with sodium chloride 9 mg/mL (0.9%) solution. If possible it is recommended to work on a special safety workbench, equipped with laminar flow, with liquid-impermeable, absorbent disposable foil. Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic medicinal products. Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
Pregnant personnel should be excluded from handling cytotoxics.

Instructions for reconstitution of treosulfan:
1. Treosulfan is reconstituted in its original glass container. Reconstituted solutions of treosulfan may be combined into a larger glass vial, PVC bag or PE bag.
2. To avoid solubility problems, warm the solvent, sodium chloride 4.5 mg/mL (0.45%) solution, to 25 °C - 30 °C (not higher), for example by using a water bath.
3. Remove the treosulfan powder carefully from the inner surface of the vial by shaking. This procedure is very important, because moistening of powder that sticks to the surface results in caking. If this happens, vigorously shake the vial to redissolve the cake.
4. Reconstitute each vial of Trecondi containing 1 g treosulfan in 20 mL of pre-warmed (maximum 30 °C) sodium chloride 4.5 mg/mL (0.45%) solution by shaking.
   Reconstitute each vial of Trecondi containing 5 g treosulfan in 100 mL of pre-warmed (maximum 30 °C) sodium chloride 4.5 mg/mL (0.45%) solution by shaking.

For preparation of sodium chloride 4.5 mg/mL (0.45%) solution equivalent volumes of sodium chloride 9 mg/mL (0.9%) solution and water for injections can be mixed.

The reconstituted solution contains 50 mg treosulfan per mL and appears as a clear colourless solution. Solutions showing any sign of precipitation should not be used.

Treosulfan has mutagenic and carcinogenic potential. Remnants of the medicinal product as well as all materials that have been used for reconstitution and administration must be destroyed according to standard procedures applicable to antineoplastic agents.

7. PRODUCT REGISTRANT

Link Healthcare Singapore Pte Ltd
10 Changi South Street 2
#02-01
Singapore 486596
Batch Releaser
medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. REGISTRATION NUMBER

TBA

9. DATE OF HSA APPROVAL

TBA