20 June 2019
EMA/235233/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Trecondi (treosulfan)
Conditioning treatment prior to haematopoietic progenitor cell transplantation
EU/3/04/186 (EMEA/OD/075/03)
Sponsor: medac Gesellschaft für klinische Spezialpräparate mbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

The part of the Orphan Maintenance Assessment Report that compares Trecondi (treosulfan) with melphalan- and cyclophosphamide-containing medicinal products has been rendered obsolete for the purpose of the orphan designation of Trecondi, further to the Judgment of the General Court of 23 September 2020 in *Medac Gesellschaft für klinische Spezialpräparate v Commission*, T-549/19.

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Table of contents

1. Product and administrative information

Product	
Active substance	Treosulfan
International Non-Proprietary Name	Treosulfan
Orphan indication	Conditioning treatment prior to haematopoietic progenitor cell transplantation
Pharmaceutical form	Powder for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L01A B02
Sponsor's details:	medac Gesellschaft für klinische Spezialpräparate mbH Theaterstraße 6 D-22880 Wedel Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	medac Gesellschaft für klinische Spezialpräparate mbH
COMP opinion date	14 January 2004
EC decision date	23 February 2004
EC registration number	EU/3/04/186
Marketing authorisation	
Rapporteur / co-Rapporteur	N. Nagercoil, B. Sepodes
Applicant	medac Gesellschaft für klinische Spezialpräparate mbH
Application submission date	12 December 2017
Procedure start date	1 February 2018
Procedure number	EMA/H/C/004751
Invented name	Trecondi
Therapeutic indication	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. Further information on Trecondi can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/Trecondi
CHMP opinion date	13 December 2018
COMP review of orphan medicinal product designation procedural history (case EMA/OD/0000002579)	
COMP Co-ordinators	F. Naumann-Winter, B. Dembowska-Baginska
Sponsor's report submission date	12 December 2017
COMP discussion and adoption of list of questions	9-11 November 2018
Oral explanation	4 December 2018
COMP opinion date	19 December 2018

Appeal to the COMP opinion (case EMA/OD/0000006269)	
COMP Rapporteurs	A. Magrelli / K. Penttila
EMA Scientific Officer	S. Tsigkos
Expert	Not applicable
Appeal submission	20 March 2019
Appeal oral explanation	15 April 2019
COMP final opinion (adoption via written procedure)	8 May 2019
Withdrawal from the Community Register	20 June 2019

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2004 was based on the following grounds:

- the diseases in which the myeloid or lymphoid systems are intrinsically absent, dysfunctional or neoplastic and justify hematopoietic progenitor cell transplantation (hereinafter referred to as "the condition") was estimated to be affecting 0.7 in 10,000 persons in the Community at the time the application was made;
- the condition is life-threatening due to the underlying primary diseases;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that treosulfan may be of significant benefit to those affected by the condition;

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Haematopoietic stem cell transplant (HSCT) involves the intravenous infusion of autologous or allogeneic haematopoietic stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to re-establish haematopoietic function in patients with damaged or defective bone marrow or immune system.

When the stem cells are collected from another person, either from relatives (identical twins, HLA-matched related, mismatched related) or unrelated donors (matched unrelated, umbilical cord blood) it is called allogeneic transplant.

Allogeneic HSCT has led to the cure of some forms of cancer (especially leukaemias), bone marrow failure, hereditary metabolic disorders, and severe congenital immunodeficiencies that would otherwise have been fatal.

At the time of designation, the orphan condition was "conditioning treatment prior to haematopoietic progenitor cell transplantation". The COMP recognises HSCT as a treatment modality for the delineation of an orphan condition, which is only used in exceptional cases (in alignment with EC guideline ENTR/6283/00 Rev 4). In light of this exception, the initial orphan indication "Conditioning treatment prior to haematopoietic progenitor cell transplantation" remains acceptable for the purpose of orphan designation maintenance. Nevertheless, it should be highlighted that at the time of this review and for future designations the COMP generally designates the slightly reworded orphan condition "treatment in HSCT".

The approved therapeutic indication "in combination with fludarabine 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" falls within the scope of the designated orphan condition "conditioning treatment prior to haematopoietic progenitor cell transplantation".

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

At the time of designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening. At the time of this review, HSCT is described to be the only chance for cure of patients with life-threatening underlying diseases.

The COMP concluded that the condition remains life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also associated with complications such as graft-versus-host disease. The COMP recognises HSCT as a treatment modality for the delineation of an orphan condition, which is only used in exceptional cases (in alignment with EC guideline ENTR/6283/00 Rev 4).

Number of people affected or at risk

At the time of designation the prevalence was agreed to be 0.7 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000.

Prevalence was estimated to be 0.24 per 10,000. No systematic literature search on epidemiology has been performed. The estimate stems from incidence figures derived from the report of the European Group for Blood and Marrow Transplantation (EBMT): 43 636 HSC transplants were reported in 39 313 patients in Europe in the year 2016; 17 641 HSCTs (40%) were allogeneic. An increase in alloHSCTs by about 2% per year was assumed to estimate incidence of alloHSCTs in 2017 (at the time of submission) resulting in 18 000 alloHSCT transplants. When taking into consideration the European population of approximately 740 000 000 in 2017, the incidence of alloHSCTs was estimated to be about 0.24 in 10 000 people in Europe. However, the full orphan indication has to be considered without focussing on alloHSCT figures, even though it is understood that the treatment is targeting patients undergoing alloHSTCs. The presented figure should be revised taking into consideration an increase in 2018 and all types of HSCTs.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are medicinal products authorised in the EU for the conditioning treatment prior to haematopoietic progenitor cell transplantation: busulfan (Busilvex), thiotepa (Tepadina), melphalan (various authorisations), cyclophosphamide (various authorisations), filgrastim (various authorisations).

There are no European consensus treatment guidelines for patients undergoing conditioning treatment prior to haematopoietic progenitor cell transplantation. Some guidance is provided specifically for individual haematopoietic malignancies in respective ESMO guidelines.

Significant benefit

Various conditioning regimens before HSCT are used in clinical practice today. These regimens differ in their intensity and are currently divided into three categories: myeloablative conditioning (MAC), reduced intensity conditioning (RIC) and non-myeloablative conditioning (NMA). The development of NMA and RIC regimens significantly expanded the patient population that could receive alloHSCT.

In line with the therapeutic indication, significant benefit needs to be demonstrated for Trecondi in combination with fludarabine 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. Taking into consideration the authorisation status of medicinal products, it was considered that significant benefit needs to be demonstrated over busulfan (Busilvex), thiotepa (Tepadina), melphalan (various national authorisations), cyclophosphamide (various national authorisations). Filgrastim is indicated for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. It can be acknowledged that this treatment has a different purpose and aim during conditioning, and therefore no significant benefit needs to be established.

The applicant did not seek protocol assistance on significant benefit issues from the COMP during their development.

Regarding the demonstration of significant benefit over busulfan, clinical data from MC-FludT.14/L Trial II have been submitted. The same trial was assessed as pivotal evidence by the CHMP for the purpose of assessing the benefit/risk balance (please be referred to European public assessment report of Trecondi). MC-FludT.14/L II was a randomised, parallel-group, open label, multicentre, group-sequential phase III non-inferiority trial to evaluate the efficacy and safety of treosulfan-based conditioning versus a busulfan-based reduced intensity conditioning (RIC) treatment prior to allogeneic HSCT in patients with AML or MDS considered ineligible to standard conditioning. Included patients were affected by acute myeloid leukaemia (AML) or myelodysplastic syndromes (MDS) and per WHO 2008 indicated for allogeneic HSCT, but at increased risk for standard conditioning if aged $\geq$ 50 years at transplant and/or had a HSCT -Comorbidity Index (HCT-CI) score > 2. Patients required the availability of a HLA-identical sibling donor (MRD) or HLA-identical unrelated donor (MUD). The primary objective was to compare EFS within 2 years after transplantation between treosulfan based conditioning and busulfan-based conditioning. Event-free survival (EFS) within 2 years after transplantation was

measured from time of end of HSCT (= day 0) to time of event. Events were defined as relapse of disease, graft failure or death (whatever occurred first). The primary objective was to demonstrate non-inferiority of treosulfan as an alternative conditioning agent to busulfan with respect to EFS. The non-inferiority margin on the hazard ratio scale was pre-specified as 1.3. If significant non-inferiority within the Per Protocol Set (PPS) could be shown, a sequential testing was to be applied starting with testing the non-inferiority within the Full Analysis Set (FAS). In case of statistical significance, superiority within the FAS with respect to the primary endpoint was to be tested based on the 'Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)'.

Recruitment was stopped in November 2016 since the primary objective of non-inferiority of treosulfan versus busulfan had been achieved. This final analysis with 476 patients, 460 patients qualifying for the FAS, constitutes the final analysis of this trial.

The primary endpoint, EFS within 24 months after HSCT, was reported in the PPS for busulfan versus treosulfan as 51.1% (95% CI: 43.4%, 58.2%) vs 63.5% (95% CI: 55.4%, 70.5%), HR 0.67 (95% CI: 0.48, 0.93), one-sided p-value of 0.0000424 (adjusted for strata). This result showed statistically significant non-inferiority of treosulfan compared to busulfan with the p value below the one-sided significance level of 0.000149 required for this interim analysis. Confirmatory testing for non-inferiority of treosulfan versus busulfan in the FAS was demonstrated, with EFS at 24 months of 50.4% (95% CI: 42.8, 57.5) in the busulfan group, and 64.0% (95% CI: 56.0, 70.9) in the treosulfan, HR 0.65 (95% CI: 0.47, 0.90), one sided p-value 0.0000164 (table 1). Superiority testing of treosulfan vs busulfan gave a p-value of 0.0051268 (FAS, adjusted for strata) below the criteria set (nominal one-sided significance level 0.000149).

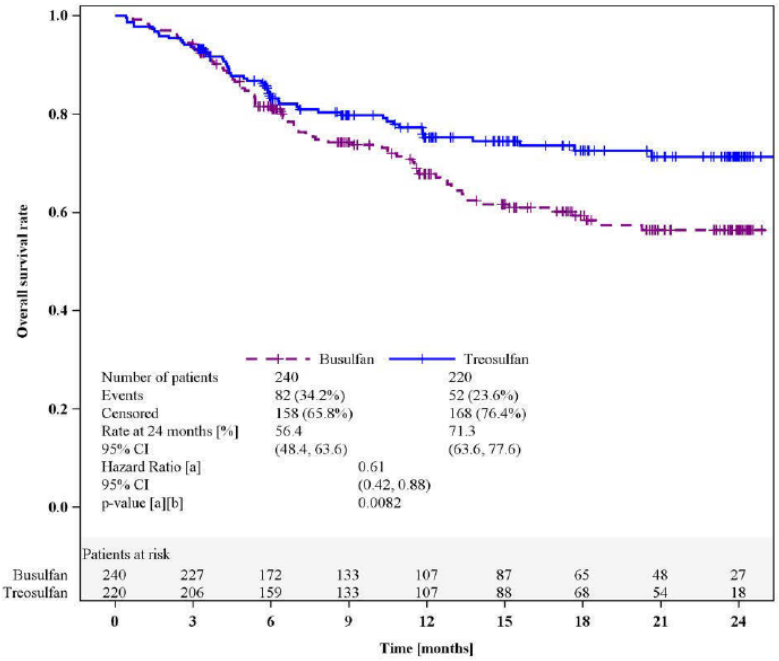
Table 1. Study MC-FludT.14/L Trial II: EFS results

Study population	**FAS**		**PPS**	
Treatment arm	TREO	BU	TREO	BU
Number of patients	220	240	215	234
Median follow-up[a], months (range)	15.4 (3.2, 26.4)	17.4 (3.0, 26.3)	15.4 (3.2, 26.4)	17.4 (3.0, 26.3)
Patients with events Death[b] Relapse/Progression[b] Primary Graft failure[b] Secondary Graft failure[b]	30.9% 23 (10.5%) 45 (20.5%) 0 (0.0%) 0 (0.0%)	41.7% 41 (17.1%) 51 (21.3%) 1 (0.4%) 7 (2.9%)	31.2% 22 (10.2%) 45 (20.9%) 0 (0.0%) 0 (0.0%)	41.5% 38 (16.2%) 51 (21.8%) 1 (0.4%) 7 (3.0%)
Patients without events	69.1%	58.3%	68.8%	58.5%
EFS at 12 months[b]; % (95% CI)	67.5 (60.3, 73.6)	58.5 (51.4, 64.9)	67.1 (59.8, 73.3)	58.7 (51.5, 65.2)
EFS at 24 months[b]; % (95% CI)	64.0 (56.0, 70.9)	50.4 (42.8, 57.5)	63.5 (55.4, 70.5)	51.1 (43.4, 58.2)
Hazard ratio[c] (95% CI)	0.65 (0.47, 0.90)		0.67 (0.48, 0.93)	
Hazard ratio[cde] (99.9702% CI)	0.65 (0.36, 1.19)		0.67 (0.37, 1.23)	
P-value[cde]for testing non-inferiority	0.0000164		0.0000424	
P-value[cd]for testing superiority	0.0051268		0.0090454	
P-value[c] for testing difference	0.0102535		0.0180908	

[a] Based on reverse Kaplan-Meier estimates for overall survival.
[b] Based on Kaplan-Meier estimates.
[c] Adjusted for donor type as factor, and risk group and centre as strata using Cox regression model.
[d] The nominal one-sided significance level resulting from an O'Brien-Fleming type of group-sequential efficacy stopping boundary is 0.000149
[e] The non-inferiority margin for the hazard ratio is 1.3.

Overall survival (OS, at 24 months after HSCT) was statistically significantly higher in the treosulfan group compared to busulfan (figure 1, HR 0.61, 95% CI: 0.42, 0.88; adjusted p-value=0.0082). The median OS for each treatment group are not available. There was no statistical difference for relapse/progression within 24 months after HSCT between treatments (p=0.5017, adjusted for donor-type as factor, and risk group as stratum using Fine and Gray model). The HR was 0.87 (95% CI: 0.59, 1.30) in favour of treosulfan. The data for the PPS were similar. Engraftment at 28 days after HSCT was similar between treatment groups for all categories. The median duration of neutropenia and leukopaenia was longer in the treosulfan group than the busulfan (neutropaenia: 12.5 days compared to 14.0 day; leukopenia: 13.0 days compared to 14.0 days, busulfan versus treosulfan respectively).

Figure 1. Study MC-FludT.14/L Trial II: OS results, Kaplan-Meier estimates of overall survival (Full Analysis Set)



Sources: Figure 14.2.3A, Table 14.2.3A, Table 14.2.3B, Listing 16.2.6F
[a] adjusted for donor type as factor, and risk group and centre as strata using Cox regression model.
[b] for testing the difference of Treosulfan compared to Busulfan.

In conclusion, MC-FludT.14/L Trial II was a non-inferiority study and therefore not designed to show improved efficacy or significant benefit versus busulfan. The study met its objective and the proposed Trecondi conditioning regimen can be considered non- inferior to a busulfan based conditioning regimen in terms of EFS. Nevertheless, the results demonstrate numerically improved EFS (even though not statistically significant). This positive trend suggesting improved efficacy is furthermore supported by improvements in secondary endpoints including OS.

During the marketing authorisation procedure, a final clinical study report for MC-FludT.14/L Trial II was supplied dated 18-Jul-2018 (cut-off date 16 March 2018) has been submitted, which covered the final analysis of all 570 randomised adult patients including the post-surveillance follow-up. The results confirmed the previously submitted efficacy data regarding statistical non-inferiority of EFS and statistical superiority regarding OS of the Trecondi based conditioning regimen. In addition, transplantation-related mortality (TRM) was statistically significantly lower in the Trecondi treatment group compared to the busulfan group (HR=0.52; 95% CI: 0.34, 0.82; adjusted p=0.0043). Graft versus host disease (GvHD)-free and relapse/progression-free survival was statistically significantly higher in the Trecondi treatment group (HR 0.73, 95% CI: 0.57, 0.92; adjusted p=0.0087). Chronic GvHD-free and relapse/progression-free survival was also statistically significantly higher in the Trecondi treatment group (HR 0.70, 95% CI: 0.55, 0.88; adjusted p=0.0030). The CHMP contests a clinically relevant long-term advantage of Trecondi compared to busulfan for clinically meaningful endpoints. In conclusion, the COMP considered that these results support a clinically relevant advantage on the grounds of improved efficacy, despite the non-inferiority design.

Table 2. Results of final clinical study report dated 18-Jul-2018 (cut-off 16 March 2018): EFS (top), OS (middle) and NRM (bottom);

	Interim analysis (Data source: CSR Table 11.4.1.1.A)		Final analysis (Data source: CSR Table 11.4.1.1.A)	
Treatment arm	**TREO**	**BU**	**TREO**	**BU**
Number of patients	215	234	262	275
Median follow-up[a], months (range)	15.4 (3.2, 26.4)	17.4 (3.0, 26.3)	29.7 (3.0, 52.1)	29.4 (3.9, 54.3)
Patients with events	67 (31.2%)	97 (41.5%)	96 (36.6%)	134 (48.7%)
Patients without events	148 (68.8%)	137 (58.5%)	166 (63.4%)	141 (51.3%)
EFS at 12 months[b]; % (95% CI)	67.1 (59.8, 73.3)	58.7 (51.5, 65.2)	69.7 (63.7, 74.9)	60.5 (54.5, 66.0)
EFS at 24 months[b]; % (95% CI)	63.5 (55.4, 70.5)	51.1 (43.4, 58.2)	65.3 (59.0, 70.9)	51.1 (44.8, 57.0)
EFS at 36 months[b]; % (95% CI)	Not reported	Not reported	58.9 (51.5, 65.6)	49.6 (43.1, 55.7)
Hazard ratio[c] (95% CI)	0.67 (0.48, 0.93)		0.64 (0.48, 0.84)	
P-value[cd] for testing non-inferiority	0.0000424		0.0000001	
P-value[c] for testing superiority	0.0090454		0.0005777	

[a] Based on reverse Kaplan-Meier estimates for overall survival.
[b] Based on Kaplan-Meier estimates.
[c] Adjusted for donor type as factor, and risk group and centre as strata using Cox regression model.
[d] The non-inferiority margin for the hazard ratio is 1.3.

	Interim analysis (Data source: CSR Table 11.4.1.2.A)		Final analysis (Data source: CSR Table 11.4.1.2.A)	
Treatment arm	**TREO**	**BU**	**TREO**	**BU**
Number of patients	220	240	268	283
Patients with events	52 (23.6%)	82 (34.2%)	81 (30.2%)	112 (39.6%)
Patients without events	168 (76.4%)	158 (65.8%)	187 (69.8%)	171 (60.4%)
OS at 12 months[a], % (95% CI)	75.3 (68.4, 80.8)	67.8 (60.8, 73.8)	77.8 (72.3, 82.3)	71.8 (66.1, 76.7)
OS at 24 months[a], % (95% CI)	71.3 (63.6, 77.6)	56.4 (48.4, 63.6)	72.7 (66.8, 77.8)	60.2 (54.0, 65.8)
OS at 36 months[a], % (95% CI)	Not reported	Not reported	66.8 (59.9, 72.9)	56.3 (49.6, 62.6)
Hazard ratio[b] TREO vs. BU (95% CI)	0.61 (0.42, 0.88)		0.64 (0.48, 0.87)	
P-value[b]	0.0082		0.0037	

[a]based on Kaplan-Meier estimates; [b]adjusted for donor type, risk group and centre using Cox regression model

Study	Interim analysis (Data source: CSR Table 11.4.1.5.A)		Final analysis (Data source; CSR Table 11.4.1.5.A)	
Treatment arm	**Treosulfan**	**Busulfan**	**Treosulfan**	**Busulfan**
Number of patients	220	240	268	283
Patients with events	23 (10.5%)	41 (17.1%)	35 (13.1%)	56 (19.8%)
Patients without events	197 (89.5%)	199 (82.9%)	233 (86.9%)	227 (80.2%)
NRM at 12 months; % (95% CI)	11.4 (7.0, 15.9)	15.2 (10.2, 20.3)	10.5 (6.8, 14.2)	14.3 (10.2, 18.4)
NRM at 24 months; % (95% CI)	11.4 (7.0, 15.9)	22.6 (16.2, 28.9)	12.0 (8.0, 15.9)	20.4 (15.5, 25.2)
NRM at 36 months; % (95% CI)	Not reported	Not reported	14.2 (9.5, 18.9)	21.0 (16.1, 26.0)
Hazard ratio[a] TREO vs. BU (95% CI)	0.60 (0.36, 1.01)		0.63 (0.41, 0.97)	
P-value[a]	0.0530		0.0343	

[a]adjusted for donor type and risk group using Fine and Gray model

Regarding thiotepa, no data has been submitted to support significant benefit. It is indicated, in combination with other chemotherapy medicinal products with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients. The sponsor is requested to provide a data-driven discussion of significant benefit versus thiotepa-containing regimens.

Regarding melphalan, no data has been submitted in support of significant benefit. The COMP has previously considered melphalan for significant benefit based on its indication in a number of EU countries: 'at high intravenous dosage with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma'. In France the authorised indication covers additionally the use of melphalan, alone or in combination with other cytotoxic agents and/ or extended or total body irradiation, in the treatment of malignant lymphomas (Hodgkin's disease, non-Hodgkin's lymphomas), acute lymphoblastic and myeloblastic leukaemias and mammary and ovarian adenocarcinoma. The sponsor is requested to provide a data-driven discussion of significant benefit versus melphalan-containing regimens.

Regarding cyclophosphamide, no data has been submitted in support of significant benefit. It is indicated as conditioning for a bone marrow transplantation, in the treatment of Acute Lymphoblastic Leukemia, Chronic Myelogenous Leukemia and Acute Myelogenous Leukemia, in combination with whole body irradiation or busulfan (UK therapeutic indication, national therapeutic indications across EU can vary). The sponsor is requested to provide a data-driven discussion of significant benefit versus cyclophosphamide-containing regimens.

There is further evidence of treosulfan from retrospective EBMIT registry analyses, but it is unclear if these studies include data that could be useful in establishing significant benefit over regimens including authorised products (Nagler 2017; Shimoni 2015; Peters 2011/2017).

In conclusion, taking into consideration the totality of evidence, a clinically relevant advantage over busulfan can be established based on improvements in clinically relevant secondary endpoints. However, there currently is no data-driven discussion over other authorised treatments in the target patient population. At this point in time, significant benefit remains unsubstantiated. The sponsor is invited to provide further evidence from the registry studies or other direct or indirect evidence to support significant benefit over the other authorised products.

4. COMP list of issues

The sponsor is requested to provide an updated prevalence figure that encompasses all patients receiving haematopoietic stem cell transplantation without focus on patients receiving allogeneic HSCT.

The sponsor is requested to provide clinical data in support of significant benefit over regimens including thiotepa (Tepadina), melphalan (various authorisations), cyclophosphamide. Significant benefit can be established on the basis of improved efficacy, improved safety or major contribution to patient care.

Comments on sponsor's response to the COMP list of issues

Issue 1 - Prevalence:

As requested by the COMP, the original prevalence calculation was revised to include all type of HSCTs. The basis for the HSCT incidence is the EBMT report from 216, which is described to be the latest one available. The proposed incidence of all types of HSCT is 0.67 per 10,000, when extracting the data of 28 EU member states. This prevalence estimate was adjusted to take into consideration population data in 2018. The COMP considered that this figure is acceptable for maintenance of orphan designation.

Issue 2 - Significant benefit:

Various indirect comparisons have been presented in order to justify significant benefit over other conditioning regimens that contain the currently authorised products. These compare the pivotal trial

data (MC-FludT.14/L Trial II) to historic observational trial or registry data, which have been retrospectively collected and published in the scientific literature. It must be noted that various known (and unknown) confounding factors could influence the outcome of HSCT patients, independent of their conditioning regimen. This was also acknowledged by the applicant. It was also confirmed that patient-level data were not available for the published studies so that there was not the possibility to provide indirect comparisons of more robust methodology. The possibility of patient-matched analyses with the help from the EBMT was discussed in this context. The COMP considered that such analyses could potentially provide a higher methodological validity, but these analyses were not presented by the applicant.

The following patient population characteristics were considered of importance for the determination of the validity of the provided indirect comparisons: age of patients, stage of disease (complete remission CR1 or CR2+), severity of disease by cytogenetic factors or HCT-CI score, donor type (matched related MRD, matched-unrelated MUD, unmatched, time of observation (changes in best standard of care). In this context, the exclusion and inclusion criteria as well as the baseline characteristics of the pivotal trial MC-FludT.14/L II are of importance and are outlined below.

Inclusion/exclusion criteria:

- Patients with AML or MDS per WHO 2008 indicated for allogeneic HSCT but at increased risk for standard conditioning if aged ≥ 50 years at transplant and/or had a HSCT -Comorbidity Index (HCT-CI) score > 2.
- Availability of a HLA-identical sibling donor (MRD) or HLA-identical unrelated donor (MUD)..
- Adult patients 18 to 70 years of age
- No previous allogeneic HSCT
- In some countries promyelocytic leukaemia was excluded
- In some countries low or very low risk patients were excluded
- Patient enrolment: 13-Jun-2013 to 07-Dec-2016

Table 3. MC-FludT.14/L Trial II: AML patient baseline characteristics

	Busulfan (N=138)	Treosulfan (N=155)	Total (N=293)
Time between diagnosis and HSCT [months]			
Mean (SD)	7.69 (7.99)	8.15 (7.23)	7.93 (7.59)
Median (Q1, Q3)	5.14 (3.52, 8.25)	5.32 (3.88, 9.36)	5.26 (3.68, 8.51)
Min, Max	1.2, 56.2	1.7, 46.9	1.2, 56.2
Classification of AML [n (%)]			
Any category	138 (100.0%)	155 (100.0%)	293 (100.0%)
AML with myelodysplasia-related changes	29 (21.0%)	30 (19.4%)	59 (20.1%)
AML with maturation	23 (16.7%)	21 (13.5%)	44 (15.0%)
AML with mutated NPM1	17 (12.3%)	27 (17.4%)	44 (15.0%)
AML without maturation	19 (13.8%)	21 (13.5%)	40 (13.7%)
AML, Acute myelomonocytic leukaemia	16 (11.6%)	10 (6.5%)	26 (8.9%)
AML, Acute monoblastic and monocytic leukaemia	8 (5.8%)	14 (9.0%)	22 (7.5%)
AML with minimal differentiation	7 (5.1%)	9 (5.8%)	16 (5.5%)
AML, Therapy-related myeloid neoplasms	3 (2.2%)	6 (3.9%)	9 (3.1%)
AML with t(8;21)(q22;q22); RUNX1-RUNX1T1	3 (2.2%)	3 (1.9%)	6 (2.0%)
AML, Acute erythroid leukaemia	4 (2.9%)	1 (0.6%)	5 (1.7%)
AML with mutated CEBPA	1 (0.7%)	3 (1.9%)	4 (1.4%)
AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); (CBFbeta-MYH11)	0 (0.0%)	3 (1.9%)	3 (1.0%)
AML, Acute megakaryoblastic leukaemia	1 (0.7%)	2 (1.3%)	3 (1.0%)
AML, not otherwise categorised (unspecified)	2 (1.4%)	1 (0.6%)	3 (1.0%)
AML with inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1	1 (0.7%)	1 (0.6%)	2 (0.7%)
AML with recurrent genetic abnormalities (unspecified)	0 (0.0%)	2 (1.3%)	2 (0.7%)
AML with t(9;11)(p22;q23); MLLT3-MLL	2 (1.4%)	0 (0.0%)	2 (0.7%)
AML, Acute basophilic leukaemia	1 (0.7%)	0 (0.0%)	1 (0.3%)
AML, Blastic plasmacytoid dendritic cell neoplasm	0 (0.0%)	1 (0.6%)	1 (0.3%)
AML, Mixed phenotype acute leukaemia, T/myeloid, NOS	1 (0.7%)	0 (0.0%)	1 (0.3%)
Remission status AML [n (%)]			
CR1	117 (84.8%)	133 (85.8%)	250 (85.3%)
>CR1	21 (15.2%)	22 (14.2%)	43 (14.7%)
Blast count in bone marrow [%]			
n	138	154	292
Mean (SD)	2.12 (1.58)	1.97 (1.29)	2.04 (1.43)
Median (Q1, Q3)	2.50 (1.00, 3.00)	2.50 (1.00, 2.50)	2.50 (1.00, 3.00)
Min, Max	0.0, 11.5	0.0, 5.0	0.0, 11.5
Missing	0	1	1
AML risk group stratification [n (%)]			
Low risk	13 (9.4%)	15 (9.7%)	28 (9.6%)
Intermediate risk	61 (44.2%)	55 (35.5%)	116 (39.6%)
High risk	43 (31.2%)	63 (40.6%)	106 (36.2%)
NA if > CR1	21 (15.2%)	22 (14.2%)	43 (14.7%)

Table 4. MC-FludT.14/L Trial II: MDS patient baseline characteristics

	Busulfan (N=102)	Treosulfan (N=65)	Total (N=167)
Time between diagnosis and HSCT [months]			
n	100	65	165
Mean (SD)	14.17 (18.99)	15.93 (24.52)	14.86 (21.28)
Median (Q1, Q3)	7.59 (4.88, 14.09)	7.62 (4.47, 16.99)	7.62 (4.76, 16.16)
Min, Max	0.2, 128.3	0.5, 135.9	0.2, 135.9
Missing	2	0	2
Etiology [n (%)]			
De novo MDS	80 (78.4%)	51 (78.5%)	131 (78.4%)
Therapy-related MDS	22 (21.6%)	14 (21.5%)	36 (21.6%)
Classification of MDS [n (%)]			
Any category	102 (100.0%)	65 (100.0%)	167 (100.0%)
MDS, Refractory anaemia with excess blasts -2	40 (39.2%)	21 (32.3%)	61 (36.5%)
MDS, Refractory cytopenia with multilineage dysplasia (unspecified)	31 (30.4%)	22 (33.8%)	53 (31.7%)
MDS, Refractory anaemia with excess blasts -1	23 (22.5%)	19 (29.2%)	42 (25.1%)
MDS, Myelodysplastic syndrome associated with isolated del(5q)	2 (2.0%)	1 (1.5%)	3 (1.8%)
MDS, Myelodysplastic syndrome, unclassifiable	3 (2.9%)	0 (0.0%)	3 (1.8%)
MDS, Refractory cytopenia with unilineage dysplasia	1 (1.0%)	2 (3.1%)	3 (1.8%)
MDS, Refractory anaemia with ringed sideroblasts	1 (1.0%)	0 (0.0%)	1 (0.6%)
MDS, Refractory thrombocytopenia	1 (1.0%)	0 (0.0%)	1 (0.6%)

Regarding melphalan, various indirect comparisons were presented for the demonstration of significant benefit (table 5). The results collected in the Treosulfan arm of the MC-FludT.14/L Trial II seem to compare favourably with the published scientific literature regarding overall survival and non-relapse mortality. However, the compared patient populations are relatively dissimilar regarding important patient characteristics. These 'crude' indirect comparisons were not considered sufficiently reliable in view of potential confounding and the COMP concluded that significant benefit over melphalan was not sufficiently substantiated at the time of review.

Table 5. Significant benefit over melphalan: overview and characteristics of the studies that have been submitted for indirect comparisons

Study **(observation period)**	**Evidence**	**Similarities** **(Characteristics of literature study)**	**Differences** **(Characteristics of literature study)**	**Results of indirect comparison** **(OS/NRM)**
Baron et al, Cancer. 2015 Apr 1; 121(7):1048-55. PMID: 25424330 (2000-2012)	Indirect comparison of pivotal trial data in AML patients	None identified based on available information	- Age: 6 years younger - Stage of disease: includes more advanced patients at CR2 - Risk: more good and intermediate risk cytogenetics)	TREO/FLU regimen vs. FLU/MEL regimen (2-years): - OS: 72.8 (65.5, 78.8) vs. 62 ± 4 - NRM: 8.4 (4.3, 12.5) vs. 20 ± 3
Van Besien et al, Biol Blood Marrow Transplant. 2009 May; 15(5):610-7. PMID: 19361753 (1999-2003)	Indirect comparison of pivotal trial data in AML and MDS patients	- Cytogenetic risk	- Age: 5 years younger) - Case mix: 15% more AML patients - Stage of disease: patients with previous HSCT procedure - Risk: more patients beyond CR1 (as per ASBMT classification)	TREO/FLU regimen vs. FLU/MEL regimen (2-years): - OS: 72.8 (65.5, 78.8) vs. 45.7 (32.8-57.8) - NRM: no data

Study **(observation period)**	**Evidence**	**Similarities** **(Characteristics of literature study)**	**Differences** **(Characteristics of literature study)**	**Results of indirect comparison** **(OS/NRM)**
Kawamura et al, Biol Blood Marrow Transplant. 2017 Dec; 23(12):2079-2087. PMID: 28890406 (Not reported)	Indirect comparison of pivotal trial data in AML and MDS patients	- Age	- Risk: higher disease risk (standard, high risk) - Case mix: unmatched donors were allowed (one antigen mismatched related and one locus mismatched unrelated) - Risk: fewer with HCT-CI score	TREO/FLU regimen vs. FM140 regimen (3-years): - OS: 68.4 (60.1, 75.3) vs. 37.0 (26.6-47.4) NRM: 14.2 (9.5, 18.9) vs. 28.0 (23.4, 32.7)
Yerushalmi et al, Bone Marrow Transplant. 2015 Dec; 50(12):1526-35. PMID: 26237166 (2009-2013, historical control 2001-2011)	Published report on open-label single arm trial with treosulfan and indirect comparison with historic control group. Indirect comparison of patient with lymphoid malignancies.	- Age	- Case-mix: patients with prior autoHSCT, differences regarding disease backgrounds - Stage of disease: less prior lines of therapy	TREO/FLU regimen vs. FLU/MEL regimen (3-years): - OS: 54 (36-72) vs. 29 (17-40 - NRM: 24 (14-41) vs. 54 (42-68)
Shimoni et al, 41st Annual Meeting of the EBMT. 22nd - 25th March 2015. Istanbul, Turkey. Abstract O118 (2000-2011)	Retrospective EBMT analysis between TREO and RIC and MAC (no granularity regarding melphalan)	None identified only poster presentation	None identified, only poster presentation	TREO/FLU regimen vs. RIC regimen (5-years) - OS: 47 (41-52) vs. 39 (34-43) - NRM: 33 (28-38) vs. 32 (28-35)

Study **(observation period)**	**Evidence**	**Similarities** **(Characteristics of literature study)**	**Differences** **(Characteristics of literature study)**	**Results of indirect comparison** **(OS/NRM)**
Gran, ASH Annual Meeting 2018; abstract 4364 (2008-2016)	Retrospective EBMT analysis between TREO and NON-TREO RIC and MAC (no granularity regarding melphalan)	None identified, only poster presentation	None identified, only poster presentation	TREO regimen vs. Non-TREO-RIC regimen (5-years) - OS: 62 (52-71) vs. 57 (52-62) - NRM: 10 (4-15) vs. 17 (13-20)

Regarding cyclophosphamide, again various indirect comparisons were presented for the demonstration of significant benefit (table 6). The results collected in the Treosulfan arm of the MC-FludT.14/L Trial II seem to compare favourably with the published scientific literature regarding overall survival and non-relapse mortality. However, the compared patient populations are relatively dissimilar regarding important patient characteristics. These 'crude' indirect comparisons were not considered sufficiently reliable in view of potential confounding.

In addition, a report from Center for International Blood and Marrow Transplant Research (CIBMTR) database has been provided. The objective of this comparison study "medac versus CIBMTR" was the assessment of the comparability of clinically relevant outcomes after alloHSCT of European and US patients. This study was not designed to demonstrate improved efficacy of the treosulfan based regimen over regimens containing cyclophosphamide. The CIBMTR study population included recipients on commonly used myeloablative and RIC regimens in the United States. No matching was performed but both study populations seem to be mostly comparable since patients in the CIBMTR were selected according to the inclusion/exclusion criteria of study MC-FludT.14/L II. It is claimed that overall and event-free survival, relapse incidence as well as treatment related mortality were considerably better with the treosulfan based regimen compared to the cyclophosphamide and busulfan containing regimen (BU/CY). However, these claims and conclusions are not supported by data from the full study report. The data in the full report suggest similar efficacy between the treosulfan arm in trial MC-FludT.14/L and CIBMTR BU/CY data (table 7). The COMP concluded that significant benefit over cyclophosphamide had not been demonstrated at the time of review due to the uncertainty regarding the indirect comparisons and the unsubstantiated claims derived from the "medac versus CIBMTR" analysis.

Table 6. Significant benefit over cyclophosphamide: overview and characteristics of the studies that have been submitted for indirect comparisons

Study **(observation period)**	**Evidence**	**Similarities** **(Characteristics of literature study)**	**Differences** **(Characteristics of literature study)**	**Results of indirect comparison** **(OS/NRM)**
CIBMTR database (2008-2016)	Indirect comparison of pivotal trial data in AML and MDS patients Selected patients from the CIBMTR database (no matching)	- HCT-CI - AML CR1	- Age - Risk: cytogenetic risk	TREO/FLU regimen vs. BU/CY regimen (2-years): - OS: 72.7 (66.8-77.8) vs. 57 (50-62) - NRM: no data
Nagler et al, J Clin Oncol. 2013 Oct 1; 31(28):3549-56. PMID: 23980086 (2004-2010)	Indirect comparison of pivotal trial data in AML	- CR1	- Age: ~20 years younger - Risk: overall low risky patient (low and intermediate cytogenetic risk)	TREO/FLU regimen vs. BU/CY regimen (2-years): - OS: 72.7 (66.8-77.8) vs. 68 ± 2 - NRM: 8.4 (4.3, 12.5) vs. 12 ± 1
Malard et al, Biol Blood Marrow Transplant. 2017 Feb; 23(2):278-284. PMID: 27816650 (2002-2014)	Indirect comparison of pivotal trial data in AML	- Age - CR1	- Case-mix: ~20% of patients were unmatched	TREO/FLU regimen vs. FLAMSA+ BU/CY regimen (2-years): - OS: 72.7 (66.8-77.8) vs. 46.7 (36.1-57.3) - NRM: 8.4 (4.3, 12.5) vs. 31.1 (24-38.4)

Study **(observation period)**	**Evidence**	**Similarities** **(Characteristics of literature study)**	**Differences** **(Characteristics of literature study)**	**Results of indirect comparison** **(OS/NRM)**
Rambaldi et al, Lancet Oncol. 2015 Nov; 16(15):1525-1536. PMID: 26429297 (2008-2012)	Indirect comparison of pivotal trial data in AML	- CR1	- Age: 9 years younger - Risk: lower HCT-CI score	TREO/FLU regimen vs. BU/CY regimen (2-years): - OS: 72.7 (66.8-77.8) vs. 64.2 (56.1-73.4) - NRM: 8.4 (4.3, 12.5) vs. 9.5% (5.5-16.3%)

Table 7. "Medac versus CIBMTR": two-year probabilities of transplant outcomes adjusted for other factors in the final mulitvariate model. Yellow highlights indicate the indirect comparisons of interest: Trial TREO/FLU (FT10) versus BU/CY4

	Probability (95%CI), %
Overall survival	
Trial	58 (51-63)
Flu/Bu4	54 (48-59)
Flu/Bu4+ATG	48 (40-55)
Cy/Bu4	57 (50-62)
Flu/Bu2	55 (49-60)
Flu/Bu2+ATG	47 (40-54)
Event free survival	
Trial	50 (44-55)
Flu/Bu4	49 (43-54)
Flu/Bu4+ATG	41 (33-48)
Cy/Bu	50 (44-55)
Flu/Bu2	42 (36-47)
Flu/Bu2+ATG	32 (25-38)
Relapse	
Trial	25 (20-30)
Flu/Bu4	30 (25-35)
Flu/Bu4+ATG	38 (31-46)
Cy/Bu	28 (23-33)
Flu/Bu2	44 (38-49)
Flu/Bu2+ATG	54 (47-60)
Treatment-related mortality	
Trial	23 (18-28)
Flu/Bu4	22 (18-27)
Flu/Bu4+ATG	22 (15-28)
Cy/Bu	27 (21-32)
Flu/Bu2	13 (9-17)
Flu/Bu2+ATG	14 (10-19)
Chronic GVHD	
Trial	57 (51-63)
Flu/Bu4	51 (45-57)
Flu/Bu4+ATG	38 (31-46)
Cy/Bu	60 (54-65)
Flu/Bu2	44 (38-49)
Flu/Bu2+ATG	31 (24-37)

Regarding thiotepa, one indirect comparison was presented that compares the pivotal trial results to published literature (table 8). The results collected in the Treosulfan arm of the MC-FludT.14/L Trial II seem to compare favourably with the published scientific literature regarding overall survival and non-relapse mortality. However, the compared patient populations are relatively dissimilar regarding important patient characteristics. These 'crude' indirect comparisons were not considered sufficiently reliable in view of potential confounding.

Additionally, significant benefit was claimed in the paediatric patient population as an add-on to thiotepa containing regimens. Reference was made to the most recent 2016 "Guidelines for Hematopoietic Stem Cell Transplantation (HSCT) in Childhood myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukaemia (JMML) for Patients enrolled in EWOG-MDS Studies". Clinical evidence is presented in this consensus guidance document in support of the recommendation to use treosulfan based regimens, which contain thiotepa, in HSCT patients with refractory cytopenia of childhood (RCC), secondary MDS following treatment for a first malignancy, secondary MDS following severe aplastic anaemia, or juvenile myelomonocytic leukaemia (with somatic KRAS mutation or no mutation in one of the known genes). The COMP acknowledged that there exist paediatric patient populations that will benefit from a combination therapy of treosulfan and thiotepa. This will also be reflected in the posology section of the summary of product characteristics (SmPC) of Trecondi. The COMP considered that Trecondi has significant benefit over thiotepa on the grounds of a clinically relevant advantage, because it has been established that it provides improved clinical efficacy when combined with thiotepa in certain paediatric patients that are undergoing HSCT.

Table 8. Significant benefit over thiotepa: overview and characteristics of the studies that have been submitted for indirect comparisons

Study **(observation period)**	**Evidence**	**Similarities** **(Characteristics of literature study)**	**Differences** **(Characteristics of literature study)**	**Results of indirect comparison** **(OS/NRM)**
Eder et al, Eur J Haematol. 2016 Jan; 96(1):90-7. PMID: 25807864 (2000-2012)	Indirect comparison of pivotal trial data in AML	None identified based on available information	- Age: ~12 years younger - Stage of disease: CR1 only	TREO/FLU regimen vs. TT-based regimen (2-years): - OS: 72.7 (66.8-77.8) vs. 61.4 (51.9-70.8) - NRM: 8.4 (4.3, 12.5) vs. 22.4 (14.9-30.7)

5. COMP position adopted on 19 December 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of conditioning treatment prior to haematopoietic progenitor cell transplantation (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.67 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition remains chronically debilitating and can be life-threatening due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also associated with complications such as graft-versus-host disease;
- satisfactory methods of treatment of the condition have been authorised in the European Union. Trecondi was found to be of significant benefit over busulfan and thiotepa. Significant benefit over busulfan was accepted on the basis of a randomised controlled trial showing numerical improvements with regards to event free survival, overall survival and non-relapse mortality in patients treated with a Trecondi based regimen when compared to outcomes in patients treated with a busulfan based regimen. Significant benefit over tiothepa was supported by clinical data from the scientific literature supporting that Trecondi based regimens in combination with thiotepa are a preferred treatment option in paediatric patients undergoing HSCT in malignant diseases;
- however, significant benefit of Trecondi over melphalan and cyclophosphamide has not been demonstrated. Significant benefit over melphalan and cyclophosphamide was claimed on the grounds of a clinically relevant advantage. Indirect literature-based comparisons were provided to substantiate the claim that overall survival and non-relapse mortality associated with Trecondi-based conditioning regimen compare favourably to published efficacy data that were collected with other conditioning regimens that contain melphalan or cyclophosphamide. These indirect comparisons were not considered sufficiently reliable in view of potential confounding. The claim for a significant benefit of Trecondi over melphalan and cyclophosphamide on the grounds of a clinically relevant advantage was therefore not accepted.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The Committee for Orphan Medicinal Products has recommended that Trecondi, treosulfan, EU/3/04/186 for conditioning treatment prior to haematopoietic progenitor cell transplantation is removed from the Community Register of Orphan Medicinal Products.

6. Appeal to the negative opinion adopted on 19 December 2018

Grounds for appeal

The sponsor submitted detailed grounds for appeal on 20 March 2019. The detailed grounds for appeal were further presented by the sponsor at an oral explanation before the COMP on 15 April 2019.

Comments on the grounds of appeal

In its opinion of 19 December 2018, the COMP had concluded that significant benefit of Trecondi over melphalan and cyclophosphamide has not been demonstrated. The sponsor appealed the negative opinion by further elaborating on the efficacy comparisons of the proposed product versus melphalan- and cyclophosphamide-containing induction regimens. This exercise was performed by juxtaposing MC-FludT.14/L test arm observations to EBMT registry data, CIBMTR registry data, and literature studies.

- Claims based on EBMT registry data

Firstly, the sponsor submitted a "Re-analysis of EBMT-registry data on Fludarabine/Melphalan and Busulfan/Cyclophosphamide based conditioning treatment compared to Fludarabine/Treosulfan based conditioning of adult AML and MDS patients treated in MC-FludT.14/L phase III by matched pairs". For the purpose of this comparison, propensity score based matching was performed, taking into consideration the following variables: patient age, sex, indicator of disease of secondary origin, disease stage, MDS WHO subclassification (for MDS only), Karnofsky score, donor type, source of stem cells, calendar year, gender mismatch, donor age, time diagnosis-transplant, CMV combination patient-donor, and, when convenient HCT-comorbidity index. The COMP noted that a considerable number of patients from the test arm had been excluded from this analysis, as no matches could be identified in the EBMT registry for the purpose of the comparison. In particular, approximately 70% of the test data for MDS were excluded, as well as approximately 40-55% of AML test data.

This significant exclusion of test data was also acknowledged by the sponsor in their grounds for appeal. Secondly, and in an effort to compensate for this exclusion, the sponsor included two further analyses in the context of the EMBT-based exercise. First, a reanalysis was performed which allowed for control patients that used MEL/FLU and CY/BU in combination with other chemotherapeutics (extended definition of controls). However, this extended analysis did not result in any considerable additional matches, and the reported results were similar to the results when using the strict definitions of controls (see tables 9 and 10 below). Second, a sensitivity analysis using adjusted Cox regression methods without performing 1:1 patient-matching beforehand was also conducted.

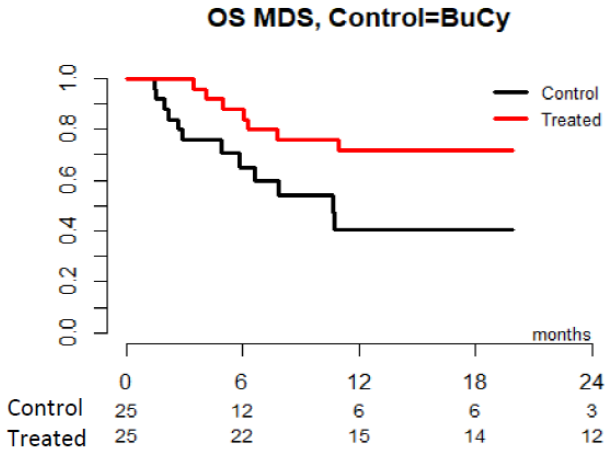
Results of the matched comparison were presented separately for AML and MDS. For MDS, the matched 2-year estimates for Overall survival (OS), relapse incidence (RI) and non-relapse mortality (NRM) are presented in table 9; the relevant results for AML are presented in table 10 below.

Table 9. Sourced from the EMBT report - results for matched MDS comparison

		OS	p	RI	p	NRM	p
Strict	**FluMel**	56.5 (33.9-79.1)	0.57 (0.62)	23.8 (5.1-42.5)	0.5 (0.74)	12.5 (0-25.9)	0.72 (0.71)
	FluTreo	70 (53.6-86.4)		13.3 (1.2-25.5)		16.7 (3.3-30)	
	BuCy	30.5 (6.1-54.9)	0.01 (0.01)	25.8 (1.8-49.9)	0.098 (0.31)	43.1 (17.2-69)	0.17 (0.13)
	FluTreo	72 (54.4-89.6)		4 (0-11.7)		24 (7.3-40.7)	
Extended	**FluMel**	51.7 (32.8-70.7)	0.09 (0.18)	10.7 (0-22.3)	0.58 (>0.99)	40.3 (22.2-58.4)	0.09 (0.13)
	FluTreo	74.3 (59.8-88.8)		5.7 (0-13.4)		20 (6.7-33.3)	

An improved OS is reported for the MDS population in favour of the treosulfan regimen. Other endpoints examined have not yielded statistically significant differences.

Figure 2. Sourced form EBMT report MDS, OS comparison using strict controls

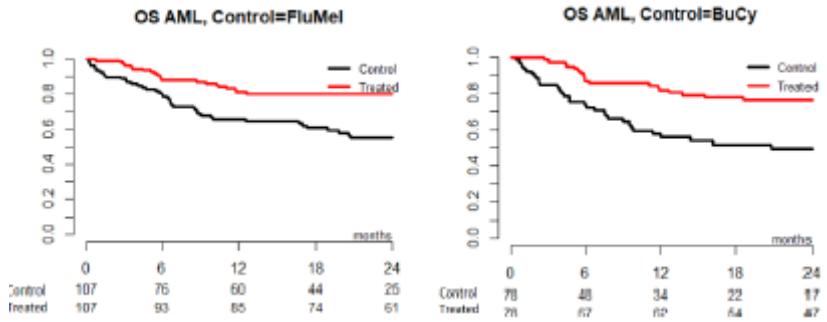


With regards to the AML population, the matched comparisons yielded statistically significant differences in OS as well as NRM.

Table 10. Sourced from EBMT report - results for matched AML comparison

		OS	p	RI	p	NRM	p
Strict	**FluMel**	58.7 (48.3-69.1)	0.04 (0.21)	24.7 (15.8-33.6)	0.28 (0.11)	17.5 (9.6-25.5)	0.019 (0.11)
	FluTreo	72.7 (63.7-80.7)		30.6 (21.9-39.4)		6.4 (1.8-11)	
	BuCy	49.2 (36.4-62.1)	<0.001 (<0.001)	30.3 (18.6-42)	0.98 (0.46)	23.5 (13.1-33.9)	<0.001 (0.001)
	FluTreo	76.4 (66.8-85.9)		29.1 (18.8-39.4)		3.9 (0-8.2)	
Ext	**FluMel**	54.9 (44.5-65.4)	<0.001 (0.003)	18.4 (10.4-26.3)	0.31 (0.58)	26.1 (17.1-35)	<0.001 (<0.001)
	FluTreo	80.2 (72.7-87.8)		23.4 (15.1-31.7)		4.7 (0.7-8.7)	

Figure 3. OS in the matched comparison in AML population using strict definitions of Fludarabine /Melphalan and Busulfan/Cyclophosphamide regimens



The COMP acknowledged the methodology of the submitted matched comparisons but was seriously concerned about the large number of patients in the test arm that could not be matched to the registry patients (applicable to both strict and extended definitions of treatment controls). It was noted that only 25 out of 78 treated MDS patients were matched for the purpose of the propensity score analysis for the strictly defined control regimens. This means that approximately 70% of the test data for MDS were excluded from the sponsor's analysis. Similarly, out of 174 treated AML patients, only 107 or 78 (depending on the control used, see figure 3 above) patients were matched. This means that, again, a

very significant percentage of test data (approximately 40% to 55%) were excluded from the sponsor's analysis.

Under both the strict and extended definitions of controls, similarly significant amounts of data were excluded from the matched analysis. While the sponsor does not explicitly state the number of matches achieved with the extended definition, it is stated [by reference to MDS] that "In fact if using the strict def we would exclude only 4 controls". In addition, the number of AML patients matched to extended controls is shown to be 110 (for both comparators), which is very close to the number of AML patients included in the strict analysis. Therefore, both definitions of controls (strict and extended) resulted in the exclusion of very significant numbers of test data from the sponsor's analysis.

The COMP concluded that due to the high number of patients excluded from the comparisons, the results were not representative of the totality of studied population and that for this reason the matched comparisons could not be relied upon for the demonstration of a significant benefit. The sponsor was asked to comment during the OE on the characteristics of the excluded patients and on any conclusions that could be drawn from those characteristics on the effects of the product. The sponsor responded that they had not looked into that issue.

As also described above, an additional Cox-regression sensitivity analysis comparing the treosulfan clinical trial versus the EBMT registry data was also provided to compensate for the loss of data and to substantiate the claim of improved survival associated with Trecondi-based conditioning. The results of this (non-matched) Cox regression analysis were in line with the results reported for the matched comparisons above. In the MDS population, an improvement of OS at 2 years versus Bu/CY (but not Flu/Mel) was reported, while in the AML population, improvements in OS and NRM were reported. The COMP noted that this analysis would not be of equal weight to a matched comparison, because it had not been justified that all possible confounders have been taken into consideration in the model used.

- Claims based on CIBMTR registry data

With regard to comparisons versus CIBMTR data, the sponsor presented two analyses. A first comparison of the treosulfan treatment arm from the pivotal trial versus busulfan/cyclophosphamide and other busulfan regimens was presented (CIBMTR report SC17-04b) based on a multivariate analysis. This was a reanalysis of the CIBMTR data already presented in the SC17-04 report in the LOQ stage. The sponsor refers to this analysis as "direct", but the COMP considered that this term would be more appropriate when controls are included in the same clinical study. In any case, an improvement in OS with TREO/FLU versus BU/CY was claimed. The adjusted 2-year OS rate was reported to be 72% (95% CI, 65-77%) with TREO/FLU and 57% (95% CI, 51-63%) with BU/CY. The OS results from the multivariate analysis are stated in the table below, as copied from the submitted report. Despite the fact that the outcomes reported by the sponsor are in line with the other observations, the outcomes still have to be interpreted with caution, as the report noted differences between the compared groups; in particular, in terms of age, performance score, cytogenetic risk, times of intervention. The COMP noted that this was not a matched comparison (as the one performed using EBMT data); as such, this comparison was insufficiently robust to demonstrate improved efficacy of treosulfan over cyclophosphamide.

Table 11. Multivariate analysis: OS results. Source: CIBMTR report

	N	HR	Lower CL	Upper CL	P-value
Conditioning regimen:					
Trial	268	1.00			<.0001
Flu/Bu4	327	1.82	1.35	2.46	<.0001
Flu/Bu4+ATG	169	2.18	1.56	3.04	<.0001
Cy/Bu4	317	1.65	1.20	2.25	0.002
Flu/Bu2	318	1.86	1.37	2.52	<.0001
Flu/Bu2+ATG	199	2.22	1.61	3.06	<.0001

A second indirect comparison that also includes melphalan-based regimens was conducted. The sponsor argued an improved OS effect when the data from Trial II, giving a HR of 0.64 (0.48-0.87) between the two arms, was juxtaposed to the results from the 2017 CIBMT report (report SC17-01) where MEL/FLU vs. BU/FLU gives a HR of 0.81 (0.64-1.03), and MEL/FLU/ATG/Campath vs. BU/FL which gives a HR of 1.20 (0.86-1.67). Following this, a favourable outcome was assumed for TREO/FLU vs. MEL/FLU [HR of 0.79 (0.54-1.17)] and for TREO/FLU vs. MEL/FLU/ATG/Campath [HR of 0.53 (0.34-0.84)].The COMP considered that this comparison again suffered from the indirect nature of the comparisons which is prone to confounding factors that influence the outcome of HSCT patients, independent of their conditioning regimen. As such, this non-matched comparison is not sufficiently robust to establish significant benefit.

- Claims based on indirect literature comparisons

Finally, a literature-based comparison was also provided focusing on more relevant references compared to the LOQ stage. Following predefined criteria such as concomitant use of other chemotherapeutics or treatment of patients from other disease areas potentially relevant publications were selected. As a result, two relevant studies on cyclophosphamide (Rambaldi, Lancet Oncol. 2015; 16(15): 1525-1536, Dhere et al, Leuk Lymphoma. 2018 Apr;59(4):837-843) were identified and a total of four studies for melphalan (Di Stasi et al, Biol Blood Marrow Transplant. 2014 Dec;20(12):1975-81, Dhere et al, Leuk Lymphoma 2018 Apr;59(4):837-843, Kawamura Biol Blood Marrow Transplant. 2017; 23(12): 2079-2087, Baron et al Cancer. 2015 Apr 1;121(7):1048-55).

From those studies, the following three were in particular discussed in the grounds of appeal. A study on patients treated with cyclophosphamide-based conditioning regimen was identified where differences in the population compared to MC-FludT.14/L Trial II are rather known to be associated with an improved outcome (Rambaldi, Lancet Oncol. 2015; 16(15): 1525-1536). Still in this study the observed OS was numerically lower than in treosulfan-treated patients of study MC-FludT.14/L Trial II supporting the overall conclusion of significant benefit based on improved efficacy (cyclophosphamide: 64% [95% CI 56-73%] versus treosulfan 73% [95% CI 66-79%]). Improved efficacy of treosulfan over melphalan is in particular argued on the basis of a comparison of results from MC-FludT.14/L Trial II to the study by Kawamura et al. showing improved OS in AML patients (Kawamura Biol Blood Marrow Transplant. 2017; 23(12): 2079-2087): The 3-year OS was 37% (95% CI: 27-47%) in this study compared to 68% (95% CI 60-75%) in the medac trial MC-FludT.14/L Trial II for patient treated with treosulfan. Similarly, a retrospective study comparing treatment of non-Hodgkin lymphoma (NHL) patients demonstrated higher efficacy of a TREO/FLU-based regimen over a MEL/FLU-based regimen (Yerushalmi Bone Marrow Transplant. 2015; 50(12): 1526-1535). The sponsor acknowledged in their grounds for appeal that "the heterogeneity of studies and the limited amount of data available did not allow for a formal meta-analysis", but argued that the data would support significant benefit because OS was numerically higher for patients with treosulfan with consistency over all studies.

This was not considered to represent a new argument as all of the publications had already been previously reviewed by the COMP and the Committee considered that the comparability of the juxtaposed populations was not acceptable. It was considered that the indirect nature of the

comparison between the treosulfan clinical trial data and literature pertaining to other regiments is prone to variables not being evenly distributed across the compared populations. This uneven distribution of the variables may influence the outcome of HSCT independently of the induction regiment used. In view of those considerations, the COMP maintained the view that the data was not sufficiently robust to demonstrate the existence of a clinically relevant advantage (of improved efficacy).

By way of summary, the COMP considered that most of the comparisons presented by the sponsor were non-matched regarding the patient particulars which may influence the outcome of HSCT independently of the induction regimen used. Only one such matched comparison (using both strict and extended definitions of control regimens) was included, using 1:1 matching based on propensity scores versus data from the EBMT registry. However, this comparison has significant limitations regarding the large number of excluded patients that could not be matched to an appropriate control in the EBMT registry. Therefore, the result of the comparisons was not considered representative of the proposed target population. Moreover, with regard to the non-matched comparisons, it was considered that the relevant characteristics of the patients and treatments were not balanced across the compared populations. Such differences could influence the outcome of HSCT independently of the induction regimen used. As such, the sponsor failed to ensure the robustness of the comparisons made and, therefore, failed to demonstrate the existence of a significant benefit of Trecondi over melphalan and cyclophosphamide.

7. COMP final position on review of criteria for orphan designation adopted on 8 May 2019

Based on the assessment of the detailed grounds for appeal and the explanations presented by the sponsor during the oral explanation, the COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated orphan medicinal product;
- the prevalence of conditioning treatment prior to haematopoietic progenitor cell transplantation (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.67 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition remains chronically debilitating and can be life-threatening due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also associated with complications such as graft-versus-host disease;
- significant benefit over busulfan was accepted on the basis of a randomised controlled trial showing numerical improvements with regards to event free survival, overall survival and non-relapse mortality in patients treated with a Trecondi based regimen when compared to outcomes in patients treated with a busulfan based regimen;
- significant benefit over thiothepa was supported by clinical data from the scientific literature supporting that Trecondi based regimens in combination with thiotepa are a preferred treatment option in paediatric patients undergoing HSCT in malignant diseases;
- in the context of the initial opinion of the COMP, significant benefit of Trecondi over melphalan and cyclophosphamide has not been demonstrated. Significant benefit over melphalan and cyclophosphamide was claimed on the grounds of a clinically relevant advantage. Indirect literature-based comparisons were provided to substantiate the claim that overall survival and non-relapse mortality associated with Trecondi-based conditioning regimen compare favourably to published efficacy data that were collected with other conditioning regimens that contain melphalan or cyclophosphamide. These indirect comparisons were not considered sufficiently reliable in view of potential confounding. The claim for a significant benefit of Trecondi over melphalan and cyclophosphamide on the grounds of a clinically relevant advantage was therefore not accepted;
- in the context of the appeal, the sponsor presented a matched 1:1 comparison based on propensity scores, comparing the data from the pivotal trial to data from the EBMT registry, but a significant number of patients could not be matched, and as such the outcomes were not considered representative of the studied population. Therefore, the presented matched-patient analysis versus EBMT registry data was not considered conclusive evidence, and as such the sponsor failed to support the existence of a significant benefit. Further non-matched comparisons (including a Cox-regression analysis versus the EBMT registry data, comparisons versus CIBMTR data, juxtaposition of the clinical study data versus selected literature studies) were considered by the COMP as insufficiently robust since it had not been established that relevant characteristics of the patients and treatments were balanced across the compared populations and since such differences in patients' characteristics could influence the outcome of HSCT independently of the induction regimen used;

- therefore, the COMP considered that the provided comparisons of treosulfan with melphalan and cyclophosphamide, respectively, were insufficiently robust and did not adjust for all potential confounding factors that could have influenced the outcome of the comparisons independently of the regimens compared. Consequently, the committee considered that the sponsor failed to establish that Trecondi provides a significant benefit over melphalan and cyclophosphamide.

The COMP, having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The COMP recommends that Trecondi, treosulfan (EU/3/04/186) for conditioning treatment prior to haematopoietic progenitor cell transplantation is removed from the Community Register of Orphan Medicinal Products.