CLOSING REPORT

A prospective, single-arm pilot study on treosulfan, fludarabine, and cyclophosphamide (TreoFC) as conditioning treatment before haploidentical hematopoietic stem cell transplantation for older patients with acute myeloid leukemia or myelodysplastic syndrome	
Investigational drug(s)	Treosulfan (Trecondi®), MEDAC GmbH (Deutschland) Fludarabin (Neoflubin®), EBEWE Pharma GmbH (Deutschland) Cyclophosphamid (Endoxan®), BAXTER ONCOLOGY GmbH (Deutschland)
Reporting period	February 04, 2022 – February 17, 2024
Version / Date of the report	Version 1.0 / February 17, 2024
Sponsor(s) name(s) and address(es)	Medical University of Vienna Department of Internal Medicine I Waehringer Guertel 18-20 1090 Vienna Austria

Confidentiality Statement

SIGNATURES

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1 LIST OF ABBREVIATIONS

AML	Acute myeloid leukemia
BASG	Bundesamt für Sicherheit im Gesundheitswesen
CTCAE	Common Toxicity Criteria of Adverse Events
DSUR	Development Safety Update Report
HCT-CI	Hematopoietic Cell Transplantation Comorbidity Index
HLA	Human Leukocyte Antigen
HSCT	Hematopoietic Stem Cell Transplantation
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
LLT	Lower level terms
MDS	Myelodysplastic Syndrome
NRM	Non-relapse Mortality
OS	Overall Survival
RFS	Relapse-free Survival
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction

2 INTRODUCTION

This document is the closing report for the study "TreoFC conditioning before haploidentical HSCT," hereafter referred to as "TreoFC study," covering the period from February 04, 2022 (first patient, first visit) to February 17, 2024 (end of recruitment). The study was closed prematurely due to slow accrual.

The Ethics Committee of the Medical University of Vienna granted the first authorization to conduct this clinical trial on November 15, 2021. The study was initiated in January 2022, and the first patient was included in February 2022.

The TreoFC study was a single-center, prospective, single-arm trial investigating Treosulfan, Fludarabine, and Cyclophosphamide (investigational medicinal products; IMPs) as conditioning therapy before haploidentical HSCT in patients at high risk for complications (age ≥50 years and/or HCT-CI ≥3) after conventional conditioning. This study aimed assessed overall survival and secondary transplant-related outcomes following the study protocol. This study is being conducted at the Department of Medicine I, Stem Cell Transplantation Unit, Medical University of Vienna.

Table 1: Investigational Medicinal Products (IMPs)

IMP	**Role in the trial**
Treosulfan	Study drug (all patients); administered as 10 g/m² on days -4 to -2 before haploidentical HSCT
Fludarabine	Study drug (all patients); administered as 30 mg/m² on days -6 to -2 before haploidentical HSCT
Cyclophosphamide	Study drug (All patients); administered as 14,5 mg/kg on days -6 and -5 before haploidentical HSCT

3 WORLDWIDE MARKETING APPROVAL STATUS

Treosulfan, fludarabine, and cyclophosphamide are approved for several indications in different formulations summarized in Table 2 (substances and approval dates were taken from the BASG medicinal product database).

Table 2: Approved drugs containing the IMPs

Name	**Active substance**	**Indication**	**Approval**	**Route of administration**
Trecondi	Treosulfan	Conditioning before HSCT	June 20, 2019	Intravenous
Treosulfan telomer	Treosulfan	Advanced ovarian cancer	March 25, 2019	Intravenous

Neoflubin	Fludarabine phosphate	Chronic lymphocytic leukemia	July 09, 2008	Intravenous
Fludarabine Accord	Fludarabine phosphate	Chronic lymphocytic leukemia	January 07, 2015	Intravenous
Endoxan	Cyclophosphamide	Various malignancies, conditioning before HSCT	November 11, 1959	Intravenous, oral
Cyclophosphamid Sandoz & other generics	Cyclophosphamide	Various malignancies, conditioning before HSCT	September 19, 2014	Intravenous, oral

4 ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

No actions were taken for safety reasons during the study period. The first DSUR was pushlised on June 16, 2023.

5 CHANGES TO REFERENCE SAFETY INFORMATION

The summary of medicinal product characteristics (SMPCs) of the IMPs served as the Reference Safety Information (RSI) during the reporting period. The SMPC of Trecondi was updated on January 25, 2023. The changes made in the updated SMPC only concerned the indication of the product without updated safety information.

6 INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

Table 3: Ongoing or completed studies

Study ID	Study name	Phase	Country	Dosing regimen (Treosulfan)	Study population	First patient first visit	Planned enrolment	Recruiting status
NCT04965597	Treosulfan-Based Conditioning Regimen Before a Blood or Bone Marrow Transplant for the Treatment of Bone Marrow Failure Diseases (BMT CTN 1904)	II	USA	Treosulfan, fludarabine (dosing not known)	Patients with bone marrow failure undergoing HSCT	April 19, 2022	40	Active, recruiting

NCT05636787	Clinical Trial Investigating the Chemotherapeutic Compound Treosulfan (Treosul Ideogen) in Myeloma Patients (TreoMel)	II	Switzerland	Treosulfan/Melphalan versus Melphalan	Patients with myeloma undergoing autologous HSCT	May 04, 2023	120	Active, recruiting
EUDRACT 2021-004730-11	TreoFC conditioning before haploidentical HSCT	II	Austria	Treosulfan, fludarabine, and cyclophosphamide as conditioning before haploidentical HSCT	Patients with AML or MDS at increased risk for NRM (age ≥50 or HCT-CI ≥3)	February 04, 2022	30	Closed, November 2023

7 DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

7.1 Subject Log and Follow-up

Subject ID	Date of Informed Consent	Enrollment Date	Date last follow-up, status
001	2022-02-04	2022-02-04	2023-11-28, Alive
002	2022-03-08	2022-03-10	2022-08-10, Dead (Relapse)
003	2022-04-06	2022-04-13	2024-02-14, Alive
004	2022-07-26	2022-07-26	2024-02-01, Alive
005	2022-08-04	2022-08-16	2022-10-18, Dead (Non-relapse)
006	2022-08-12	2022-08-12	2023-11-29, Alive
007	2022-08-15	2022-08-16	2022-11-21, Dead (Non-relapse)
008	2022-11-14	Screening faiure	
009	2023-03-21	Screening failure	

7.2 Reference information for adverse events

The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (published November 27, 2017) was used to code serious adverse events (SAEs). The line listing and summary tabulations are arranged by primary System Organ Class (SOC) and CTCAE term level.

7.3 Cumulative Summary Tabulations of Serious Adverse Reactions

No serious adverse reactions occurred during the reported study period.

7.4 Line Listing of Serious Adverse Events during the Reporting Period

Table 4: Line listing of SAEs

System Organ Class	CTCAE Term	Patient Number	Age	Gender	SAE Onset Date	SAE Stop Date	Type of SAE	Outcome	Date of HSC	Relationship to study treatment
Infections and infestations	Enterocolitis infectious (Clostridoides difficile)	002	62	Male	20.06.2022	02.07.2022	Hospitalization	Resolved	17.03.2022	Not related
Metabolism and nutrition disorders	Hyponatremia	002	62	Male	23.06.2022	02.07.2022	Hospitalization	Resolved	17.03.2022	Not related
NA	AML relapse	002	62	Male	23.06.2022	10.08.2022	Results in Death	Fatal	17.03.2022	Not related
NA	MDS relapse	003	62	Male	26.06.2023		Hospitalization	Not resolved	27.04.2022	Not related
Infections and infestations	Enterocolitis infectious	004	60	Male	11.11.2022	22.11.2022	Hospitalization	Resolved	02.08.2022	Not related
Metabolism and nutrition disorders	Hypokalemia	004	60	Male	11.11.2022	12.11.2022	Hospitalization	Resolved	02.08.2022	Not related
Infections and infestations	Enterocolitis infectious	004	60	Male	24.01.2023	31.01.2023	Hospitalization	Resolved	02.08.2022	Not related
Infections and infestations	Enterocolitis infectious	004	60	Male	23.04.2023	29.04.2023	Hospitalization	Resolved	02.08.2022	Not related
Infections and infestations	Other (Infection without identified focus)	004	60	Male	22.06.2023	27.06.2023	Hospitalization	Resolved	02.08.2022	Not related

NA	Graft-versus-Host Disease	004	60	Male	16.08.2023	04.09.2023	Hospitalization	Resolved	02.08.2022	Not related
Infections and infestations	Shingles	004	60	Male	11.11.2023	17.01.2024	Hospitalization	Resolved	02.08.2022	Not related
Infections and infestations	Febrile neutropenia	005	63	Male	30.08.2022	26.09.2022	Is Life-threatening	Resolved	23.08.2022	Related
Renal and urinary disorders	Acute kidney injury	005	63	Male	01.09.2022	18.10.2022	Results in persisting disability	Not resolved	23.08.2022	Not related
Hepatobiliary disorders	Sinusoidal obstruction syndrome	005	63	Male	31.08.2022	18.10.2022	Important medical event	Not resolved	23.08.2022	Unlikely
Nervous system disorders	Peripheral motor neuropathy	005	63	Male	26.09.2022	18.10.2022	Results in persisting disability	Not resolved	23.08.2022	Not related
Infections and infestations	Sepsis (Candida)	005	63	Male	23.09.2022	18.10.2022	Fatal	Results in death	23.08.2022	Not related
Infections and infestations	Sepsis (Candida)	006	61	Male	12.09.2022	17.11.2022	Is Life-threatening	Resolved	24.08.2022	Related
Renal and urinary disorders	Acute kidney injury	006	61	Male	13.09.2022	15.12.2022	Is Life-threatening	Resolved	24.08.2022	Not related
Infections and infesations	Sepsis (Staphylococcus aureus)	006	62	Male	08.11.2022	17.12.2022	Hospitalization	Resolved	24.08.202	Not related
Gastrointestinal disorders	Gastric hemorrhage	006	62	Male	29.10.2022	30.11.2022	Is Life-threatening	Resolved	24.08.2022	Not related
Immune system disorders	Cytokine release syndrome	007	66	Male	30.09.2022	05.10.2022	Hospitalization	Resolved	09.09.2022	Not related

Injury, poisoning, procedural complication	Other (Hemorrhage after bone marrow biopsy)	007	66	Male	23.10.2022	25.10.2022	Hospitalization	Resolved	09.09.2022	Not related
Gastrointestinal disorders	Lower gastrointestinal hemorrhage	007	66	Male	13.11.2022	21.11.2022	Hospitalization	Not resolved	09.09.2022	Not related
Infections and infestations	Lung infection	007	66	Male	13.11.2022	21.11.2022	Results in Death	Fatal	09.09.2022	Not related

7.5 Cumulative Summary Tabulations of Serious Adverse Events during the Reporting Period

System Organ Class **CTCAE Term**	Number of events
Infections and infestations	**10**
Enterocolitis infectious	4
Sepsis	3
Lung infection	1
Febrile neutropenia	1
Other (unknown focus)	1
Renal and urinary disorders	**2**
Acute kidney injury	2
Metabolism and nutrition disorders	**2**
Hyponatremia	1
Hypokalemia	1
Gastrointestinal disorders	**2**
Gastric hemorrhage	1
Lower gastrointestinal hemorrhage	1
Hepatobiliary disorders	**1**
Sinusoidal obstruction syndrome	1
Immune system disorders	**1**
Cytokine release syndrome	1
Nervous system disorders	**1**
Peripheral motor neuropathy	1
Injury, poisoning, procedural complication	**1**
Other (Hemorrhage after bone marrow biopsy)	1
NA	**3**
AML relapse	1
MDS relapse	1
Graft-versus-Host disease	1

8 OVERALL SAFETY ASSESSMENT

We report 23 SAEs in 6 patients during the reporting period. Most observed SAEs were unrelated to the study treatment (IMPs) but are frequent adverse events after allogeneic HSCT. No SARs were reported.

During the study period, 3/7 patients died while participating in the study. One patient died due to disease relapse, and two died due to a non-relapse event. The study protocol defined a premature

termination due to safety if four non-relapse deaths occur after including 10 patients. This threshold was not reached. The observed non-relapse mortality rate of 28% (2/7) lay in the range of other published cohorts with similar patient characteristics undergoing haploidentical HSCT (e.g., [2, 3])

There were no new significant risks except those already discussed in the sections above.

9 Study closure

9.1 Reason for premature study closure

The study was closed prematurely due to slow accrual. The study protocol aimed to include 30 patients, and the last visit of the first patient was projected to be in January 2024. The study accrued 7 patients in the mentioned period, less than 25% of the initial recruitment goal. Hence, the study could not have been completed within a reasonable time, and early termination was requested on February 17, 2024.

The reasons for slow accrual were manifold and included tight inclusion criteria, preference and availability of matched related donors for most patients undergoing HSCT at our institution, and understaffing.

9.2 Follow-up of included subjects

Patients participating in the study are included in our clinic's HSCT survivors program and undergo regular medical visits in our outpatient clinic. Hence, patient health is not compromised by the early termination of the study.

10 REFERENCES

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3. Bazarbachi, A., et al., *Comparable outcomes of haploidentical transplant with TBF conditioning versus matched unrelated donor with fludarabine/busulfan conditioning for acute myeloid leukemia.* Bone Marrow Transplant, 2021. **56**(3): p. 622-634.