CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Number	208264
Application Type	Type 5
Priority or Standard	Standard
Submit Date(s)	March 31, 2016.
Received Date(s)	March 31, 2016.
PDUFA Goal Date	January 31, 2017
Mid-cycle Meeting	June 20, 2016.
Review Date	December 23, 2016.
Office / Division	Office of Hematology and Oncology Products / Division of Hematology Products
Primary Reviewer	Rosanna Setse, MD, PhD.
Team Leader	Donna Przepiorka, MD, PhD.
Established Name	Thiotepa
(Proposed) Trade Name	Tepadina
Therapeutic Class	L01A Alkylating agents
Applicant	Adienne
Formulation(s)	15 mg and 100 mg, Injection, Powder, Lyophilized, for Solution
Dosing Regimen	Two administrations of 5 mg/kg given intravenously approximately 12 hours apart on Day -6 before allogeneic HSCT in conjunction with high-dose busulfan and cyclophosphamide
Indication(s)	• To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor cell transplantation for pediatric patients with class 3 β-thalassemia. • For treatment of adenocarcinoma of the breast or ovary. • For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities. • For treatment of superficial papillary carcinoma of the urinary bladder.

Note: For the purposes of this review, "Tepadina" refers to the drug under review, "Thiotepa for Injection, USP" refers to formulations stated to comply with the USP monograph, and "thiotepa" refers to any therapeutic thiotepa, including those of unknown provenance.

Table of Contents

Table of Tables

Table of Figures

Table of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
ALG	Antilymphocyte globulin
ANC	Absolute neutrophil count
ASCT	Allogeneic stem cell transplantation
ATG	Antithymocyte globulin
BK	Polyomavirus hominis 1
BMT	Bone marrow transplant
BP	Blood pressure
BU	Busulfan
CBT	Cord blood transplantation
CMV	Cytomegalovirus
CRF	Case report form
CI	Confidence interval
CNS	Central nervous system
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYC	Cyclophosphamide
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European union
FAS	Full analysis set
FDA	Food and Drug Administration
FLU	Fludarabine
G-CSF	Granulocyte colony-stimulating factor
GVHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HLA	Human leukocyte antigen
HSCT	Hematopoietic progenitor (stem) cell transplantation
HSCT	Hematopoietic stem cell transplantation
IBD	International Birth Date
ISS	Integrated Summary of Safety
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Matched sibling donor
MUD	Matched unrelated donor
NA	Not available
4-OHCP	4-hydroxycyclophosphamide
NOS	Not otherwise specified
PBSC	Peripheral blood stem cells
PBSCT	Peripheral blood stem cell transplantation

PT	Preferred terms
PK	Pharmacokinetics
PSUR	Periodic Safety Update Report
TFS	Thalassemia Free Survival
QTc	Corrected QC
TEAE	Treatment emergent adverse events
RBC	Red blood cells
RCT	Randomized control trial
RD	Related donor
SAE	Serious adverse event
SAP	Statistical analysis plan
SCD	Sickle cell disease
SD	Standard deviation
SOC	System organ class
SPC	Summary of Product Characteristics
TRM	transplant-related mortality
TBI	Total body irradiation
TEAE	Treatment emergent adverse events
TEPA	Triethylenephosphoramide
TREO	Treosulfan
TT	Thiotepa
UD	Unrelated donor
VOD	Veno-occlusive disease
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends regular approval of Tepadina for the indication "to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 β-thalassemia". Approval is based on the finding of 0% incidence of graft rejection in Class 3 thalassemia patients treated with a Tepadina containing regimen for conditioning prior to undergoing HLA-identical, sibling allogenic HSCT.

This conclusion is strengthened by the finding of comparable safety outcomes (transplant related mortality, treatment emergent adverse reactions and graft-versus-host disease rates) in patients treated with Tepadina compared to a historical group of patients treated with the same conditioning regimen but without Tepadina. Efficacy and safety results from a systematic review of the published literature were also consistent with the findings from the pivotal study supporting this application.

1.2 Basis of the Recommendation

Table 1: Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ß-thalassemia is the most severe form of thalassemia and results from reduced or absent production of beta-globin gene that leads to ineffective erythropoiesis and hemolytic anemia. • The current conventional treatment for thalassemia major consists of chronic transfusion and iron chelation therapy throughout life. • Despite the use of chronic transfusions and development of newer chelating agents, thalassemia remains a progressive disease with major complications related to the disease and treatment associated with early death.	Thalassemia patients require chronic transfusions and iron chelation therapy. There are limited treatment options for these patients.
Unmet Medical Need	• Bone marrow transplantation is the only treatment option that can lead to cure of thalassemia. • Patients in class 3 thalassemia are considered at high risk for graft rejection and for transplant-related mortality (TRM)	There is a need for development of effective conditioning regimens to prevent graft failure and reduce transplant-related mortality in class 3 thalassemia patients.
Clinical Benefit	• RETALCLASS 3 was a retrospective, multicenter, study to assess the incidence of primary or late graft rejection following allogeneic hematopoietic stem cell transplantation (HSCT) allogeneic hematopoietic stem cell transplantation in class 3 thalassemia patients treated with a conditioning regimen including Tepadina. • Overall, no patient (0.0%) treated with Tepadina experienced graft rejection. In comparison, graft rejection occurred in 13 patients (25.5%) treated historically with a standard conditioning regimen without Tepadina.	Tepadina is effective for reducing the incidence of graft rejection in class 3 thalassemia undergoing allogeneic HSCT.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	• The limited sample size (n=25) did not permit an analysis of efficacy outcomes across subgroups. • Findings from a systematic literature review of studies evaluating Tepadina as conditioning treatment prior to allogeneic HSCT were consistent with findings from RETALCLASS3.	
Risks	• In class 3 thalassemia patients who received 5 mg/kg of IV Tepadina twice on day -6 pre-transplant, the most common (> 10%) TEAE were stomatitis, diarrhea, gastrointestinal hemorrhage, hepatic function abnormalities, cytomegalovirus infection and hematuria. • Grades 2-4 acute GvHD occurred in 7/25 (28.0%) of patients treated with Tepadina and 13/51 (25.5%) of patients in the historical group without Tepadina from Day 30 to Day 90. • Chronic GvHD occurred in 8/23 (34.8 %) patients treated with Tepadina and 7/49 (14.3%) of patients treated without Tepadina in the historical group. • Transplant related mortality at Day 100 and 1 year post transplant was 4% and 12% for patients treated with the Tepadina containing regimen. • Abnormalities in hematology and chemistry laboratory results were as expected in hematopoietic transplant recipients within the first 30 days post-transplant. • No life threatening (grade 4) serum chemistry abnormalities and no abnormalities in serum creatinine occurred in the 30 day post- transplant observation period in the Tepadina group. • No differences in safety by demographic subgroup were identified.	• Tepadina causes myelosuppression. • The safety profile of Tepadina is comparable to that of a standard conditioning regimen without Tepadina. • The safety of cumulative doses of more than 10 mg/kg of Tepadina is unknown.
Risk Management	• Safe use of Tepadina in practice will depend on the healthcare provider understanding the myelosuppressive effects of Tepadina and the potential serious risks which require vigilance. •	• To minimize risks, Tepadina should only be administered in controlled inpatient settings. • Labeling should include clear dosing instructions, and a boxed warning about severe bone marrow suppression, as well as warnings and precautions for other serious risks.

Analysis of Condition and Current Treatment Options

Thalassemia major is a hereditary hemolytic anemia caused by genetic defects in globin genes (Cao and Galanello 2010). It is one of most common autosomal recessive disorders worldwide affecting more than 100,000 children each year. ß-thalassemia major is the most severe form of thalassemia and results from reduced or absent production of the beta-globin gene that leads to ineffective erythropoiesis and hemolytic anemia. Chronic anemia in thalassemic patients is managed conventionally with blood transfusion, iron chelation, and splenectomy in cases of hypersplenism. Despite these measures, progressive disease with major complications related to the disease and treatment still remain, resulting in poor clinical outcomes for these patients. Bone marrow transplantation (BMT) is the only known cure for thalassemia (Thomas, Buckner et al. 1982, Lucarelli, Galimberti et al. 1987). Graft rejection following HSCT is a major challenge and is highly predictive of thalassemia-free survival (TFS) (Angelucci 2010), a key parameter for measuring treatment efficacy in thalassemia patients. Clinically, ß-thalassemia major is classified into risk groups (Class 1, 2 & 3) based on the number of risk factors (hepatomegaly >2 cm, hepatic fibrosis at liver biopsy, and a history of irregular chelation) present at diagnosis; each of which have a negative effect on transplant outcome (Lucarelli, Galimberti et al. 1990). Although excellent transplantation outcomes have been achieved in class 1 to 2 patients, class 3 patients have had much poorer outcomes and transplant-related mortality (TRM) mainly due to toxicity (Lucarelli, Clift et al. 1996).

Assessment of Efficacy

Study ADN010 (RETALCLASS3) was a retrospective, observational, multi-center study which assessed the impact of a myeloablative conditioning treatment (Protocol 26M) consisting of preconditioning cytoreduction with hydroxyurea, azathioprine and fludarabine followed by conditioning regimen with IV busulfan (weight based dose), Tepadina (10 mg/kg total dose) and cyclophosphamide (160 mg/kg total dose) in class 3 thalassemia major patients undergoing allogenic HSCT.

The efficacy of Tepadina was based on the number and proportion of patients with primary or late graft rejection after conditioning treatment with Protocol 26M prior to HPCT. This endpoint was considered reasonably likely to predict clinical benefit. Primary graft rejection was defined as the presence of <15% donor cells or failure to achieve an absolute neutrophil count (ANC) >500 mm^3 by day 28 post-transplant. Late graft rejection was defined as a loss of donor derived hematopoietic cells in bone marrow and peripheral blood (<15%) after initial graft function and return to erythrocyte transfusion dependence.

Twenty-five consecutive patients with class 3 thalassemia underwent first allogeneic transplantation from an HLA-identical donor and were treated according to Protocol 26M at 2 international study sites from February 2007 through November 2012. Overall, no patient treated with Tepadina experienced primary or late graft rejection (the incidence of graft rejection was 0/25 (0% (95% CI: [0, 0.12]). Among a historical control group of 51 patients who received the same preparative conditioning regimen but without Tepadina, the incidence of graft rejection was 13/51 (25.5% (95% CI: [0.13, 0.37]). Overall survival for patients who received Tepadina was 85.4% at 12 months.

A search of the Medline (PubMed) database by FDA revealed 6 eligible publications that permitted an evaluation of the efficacy of Tepadina as conditioning treatment before allogeneic hematopoietic stem cell transplantation (HSCT) in thalassemia patients. In all 6 studies, the efficacy of Tepadina containing regimes for myeloablation prior to allogeneic HSCT was demonstrated. The Applicant also conducted a meta-analysis on the efficacy of Tepadina in combination with other chemotherapy medicinal product as a conditioning treatment before HSCT in thalassemia patients from the published literature. The primary efficacy variable was the number and proportion of patients with graft rejection (primary or late). The graft failure rate in drug regimens containing Tepadina from published clinical studies was 9.6%. Studies that provided comparative data showed that Tepadina containing regimens produced a better outcome than regimens that did not include Tepadina. Due to the unavailability of comparative data in all studies included, efficacy evidence from the meta-analysis was not included in the Tepadina label.

Assessment of Safety
The safety population consisted of 76 pediatric class 3 thalassemia patients in RETALCLASS3 and 12 pediatric patients (with any hematological disease) in Study ADN009. Because the methodologies and follow up periods for RETALCLASS and study ADN009 were different, safety data from these sources were analyzed separately in this review. Additional safety information was sought in the published literature.

RETALCLASS3
Twenty-five class 3 thalassemia patients were treated with two 5 mg/kg doses of Tepadina (10 mg/kg total dose) as part of their preparative conditioning regimen (Protocol 26M) prior to allogeneic HSCT. Fifty-one class 3 thalassemia patients were also treated with the same preparative conditioning regimen, historically, without Tepadina (Protocol 26). All study subjects were less than 17 years of age at the time of transplantation (age range: 4 to 16 years); 39 patients were female. Safety follow-up was collected through Day 30 post-transplant for adverse events and through 1 year post-transplant for Graft-versus-Host disease (GVHD) and mortality outcomes. The safety results from RETALCLASS3 are presented below:

- Overall 8 deaths occurred: 3 deaths occurred in patients treated with Protocol 26M and 5 deaths were in the historical control group treated without Tepadina (Protocol 26). Transplant related mortality (TRM) at Day 100 post-transplant was 4% and 12% for Protocol 26M and Protocol 26 respectively. At 1 year post-transplant, TRM was 0.0% and 7.8% for the two groups respectively.

- Nine patients (11.8%) discontinued the study before the end of follow-up period. Eight (88.9%) of these discontinuations were due to death. One patient (11.1%) from Protocol 26 was lost to follow up. There were no early withdrawals due to adverse events.

- The most common (> 10%) TEAE among patients who received Tepadina were stomatitis, diarrhea, gastrointestinal hemorrhage, hepatic function abnormalities, cytomegalovirus infection and hematuria.

- SAEs occurred in 12 patients (23.5%) in the Protocol 26 group and 4 patients (16.0%) in the Protocol 26M group. Most SAEs were considered unrelated to Tepadina treatment. SAEs considered to be at least possibly related to Tepadina treated were gastrointestinal hemorrhage, seizure, subarachnoid hemorrhage and veno-occlusive disease.

- Subgroup analyses of adverse events by age and gender showed no safety signal.

- As expected from myeloablative treatment, profound myelosuppression occurred in all patients. All (100%) patients treated with Tepadina and 88% of patients in the historical control group engrafted. The mean time to recovery of absolute neutrophil count was 21.8 ± 4.2 days and 21.0 ± 5.5 days for the Tepadina and the historical treatment groups respectively. The mean time to recovery of platelet count was 27.8 ± 9.6 days and 28.4 ± 23.0 days for the Tepadina and the historical treatment groups respectively.

- The most common treatment-emergent key chemistry laboratory abnormalities in patients treated with Tepadina were increased AST (80%), increased ALT (88%) and increased serum bilirubin (80%). Majority of these abnormalities were Grades 1-2 in severity. No life threatening (grade 4) serum chemistry abnormalities occurred in the Tepadina treatment group.

- Grades 2 to 4 acute GVHD occurred in 28.0% of Tepadina treated patients and in 25.5% of patients in the historical control group. At 1-year post-transplantation, 34.8% of patients in the Tepadina group had developed chronic GVHD: 17.4% of these patients had extensive disease. In the control group, 14.3% were reported to have chronic GVHD: 6.0% had extensive disease.

Study ADN009
Twelve pediatric patients were treated with two scheduled doses of Tepadina 5 mg/kg (10 mg/kg total dose) as part of their conditioning treatment prior to allogeneic HSCT under Study ADN009. Safety follow up was through Day 30 post-transplant. The effect of Tepadina on ventricular repolarization (QT/QTc interval) was also evaluated in ADN009.

The 12 subjects had a mean age of 5.5 years (range, 1.1-14 years); 33.3% were female. All subjects had normal liver function (Child-Pugh score A). None had any significant clinical abnormalities at baseline. The safety results from Study ADN009 are presented below:

- There were no deaths.

- There were no early withdrawals due to adverse events.

- TEAEs were reported for 10 (83.3%) patients. The most common TEAE were mucosal inflammation, pyrexia and graft-versus-host disease of the skin. SAEs occurred in 2 patients (16.7%): both were considered not related to the study treatment.

- Demographic subgroup analyses were not feasible due to the limited sample size (n=12).

- Major limitations in the design of the QT study under Study ADN009 were identified by the Interdisciplinary Review Team (IRT). The available data is inadequate for determining the effect of Tepadina on cardiac conduction.

Literature review:
A search of the Medline (PubMed) database by the FDA revealed 7 eligible publications that permitted an evaluation of the safety of Tepadina as conditioning treatment before allogeneic HSCT in thalassemia patients. The patient population included pediatric as well as some adult patients. No new safety issues related to the use of thiotepa as a conditioning regimen prior to HSCT in thalassemia patients were identified in the literature. In all studies reviewed, thiotepa was relatively well tolerated with no significant increase in toxicity. A higher number of deaths were observed in one study among patients conditioned with thiotepa (La Nasa, Caocci et al. 2005).

The Applicant also conducted a meta-analysis of the safety data from published literature to assess the incidence of acute and chronic GVHD as a safety parameter. The proportion of patients with acute GVHD and chronic GVHD in the literature meta-analysis was 18.4% and 6.4% respectively. Due to the unavailability of comparative data in all studies reviewed, safety evidence from the meta-analysis was not included in the Tepadina label.

Overall Benefit-Risk Assessment:
Thalassemia major is a serious hereditary condition. Patients with thalassemia major have severe transfusion-dependent anemia and require chronic transfusions combined with iron chelation therapy throughout life. Bone marrow transplantation is the only known cure. Although excellent transplantation outcomes have been achieved in class 1 to 2 patients, class 3 thalassemia patients have a high risk of graft rejection (which is strongly correlated with TFS) and TRM. There is an unmet need for conditioning regimens that reduce the risk of graft rejection in class 3 thalassemia patients undergoing allogenic HCPT.

In the retrospective study of patients with class 3 thalassemia treated with a conditioning regimen including Tepadina prior to allogenic HSCT, the incidence of primary or late graft rejection was 0% (95% CI: [0, 0.12]). In a historical group of 51 patients who received the same preparative conditioning regimen, without Tepadina, the incidence of graft rejection was 13/51 (25.5% (95% CI: [0.13, 0.37]). These findings taken together provide substantial evidence of clinical benefit and support approval of Tepadina for this serious condition with a significant unmet need.

The safety review revealed mild to moderate TEAE in class 3 thalassemia patients at a total Tepadina dose of 10 mg/kg during conditioning prior to allogeneic HSCT. As expected from myeloablative treatment, profound myelosuppression occurred in all patients; however, all patients treated with Tepadina engrafted, and by 30 days post-transplant, most hematological parameters had normalized. Majority of treatment-emergent chemistry laboratory were mild – moderate (Grades 1-2) in severity. The occurrence of grades 2 to 4 acute GVHD was comparable in patients treated with Tepadina (28.0%) and in the historical control group (25.5%). Likewise, a similar proportion of patients in both groups developed chronic GVHD at 1-year post-transplantation. These risks can be moderated in part by the cautious administration of Tepadina in controlled hospital settings that will allow for appropriate intervention as needed should a

serious adverse reaction occur. Appropriate warnings, contraindications and instructions for dosing will be provided in the Prescribing Information. With the recommended mitigation strategies in place, the potential benefit from treatment with Tepadina should outweigh the risks for pediatric patients with class 3 thalassemia undergoing allogeneic HSCT.

1.3 Recommendations for Labeling

The following key recommendations for the Tepadina Prescribing Information are based on this review:

- Include a Boxed Warning for the risk of severe bone marrow suppression or ablation with Tepadina use.
- The recommended dose of Tepadina in Section 2.1 should be the exact dose of Tepadina evaluated in clinical studies.
- Include a table showing the recommended dosage regimen for Tepadina, Busulfan, and Cyclophosphamide in the Section 2.1.
- Since efficacy was based on results in patients treated with Tepadina only, (b) (4) (b) (4)
- Include summary demographic data on patients treated with Tepadina in Section 14.
- Provide the data on the occurrence of acute and chronic GVHD in RETALCLASS3 in section 6.1.
- Include a table showing the worst key chemistry abnormalities in patients treated with Tepadina through 30 days post-transplant.
- (b) (4)
- Add more detailed information to section 6.2 on the safety signals identified from Post marketing experience of Tepadina.

1.4 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

None

1.5 Recommendations for Post-market Requirements and Commitments

There are no post-market requirements or commitments for this application.

2 Introduction and Regulatory Background

2.1 Product Information

Drug Established Name:	THIOTEPA
Proposed Trade Name:	TEPADINA®
Dosage Forms:	15 mg and 100 mg, Injection, Powder, Lyophilized, for Solution
Therapeutic Class:	Conditioning regimen
Chemical Class:	Alkylating agent
Mechanism of Action:	The radiomimetic action of thiotepa is believed to occur through the release of ethylene imine radicals that disrupt the bonds of deoxyribonucleic acid (DNA).
Proposed Indication:	To reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor cell transplantation for patients with class 3 β-thalassemia.
Proposed Dose-Schedule:	The recommended dose of Tepadina class 3 β-thalassemia is two administrations of 5 mg/kg given intravenously approximately 12 hours apart (10 mg/kg total dose) on Day -6 before allogeneic HSCT in conjunction with high-dose busulfan and cyclophosphamide.

Other Indications:

In the US, Thiotepa for Injection, USP is currently approved for the following indications:

1. Adenocarcinoma of the breast.
2. Adenocarcinoma of the ovary.
3. For controlling intracavitary effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities.
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

Warnings in current drug label:

- Death has occurred after intravesical administration, caused by bone-marrow depression from systematically absorbed drug.
- Death from septicemia and hemorrhage has occurred as a direct result of hematopoietic depression by thiotepa.
- Thiotepa is highly toxic to the hematopoietic system. Weekly blood and platelet count checks are recommended during therapy and for at least 3 weeks after therapy is discontinued.

- Thiotepa can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If thiotepa is used during pregnancy, or if pregnancy occurs during thiotepa therapy, the patient and partner should be apprised of the potential hazard to the fetus.
- Like many alkylating agents, thiotepa has been reported to be carcinogenic when administered to laboratory animals. Carcinogenicity is shown most clearly in studies using mice, but there is some evidence of carcinogenicity in man. In patients treated with thiotepa, cases of myelodysplastic syndromes and acute non-lymphocytic leukemia have been reported.

In EU territories (EMA centralized procedure), Switzerland, Russia, Hong Kong and Israel, TEPADINA® is approved in an orphan medicinal product – "in combination with other chemotherapy medicinal products: 1) With or without TBI, as conditioning treatment prior to allogeneic or autologous HSCT in hematological diseases in adult and pediatric patients; 2) when high dose chemotherapy with HSCT support is appropriate for the treatment of solid tumors in adult and pediatric patients."

2.2 Currently Available Treatments for Proposed Indication

None

2.3 Availability of Proposed Active Ingredient in the United States

03/09/1959	ThioTEPA (NDA 011-683) was approved by FDA on 03/09/1959. The marketing application was subsequently withdrawn.
12/22/1994	A second formulation of thiotepa (Thioplex) was developed and approved under NDA 020058. The marketing application was also withdrawn by the applicant.
04/02/2001	ANDA for thiotepa (ANDA 075547) filed by Bedford and approved in the U.S. Thioplex NDA 020058 was used as the Reference Listed Drug.

There is currently only one approved thiotepa marketed in the US (Bedford ANDA 075547; 4/2/2001) - Thiotepa for Injection, USP. Since April 2011, due to the critical shortage of Thiotepa for Injection in the US, in conjunction with the FDA, ADIENNE has temporarily imported TEPADINA into the US market. Tepadina contains the same active ingredient as the US-registered Thiotepa for Injection, USP. However, Tepadina is provided in two different size vials, 15 mg/vial and 100 mg/vial.

2.4 Important Issues with Consideration to Related Drugs

Thiotepa is a polyfunctional alkylating agent with both myeloablative and immunosuppressive properties. It is an ethylene imine-type compound, chemically and pharmacologically related to nitrogen mustard. Alkylating agents are one of the earliest classes of chemotherapy agents developed for cancer treatments. Generally, the clinical dose-limiting toxicity for alkylating agents is hematopoietic toxicity, particularly suppression of granulocytes and platelets. This myeloablative characteristic makes thiotepa useful for immunosuppression and myeloablation in

allogeneic HSCT. As a result, thiotepa has been used for decades in combination with other chemotherapy drugs for conditioning prior to autologous and allogeneic HSCT.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

January 2007	Obtained Orphan Drug Designations by the European Medicines Agency (EMA) for the indication "conditioning treatment prior to hematopoietic progenitor cell transplantation"
April 2007	FDA granted Tepadina orphan-drug designation for "conditioning treatment prior to hematopoietic stem cell transplantation."
March 2010	Approved as an orphan drug and granted marketing authorization in the European Union (EU) through the EMA centralized procedure, relying on a *"well established use"* of the product over decades.
September 2010	FDA recommended ADIENNE requests a pre-NDA meeting in preparation for filling a 505(b)(2) application. FDA advised ADIENNE to narrow the labeling that it is seeking in the US to indications that it can support with clinical data.
April 2011	pre-NDA meeting held to discuss the adequacy of data to support the filing and approval of TEPADINA® for conditioning treatment prior to hematopoietic progenitor cell transplantation for lymphoma. FDA advised ADIENNE to isolate the role of thiotepa in the specific indication sought, providing the evidence of a sound and meaningful clinical benefit such as improvement of survival

Several pre-NDA meetings were held in order to obtain FDA's concurrence with the proposed contents of the NDA (under PIND 109219)

July 2011	ADIENNE proposed (b) (4)
August 2011	(b) (4)
May 2013	Pre-NDA meeting held. ADIENNE proposed to submit a 505(b)(2) NDA for Tepadina to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic HSCT in class 3 β-thalassemia patients. FDA recommended an analysis in which the results of the thiotepa containing regimen are compared to a larger historical control group treated with a standard condition regimen.
January 2015	Rolling review request from ADIENNE for NDA #208264 was approved. Adienne submitted the CMC and Nonclinical sections of this NDA application in eCTD format on February 25, 2015.

2.6 Other Relevant Background Information

In EU territories (EMA centralized procedure), Switzerland, Russia, Hong Kong and Israel, TEPADINA® is approved in an orphan medicinal product – "in combination with other chemotherapy medicinal products: 1)With or without TBI, as conditioning treatment prior to allogeneic or autologous hematopoietic progenitor cell transplantation (HSCT) in hematological

diseases in adult and pediatric patients; 2) when high dose chemotherapy with HSCT support is appropriate for the treatment of solid tumors in adult and pediatric patients."

2.7 Compliance with the Pediatric Research Equity Act

Since Tepadina has orphan designation for conditioning treatment prior to hematopoietic stem cell transplantation, this submission is exempt from the requirements of the Pediatric Research Equity Act.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The clinical section of this submission was received on March 31, 2016 in eCTD format. A few technical/formatting errors were identified in the clinical submission, and the Sponsor was notified of this. Following receipt of responses to the information requests and resubmission of the faulty documents, the submission was found to be technically complete for review and filed on May 30, 2016. Additional amendments are listed in the Table below.

Table 2: NDA Submission and Amendments

eCTD SN	Received	Category	Subcategory
004	5/12/2016	Amendment	Request for Proprietary Name Review
005	7/14/2016	Clinical, Clinical Pharmacology, Biopharmaceutics, CMC	Response to Information Requests
006	09/06/2016	Amendment	Request for reconsideration of proprietary name
007	10/31/2016	Labelling, CMC, Statistics, Clinical, Clinical Pharmacology	Response to Information Requests
008	11/10/2016	Amendment	Change of US Agent

3.2 Compliance with Good Clinical Practices

The pivotal study supporting this application was Clinical Study ADN010 (RETALCLASS3) - "A retrospective, non-interventional, observational study in class 3 thalassemia major patients undergoing bone marrow transplantation following myeloablative conditioning treatment preceded by cytoreduction/immunosuppression." Per the applicant, this study was conducted in compliance with the relevant guidelines of the Declaration of Helsinki, the international ICH/GCPs and to the general principles of "ICH Topic E6, CPMP/ICH/135/95", July 1996 including post Step 4 errata, status September 1997 and post Step errata (linguistic corrections), July 2002.

Informed consent was not obtained by the Investigators for this retrospective, observational study conducted at two sites which participated in an international project providing stem cell transplantation for pediatric patients with thalassemia from middle-Eastern countries. Per the Applicant, access to information about the local residence of patients was not available and as a result, patients and their families were generally not reachable for informed consent. The non-

availability of informed consents was described to the ethical committees and approval was obtained to proceed with the data collection (with reference to Authorization no. 9/2013 issued by the Italian Data Protection Authority - General Authorization to Process Personal Data for Scientific Research Purposes -as published in Italy's Official Journal no 302 of 27 December 2013).

Office of Scientific Investigations (OSI) Inspection Results
Both clinical sites for RETALCLASS3 were recommended for audit and inspection by OSI. RETALCLASS3 was conducted in Italy. The study centers were the International Center for Transplantation in Thalassemia and Sickle Cell Anemia, Mediterranean Institute of Hematology, University of Rome Tor Vergata (Rome) and Hematology and Bone Marrow Transplant Unit at San Raffaele Hospital, IRCCS (Milan).

OSI inspections were conducted from July 11-20, 2016. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verified at both study sites. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. In general, both clinical sites appeared to be in compliance with Good Clinical Practices, and data submitted from both sites were found to be acceptable in support of the sought indication. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

3.3 Financial Disclosures

The applicant provided certification on FDA Form 3454 to indicate that there were no financial arrangements between the Sponsor and Investigators which could be affected by the outcome of study Protocol RETALCLASS3 and ADN009. The Clinical Investigators also had no proprietary interest in the product or significant equity in the sponsor, and no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(1).

4 Significant Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The following is a summary of relevant information taken from the Pharmacology/Toxicology Review and Evaluation by Dr. Anamitro Banerjee dated December 10, 2016:

Thiotepa USP is manufactured by (b) (4) and will be supplied for the manufacture of Tepadina. Thiotepa USP manufactured by (b) (4) follows CMC information used in the (b) (4) process and approved under NDA 020058. The analytical methodology was originally developed to meet the requirements of the monograph for Thiotepa USP. The applicant provided the comparative impurity profile of the Thiotepa USP drug substance used in this NDA and the drug substance used for the approved NDA as well as the USP reference standard lot H. All the CMC information for the manufacture of the drug substance is provided in the Type II DMF (b) (4). DMF (b) (4) was last reviewed by Dr. Haripada Sarkar on August 29, 2016 and found to be adequate. The updated stability information submitted by the DMF holder was found to be adequate. The applicant is proposing a retest

period of (b) (4) when stored under refrigerated conditions (b) (4) based on real time stability data. The retest period was found acceptable by the Drug substance reviewer. The facility reviewer found (b) (4) the drug substance manufacturing, packaging, and testing site acceptable based on profile.

The drug product is a white lyophilisate. The formulation does not contain any excipient. (b) (4) (b) (4). The product is available in 15 mg and 100 mg vials. Based on risk assessment of the available data, the microbiology review team found the container closure system for both the15mg formulation and the 100mg formulation acceptable.

The manufacturing process for the proposed drug product involves (b) (4), (b) (4) (b) (4). The (b) (4) controls were found to be adequate. The applicant requested a waiver of the in-vivo study of the proposed drug product. Since the formulation does not contain any excipient, the Biopharmaceutics review team granted the applicant's waiver request.

Stability studies were performed in accordance with the "ICH Harmonized Tripartite Guideline, Stability Testing of new Drug Substances and Products". The applicant proposed 18 month (at 2°C to 8°C (36°F to 46°F)) expiration date was accepted. The facility reviewer found the (b) (4) (b) (4) drug product manufacturing, packaging, and testing site acceptable.

4.2 Preclinical Pharmacology/Toxicology

At the time of completion of this review, the Pharmacology/Toxicology review was pending.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Thiotepa is an ethylene imine-type compound and chemically and pharmacologically related to nitrogen mustard. It is an alkylating agent which reacts with electron-rich atoms in biologic molecules to form covalent bonds. Once bound, the altered molecule disrupts the normal action and replication of the DNA strand which causes breakage of the DNA strands and lead to cell death.

4.3.2 Pharmacokinetics

The following is a summary of relevant information taken from the Clinical Pharmacology Review by Dr. Sriram Subramaniam dated 12/22/2016.

Distribution: The mean estimated volume of distribution of Thiotepa is 30 L/m^2 following single IV dose in pediatric patients, and 1 L/kg to 1.9 L/kg for doses of 20 mg to 250 mg/m^2 as an IV bolus or up to 4 hour infusion, and appears to be independent of dose. Protein binding is less than 20%.

Metabolism and Elimination: Thiotepa undergoes hepatic metabolism. In vitro data from literature suggests that thiotepa is metabolized by CYP3A4 and CYP2B6. The major active metabolite of thiotepa is TEPA (triethylenephosphoramide). The mean elimination half-life was 1.7 hours (thiotepa) and 4 hours (TEPA) in pediatric population, and from 1.4 hours to 3.7 hours for thiotepa and from 4.9 hours to 17.6 hours for TEPA in adult population. The identified metabolites of thiotepa are all excreted in the urine. Urinary excretion of thiotepa and TEPA is complete by 6 hours and 8 hours, respectively.

Evidence submitted: Adienne submitted two clinical pharmacology studies including a study to evaluate the effect of mild hepatic impairment on thiotepa pharmacokinetics (PK) and QT/QTc prolongation in patients (ADN009) and an in vitro study to evaluate the effect on cytochrome P450 (CYP) enzymes on thiotepa metabolism (ADI/REP/01). In addition, Adienne referenced clinical pharmacology information for thiotepa from literature and the Thioplex labeling.

Review: No exploratory exposure-response analyses for efficacy endpoints and toxicities could be conducted, because no PK samples were collected in the registration trial (ADN010). The proposed dose was based on the efficacy and toxicity of Tepadina in the registration trial and meta-analysis of literature data. The key review questions focused on the appropriateness of dose recommendations for Tepadina use in patients taking concomitant CYP3A modulators, and in patients with hepatic impairment and renal impairment.

Recommendations: A dose of 3 mg/kg to 5 mg/kg, twice daily via intravenous infusion for a total to two doses appears to be effective and safe, given the limited data available. Concomitant use of strong CYP3A4 inhibitors and inducers should be avoided. No dose adjustment is recommended for patients with mild hepatic impairment and mild renal impairment. Toxicity should be monitored in patients with moderate and severe renal impairment and moderate and severe hepatic impairment following prolonged treatment. A bioequivalence trial to compare the approved thiotepa formulations and Tepadina was not necessary, as thiotepa is an intravenous drug product with no excipients. A scientific bridge exists between thiotepa products used in the literature and Tepadina to support the acceptance of the scientific bioequivalence. No post-marketing requirements were recommended.

4.4 Interdisciplinary Review Team (IRT)

The applicant evaluated the effect of Tepadina on the ventricular repolarization (QT/QTc interval) in pediatric patients in Study ADN009. The IRT identified major limitations in the design of the QT study which made the interpretation of the results of QT assessment unreliable. These include identified discrepancies between the ECG intervals in the clinical dataset and those in the paper ECG tracings; inadequate ECG assessment strategies and lack of power to exclude large increases in QTc (>20 msec). The IRT concluded that there is inadequate information to determine whether or not Tepadina has an effect on the QTc. Additional information on clinical safety experience and available pro-arrhythmic and cardiac safety data from post-marketing reports was requested. (IRT for QT Studies Consultation dated 7/19/2016). The Applicant submitted the requested information on 10/31/2016.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies as listed by the applicant in Module 5.2

Table 3: Clinical Trials

Trials / Status	Design	Population	Primary Endpoint
ADN009	Prospective, Phase IV study To assess PK, general safety and cardiac safety of Thiotepa	Pediatric patients undergoing allogeneic hematopoietic progenitor cell transplantation	Pharmacokinetics Safety
ADN010 - RETALCLASS3	Retrospective, observational, case-series, multicenter, historical-controlled study To compare the incidence of graft rejection following allogeneic BMT in class 3 thalassemia patients treated according to Protocol 26M vs. a control group treated with standard Protocol 26.	Patients (≤ 17 yrs.) with class 3 thalassemia who underwent allogeneic transplantation from an HLA-identical donor	Number and proportion of patients with graft rejection.

FDA generated table

5.2 Review Strategy

This review is based on information and analysis in this NDA submission. The key material used for the review of efficacy and safety includes:

- NDA 208264
- Systematic review of published literature
- The 6th Periodic Safety Update Report for Thiotepa marketed in Europe (IBD – 05/15/2010).

Relevant results from the review of the protocols included in this submission are described in Section 5.3.

Statistical analyses by the clinical reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and MedDRA Adverse Events Diagnostic (MAED) v1.2 (Clinical Trials & Surveys Corporation, Owings Mills, MD).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study ADN009:

A Phase IV study to assess the effect of hepatic impairment on the pharmacokinetics of thiotepa and the potential of thiotepa to alter the QT interval, in pediatric patients undergoing allogeneic hematopoietic progenitor cell transplantation

Study Design
Study ADN009 was a two-center, open label, phase IV study designed to 1) assess the effect of moderate hepatic impairment on the pharmacokinetics of Tepadina and its metabolite TEPA in pediatric patients undergoing allogeneic bone marrow transplantation (ABMT); 2) to assess the cardiac safety of Tepadina, particularly, its effects on the ventricular repolarization in pediatric patients and 3) assess the general safety of Tepadina through collection of treatment -emergent adverse events (TEAEs) and analysis of their possible association with Tepadina. The study was originally designed as a 2 arm study to compare the pharmacokinetics of Tepadina in a pediatric patients with normal versus moderately impaired liver function (Child-Pugh score A vs. B). A sample size of 15 in each group would have assured an 80% power to detect a probability of 0.8 that an observation in one study Group was less than an observation in the second study Group as to the drug clearance, using a Wilcoxon (Mann-Whitney) rank-sum test, with a 0.05 two-sided significance level. However, due to difficulty enrolling patients with Child-Pugh B liver function, the study was prematurely terminated and only 12 patients in one arm (subjects with normal liver function) were enrolled.

Methods
The study consisted of a screening period and a myeloablative conditioning phase during which patients who met all the selection criteria were treated with Tepadina (on the first day as the first drug of the conditioning regimen) and other chemotherapeutic agents prior to proceeding with HSCT. Two intravenous infusions of Tepadina (thiotepa) 5 mg/kg each were administered intravenously 12 hours apart. No other dosing schedules of Tepadina were permitted.

Blood samples for PK analysis were collected prior to the start of the first infusion, at the following time points - 180 min, 195 min, 210 min, 240 min, 360 min, 720 min after the first Tepadina infusion; and at the end of the second infusion (180 minutes duration).

To evaluate the effect of Tepadina on QT/QTc interval, 12-lead ECG tracings were collected at the following time points: - before and 3 hours after the end of the first and second Tepadina infusions, and 24 hours after the second infusion of Tepadina. Additional tracings were obtained on day 7 in patients with clinically relevant observed alterations in ECG tracings. Categorical analyses of QT/QTc interval data were performed for patients with QTc interval > 450 msec; QTc interval > 480 msec; and QTc interval > 500 msec. QTc interval changes from baseline of >30 msec and >60 msec were evaluated.

Follow-up safety information including hematological assessments was collected up to 30 days after transplantation. The flow chart below provides a general overview of the study conduct including efficacy and safety assessments.

Table 4: Study flowchart

	Screening	Day 1 1st Tepadine infusion						Day 1 2nd Tepadine infusion		Day 2		Day 7	Daily up to D30 post-trspl
		0' start	+180' end	+195'	+210'	+240'	+360' +6h	+720' +12h	0' start	+180' end	+360' +6h	+24h		
Consent / assent	X													
Demographic data	X													
Hematol. disease	X													
Conc/past diseases	X													
Conc. medications	X	→	→	→	→	→	→	→		→	→	→		
Physical examination	X													
Vital signs [1]	X							X						
Performance Status	X							X						
Pregnancy test [2]	X													
Instrumental tests [3]	X													
Laboratory tests [4]	X	X												X
Serology [5]	X													
Inclusion/Exclusion	X													
Thiotepa administr.		X						X						
pK samples		X	X	X	X	X	X	X		X				
ECG [6]	X	X					X	X			X	X	(X)	
Adverse Events [7]		→	→	→	→	→	→	→		→	→	→	→	→

[1] SBP/DBP, HR, body temperature
[2] Only in childbearing potential female patients
[3] Echocardiography (LVEF); lung function (FEV1/FVC/DLCOHb-adj); chest-X-rays
[4] Hematology (RBC, WBC and differential, platelets, hemoglobin) daily up to 30 days after transplantation.
Renal function (creatinine, creatinine clearance). Electrolytes (Na, K, Ca, Mg). Hepatic function (bilirubin, ALT/AST, alkaline phosphatase; LDH; gamma-GT), albun
prothrombin time), at screening
[5] CMV, EBV, HIV, HBV, HCV
[6] The screening ECG might have been replaced by the ECG requested on day 1 at the start of the infusion.
In case of alterations observed in the ECGs on day 1 or day 2, the ECG was repeated on day 7.
[7] SAEs were collected up to 30 days after transplantation.
Note: time 720 min after the 1st infusion and time 0 at the start of the 2nd infusion corresponded to the same time point. Therefore, a single collection of data was requested.

(Table copied from ADN009 Abbreviated Clinical Study Report-Table 9.2.1)

Results

Twelve patients with Child-Pugh score A liver function were enrolled between May and October 2015 in 2 centers in Italy. The investigators were unable to enroll any patients with Child-Pugh B liver function. As a result, the study was terminated early and the PK study was modified to a descriptive analysis for patients with Child-Pugh score A.

Analyses of the cardiac and general safety of Tepadina as well as of blood cell counts up to 30 days after transplantation were performed as planned in these patients. All 12 patients received at least one dose of Tepadina and were included in the safety set. Demographics of these patients are shown in Table 5.

Table 5: Demographic characteristics (n = 12)

Parameter	All Subjects (N=12)
Age, years	
Mean (Range)	5.5 (1.1-14.0)
Female n (%)	4 (33.3%)
Weight, kg	
Mean (Range)	20.2 (10.0-45.0)
Height, cm	
Mean (Range)	111.2 (82.0 -162.0)

Source: FDA analysis

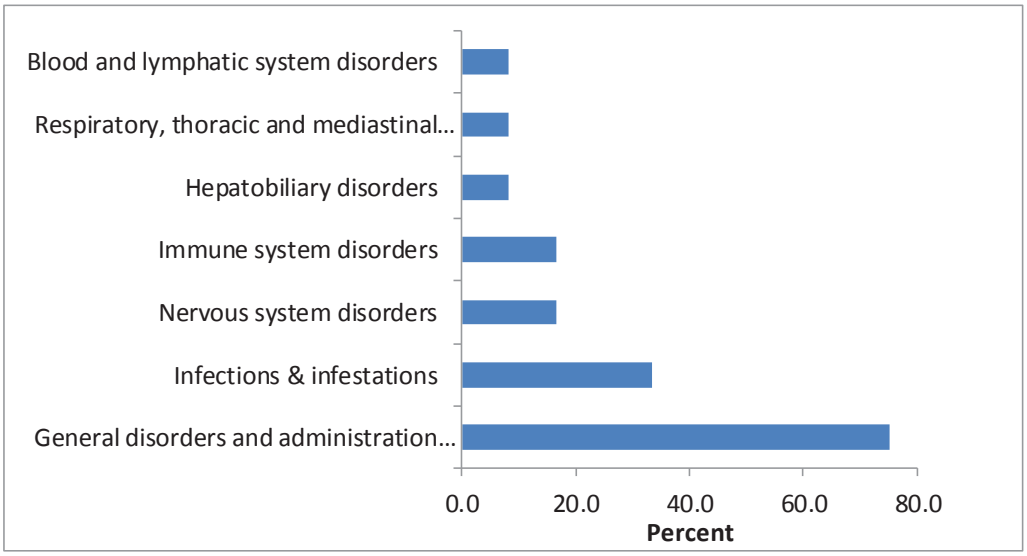
All subjects enrolled had normal liver function (Child-Pugh score A). None had any significant clinical abnormalities at baseline. One patient had a documented on-going co-morbidity (stenotrophomonas maltophilia infection) as measured via the HCT CI. Six subjects had transplantation from an unrelated donor. Treatments included in the conditioning regimen for subjects included – fludarabine, melphalan, busulfan, treosulfan, ATG, and TBI.

Safety

The applicant reported that all patients (n=12) in the safety data set received the two scheduled thiotepa infusions. Eleven patients (91.7%) experienced AEs during the study. TEAEs were reported for 10 patients (83.3%). The most frequently reported TEAEs belonged to the 'General disorders and administration site conditions' SOC, followed by 'Infections and infestations'. The number of patients with TEAEs by SOC is shown in Figure 1 below.

For 8 patients (66.7%), TEAEs were assessed by the applicant to be related to the study treatment. None of the TEAEs resulted in premature study discontinuation.

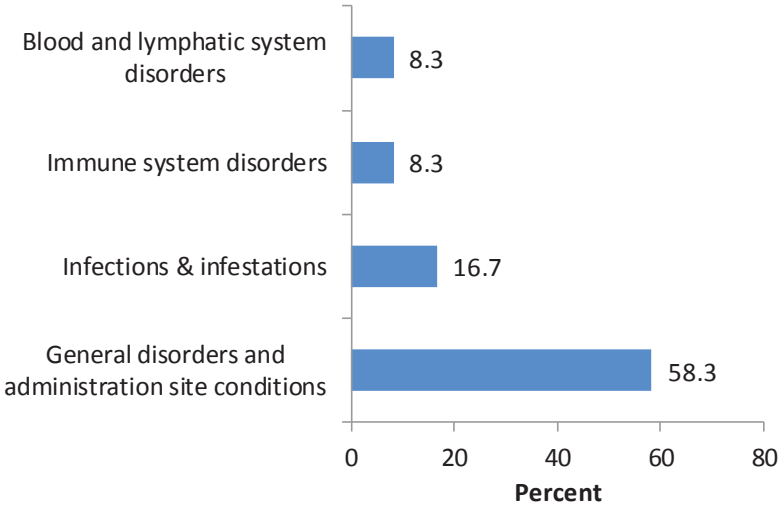
Figure 1: Percentage of patients with TEAE by SOC (Safety set, N=12)



Source: FDA Analysis.

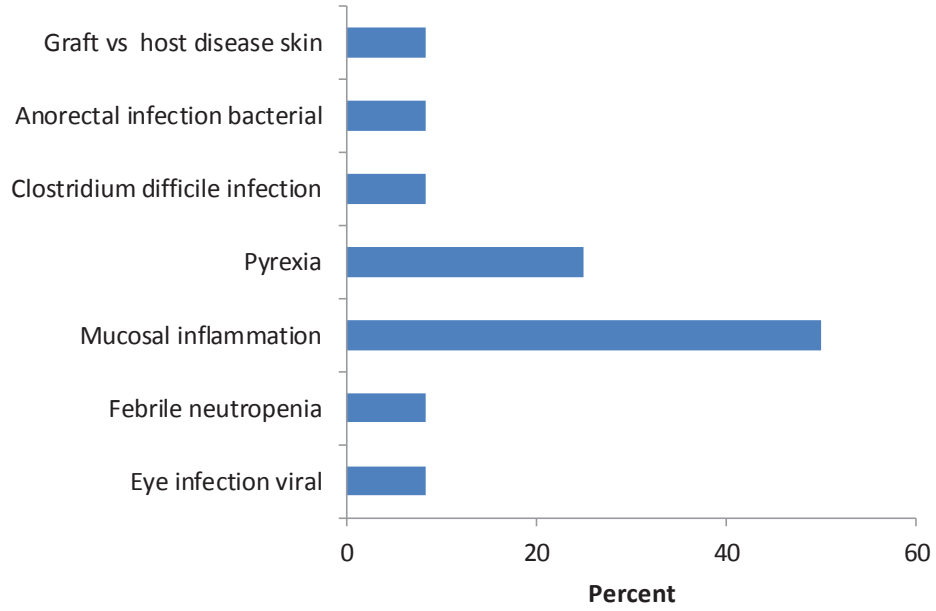
Most TEAEs considered related to the study treatment belonged to the 'General disorders and administration site conditions' SOC (Figure 2). The most frequently reported related TEAE (by PT) was 'Mucosal inflammation' (50.0%) followed by pyrexia (25.0%) (Figure 3).

Figure 2: Patients with related TEAE by SOC (Safety set, N=12)



Source: FDA Analysis.

Figure 3: Patients with related TEAE by PT (Safety set, N=12)



Narratives of Deaths and Serious Adverse Events
There were no deaths in Study ADN009. Serious TEAEs were reported for 2 patients and are described below.

Patient (b) (6) was a **2** year-old female patient with a history of B lymphoblastic Leukemia/lymphoma, NOS. She received Tepadina (70 mg IV) as part of her conditioning regimen on (b) (6), prior to HSCT on (b) (6). On (b) (6), she was diagnosed with sepsis which resolved on (b) (6). The event of sepsis was described

by the investigator as serious and life-threatening, and attributable to concurrent illness but not related to the study treatment.

Reviewer Comment: Myelosuppression is a known pharmacologic class effect of alkylating agents and an expected consequence of chemotherapy and conditioning treatments used during the transplant process. Sepsis in this patient was likely the result of hepatopoietic suppresson induced by concomitant use of Tepadina and other myelosupressive agents administered during hematopoietic cell transplantation. A possible role of Tepadina in causing sepsis in patient (b) (6) can therefore not be ruled out by FDA.

Patient (b) (6) was a 14 year-old female patient with a history of B lymphoblastic leukemia/lymphoma, diagnosed on (b) (6). She received HSCT on (b) (6) and her conditioning regimen included fludarabine, treosulfan, and ATG intravenously. She was treated with Tepadina (225 mg IV, twice) on (b) (6). On (b) (6) she experienced veno-occlusive liver disease (VOD) which was still ongoing 4 weeks post end of study, but reported to be resolving. The investigator adjudicated the event was serious, severe, and definitely related to treosulfan but not related to Tepadina.

Reviewer Comment: Hepatic VOD is a serious, life-threatening condition and a known class toxicity of alkylating agents. Therefore, FDA can not rule out a possible role of Tepadina in causing VOD in this patient.

5.3.2 RETALCLASS3 (Study ADN010):
Retrospective, non-interventional, observational study in class 3 thalassemia major patients undergoing bone marrow transplantation following myeloablative conditioning treatment preceded by cytoreduction/immunosuppression
RETALCLASS3 was the pivotal study supporting this NDA. The primary study objective was to retrospectively assess the incidence of graft rejection following allogeneic BMT from a human leukocyte antigen (HLA)-identical sibling donor in class 3 thalassemia patients treated according to Protocol 26M (a conditioning regimen with busulfan, cyclophosphamide and Tepadina, preceded by pre-conditioning with hydroxyurea, azathioprine and fludarabine), versus a control group of patients treated with standard Protocol 26 (a conditioning regimen with busulfan and cyclophosphamide only, preceded by preconditioning with hydroxyurea, azathioprine and fludarabine) ± antithymocyte globulin.

Study Design
RETALCLASS3 was a retrospective, observational, multi-center, historically controlled study to evaluate the efficacy and safety of two different treatment regimens (protocol 26M and protocol 26) in pediatric Class 3 thalassemia patients undergoing allogenic hematopoietic progenitor cell transplantation.

Study Objectives
Primary objective - to retrospectively assess the incidence of graft rejection following allogeneic bone marrow transplantation from an HLA-identical sibling donor in class 3 thalassemia patients treated according to Protocol 26M (a conditioning regimen with busulfan, cyclophosphamide and

Tepadina, preceded by preconditioning cytoreduction/ immunosuppression with hydroxyurea, azathioprine and fludarabine), in comparison with a control group of patients treated with standard Protocol 26 (a conditioning regimen with busulfan and cyclophosphamide only, preceded by pre-conditioning with hydroxyurea, azathioprine and fludarabine) ± antithymocyte globulin.

Primary Endpoint

The primary study endpoint was the number and proportion of patients with primary or late graft rejection. Primary graft rejection was defined as the presence of <15% donor cells or failure to achieve an absolute neutrophil count (ANC) >500 mm^3 by day 28 post-transplant. Late graft rejection was defined as a loss of donor derived hematopoietic cells in bone marrow and peripheral blood (<15%) after initial graft function and return to erythrocyte transfusion dependence.

Secondary endpoints

- Overall survival (OS)
- Incidence of TRM at day 100 and at 1 year post-treatment
- Thalassemia-free survival
- Absolute ANC count engraftment (3 consecutive days with ANC ≥ 500/mm^3) and platelet engraftment (>20 × 10^9/L at the first day of at least three consecutive days, in the absence of platelet transfusions in the prior 7 days);
- Time to recovery of ANC and platelet counts
-

Study Population

The study population consisted of 76 patients with class 3 thalassemia who underwent first allogeneic transplantation from an HLA-identical donor at the BMT Center of San Raffaele Hospital of Milan and the International Center for Transplantation of the Mediterranean Institute of Hematology of Rome. This included 25 consecutive patients treated according to Protocol 26M from February 2007 to November 2012 (study group) and 71 patients treated according to standard Protocol 26 (control group) over the period May 2004 - September 2008.

Eligibility Criteria

Inclusion Criteria: Patients were eligible for enrollment if all the following conditions were met:

1. Patients having completed the (pre) conditioning phase as planned and the transplantation procedure;
2. Parents'/guardian's written informed consent and patient's written informed assent or consent (if applicable) for the retrospective study was obtained;
3. Age ≤ 17 years at the time of the transplantation;
4. Diagnosis of thalassemia or drepano-thalassemia with risk class 3
5. Patients who had an HLA-genotypically identical(sibling) donor;
6. Patients who received the first hematopoietic stem cell transplantation

Exclusion Criteria: Patients' were ineligible for enrollment if any of the following conditions were met at the time of transplantation:

1. HIV positive patients
2. Severe neurological impairment;
3. Severe organ impairment, defined as LVEF<40%, or Forced expiratory volume in the 1st second (FEV1) and/or forced vital capacity (FVC) and/or, diffusion lung for carbon monoxide (DLCO) <50% of predicted normal value, or Advanced liver cirrhosis, or liver

function tests (e.g. ALT, AST or gamma-GT) > 10 x upper limit of normal (ULN), or Creatinine clearance < 40 ml/min.

Selection of Controls

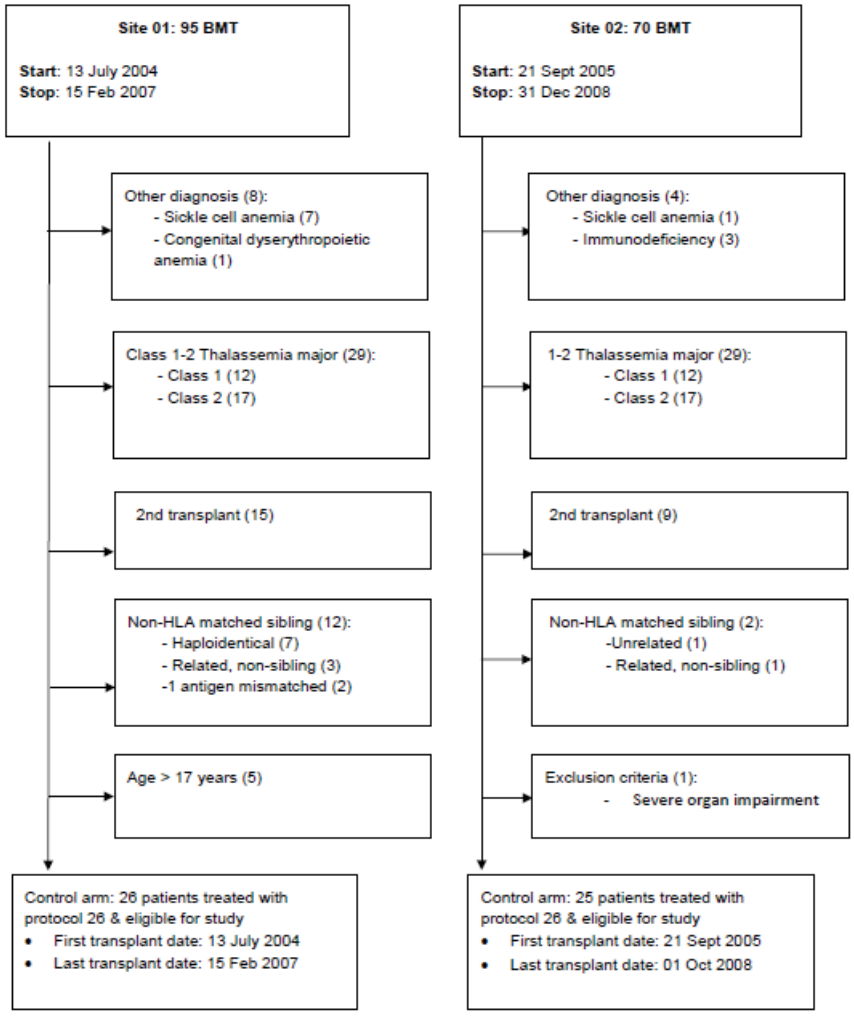
Patients with class 3 thalassemia, transplanted with HLA identical, sibling-matched donors and treated according to the standard Protocol 26 (n=51) at Site 01 (Mediterranean Institute of Hematology, Rome) and Site 02 (Ospedale San Raffaele, Milan) were selected as the control group.

The first pediatric allogeneic bone marrow transplant procedures were conducted at Site 01 and Site 02 on 13 July 2004 and on 21 September 2005 respectively. From these dates, all consecutive, eligible thalassemia class 3 patients aged ≤ 17 years and with HLA-matched sibling donors underwent transplant conditioning according to Protocol 26 until the introduction of the modified Protocol 26M on 15 February 2007 and 01 October 2008 for Sites 01 and 02 respectively.

For site 01, 26 consecutive patients aged ≤ 17 years were transplanted for the indication of thalassemia class 3 between July 2004 and February 2007. All 26 patients met eligibility criteria and were included in the study. For site 02, 26 consecutive patients aged ≤ 17 years were transplanted for this indication between September 2005 and October 2008. Twenty-five patients met eligibility criteria and were included in the study. One patient met the exclusion criteria of severe organ impairment (cardiac impairment), could not receive Protocol 26 and was not included in the study.

The stepwise process used for selecting control patients in each study site is shown in figure 4.

Figure 4: Control Group Patient Selection per Site, RETALCLASS3



Source: RETALCLASS3 - Addendum to Clinical Study Report Figure 1 (Module 5.3.5.1)

Treatments administered

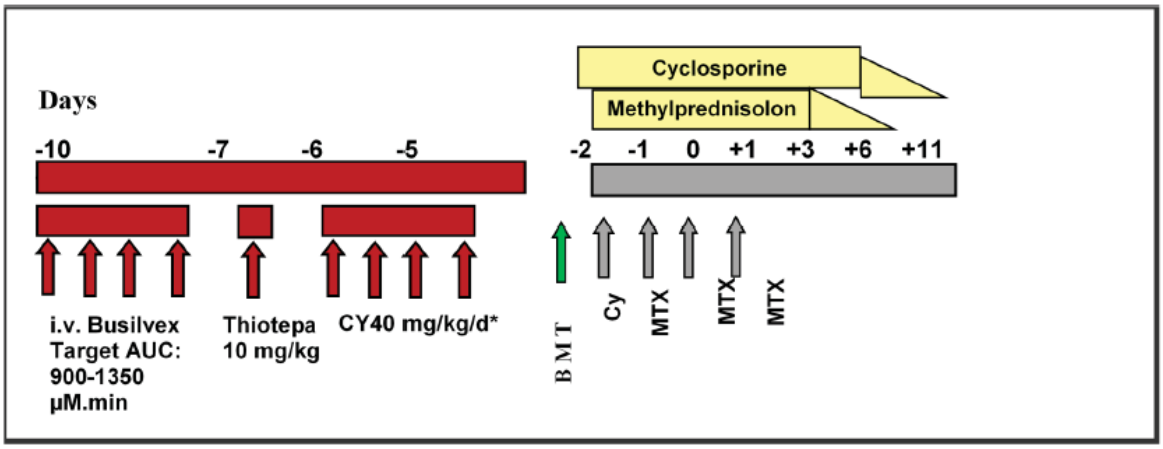
In this observational, retrospective study, no treatments were administered. Procedures and transplant related treatments that were performed or administered to the patients in the past are described below.

Protocol 26M (modified)

There were 2 transplant preparation phases: the pre-conditioning phase and the conditioning regimen.

For pre-conditioning, patients were treated with hydroxyurea, azathioprine (from day -45 through day -12) and fludarabine (from day -16 though day -12). The goal of this phase (Day -45 to -10 pre-transplantation) was to reduce the bone marrow mass expansion in patients and to gradually increase the level of immunosuppression prior to conditioning and thus avoid the extra-hematological toxicity during conditioning. This was followed by conditioning with IV busulphan (weight based dosing), Tepadina (10 mg/kg total dose) and cyclophosphamide (160 mg/kg total dose) as shown in Figure 5.

Figure 5: Conditioning scheme and GvHD prophylaxis for Protocol 26M



Source: Copied from RETALCLASS3 CTR Figure 9.3.1

Day of transplantation (day 0)
At 40-42 hours after the end of cyclophosphamide infusion, bone marrow cells were administered intravenously. The required bone marrow cellularity was > 3.5 x 10^8/kg patient's weight.

Standard Protocol 26
Patients treated according to Protocol 26 received preconditioning cytoreduction/immunosuppression with hydroxyurea, azathioprine (from day -45 through day -12) and fludarabine (from day -17 though day -13) followed by conditioning regimen with oral or weight strata based IV busulfan 14 mg/kg total dose and cyclophosphamide 160 mg/kg total dose. The treatment procedures in the standard protocol 26 are shown in Table 6 below.

Table 6: Treatment procedures in standard protocol 26

Day	Treatment	Time
-45-11	Pretransplantcytoreduction/immunosuppression with Hudroxyurea, Azathioprine and Fludarabine	
-9	Busulfan 3.5 mg/kg/day or weight-based i.v.Busilvex	q6h
-8	Busulfan 3.5 mg/kg/day or weight-based i.v.Busilvex	q6h
-7	Busulfan 3.5 mg/kg/day or weight-based i.v.Busilvex	q6h
-6	Busulfan 3.5 mg/kg/day or weight-based i.v.Busilvex	q6h
-5	Cyclophosphamide 40 mg/kg/day	4pm
-4	Cyclophosphamide 40 mg/kg/day	4pm
-3	Cyclophosphamide 40 mg/kg/day	4pm
-2	Cyclophosphamide 40 mg/kg in 250 ml/2h	4pm
-2	Start Cyclosporine 2.5 mg/kg, i.v. BID	8am-8pm
-1	Continue IV hydration at 3000 ml/m² Start Methylprednisolone 0.5 mg/kg/day Start Ceftriaxone (20-80 mg/kg) OD Start Acyclovir 5 mg/kg TID Immunoglobulins 500 mg/kg see leaflet	
0	Stem cell Infusion; i.v.hydration	
+1	Cyclophosphamide 7.5 mg/kg/day	24h afterBM infusion
+3	Methotrexate 10 mg/m²	
+4	Leucovorin 10 mg/mg2 TID	q8h
+6	Methotrexate 10 mg/m²	
+7	Leucovorin 10 mg/mg² TID	q8h
+8	Immunoglobulins 500 mg/kg	q8h
+11	Methotrexate 10 mg/m²	
+12	Leucovorin 10 mg/mg² TID	q8h
+15	Immunoglobulins 500 mg/kg see leaflet	
+20	BM aspiration for engraftment	
+22	Immunoglobulins 500 mg/kg see leaflet	

NOTES:
1) i.v. Hydration during Busilvex (2000 ml/m²) with N. Saline ml + S. Bicarbonate 8.4%, ml + KCl ml
2) i.v. Hydration during Cyclophosphamide (3000 ml/m²; tot. ml/24h) started 24h before.
Total hydration: ml
ECG daily performed, and urine analysis from day -5 through day 0
Start Acetazolamide mg and Phenobarbital mg per os at 3 pm.
Lasix mg administered 1h and 6h after the end of Cyclophosphamide
Place urine bladder catheter before infusion of Cyclophosphamide on and removed it on
3) The urine output had to be followed in 2 h intervals and to be maintained at least equal to fluid input.
If urine input minus urine output > 300 ml/h, extra Lasix 5-10 mg i.v. given
Check of electrolytes and body weight in 12 h intervals at day -10 through d 0 and substitution of electrolytes as needed.
4) i.v. hydration continued until day 0, then start maintenance hydration according to protocol.
5) Central venous pressure checked (CVP) in 12 h intervals during i.v. hydration, then according to

Source: Copied from RETALCLASS3 CTR, Table 9.3.2

Acute GvHD prophylaxis

For acute GvHD prophylaxis, all patients received cyclosporine from day -2 in 2 IV doses initially and then switched to oral administration. At 24 hours after bone marrow infusion (day +1), cyclophosphamide 7.5 mg/kg was administered, and methotrexate 10 mg/m² on days +3, +6 and +11 from transplant. From day + 60, in the absence of signs of acute GvHD the dose of cyclosporine was gradually reduced until suspension 1 year after transplantation. Patients who developed acute GvHD grade ≥ 2 were treated with methylprednisolone at a dose of 2 mg/kg/day.

Study Methods

The clinical records of pediatric Class 3 thalassemia patients who received allogeneic transplantation from an HLA-identical sibling donor between February 2007 and November 2012 at the two clinical sites in Italy were collected. The period of observation for each patient was one year.

Retrospective clinical and laboratory data at the following study periods and time-points were abstracted:

- Baseline visit pre-transplant
- The transplant phase
- Visits on Post-transplant Days 30, 60, 90, 180 and 365

Retrospective data on the occurrence of RBC transfusion was collected at the transplant visit, 30, 60, 90, 180 and 365 days post-transplant. At day 365 post-transplant, transfusion dependence (after independence) was assessed.

Acute and chronic GvHD

Occurrence and grade (1, 2, 3 or 4) of acute GvHD was recorded at days 30, 60 and 90 post-transplant. The presence of chronic GvHD was reported at day 90, day 180 and day 365 post-transplant, along with the grade (limited or extensive) and localization (skin, liver, gut, lung, other).

Treatment Compliance

Compliance during Tepadina administration (only for Protocol 26M patients) was assessed by number and percentage of subjects with completed and non- completed Tepadina administration, and those in whom Tepadina was not administered at all.

The schedule of study assessments are shown in below.

Table 7: RETALCLASS3 - Schedule of Assessments

	Baseline	Transplant	Days post-transplant				
			+30	+60	+90	+180	+365
	V1	V2	V3	V4	V5	V6	V7
Informed Consent	X						
Demographic data	X	X					
Hematological Disease	X						
Vital signs	X	X					
Pregnancy Test	X						
Instrumental Tests	X	X					
Laboratory Tests	X	X	X				
Serological Assessments	X						
Inclusion/Exclusion criteria	X						
Hematopoietic Stem Cell Transplantation Details		X					
Conditioning regimen		X					
Tepadina Administration		X					

GvHD Prophylaxis		X					
Engraftment			X				
Rejection			X	X	X	X	X
Acute GvHD evaluation			X	X	X		
Chronic GvHD evaluation					X		
Overall Survival			X	X	X	X	X
Thalassemia Recurrence			X	X	X	X	X
Infection		X	X	X	X		
Veno-occlusive disease		X	X	X	X		
Idiopathic Pneumonia		X	X	X	X		
Hemorrhagic Cystitis		X	X	X	X		
Skin Toxicity		X	X	X	X		
Adverse Events		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X

Source: Protocol RETALCLASS3 Section 9.4. Table 9.4.1 Schedule of assessments

The following laboratory parameters were collected at baseline and at transplant visit; from day -10 to day -1 prior to transplantation and from day 1 to day 30 post-transplant.

Table 8: Laboratory parameters evaluated, RETALCLASS3

Parameter	
Hematology	Blood chemistry
Erythrocytes Leukocytes Neutrophils Lymphocytes Monocytes Eosinophils Basophils Hemoglobin Platelets	Renal function: serum creatinine, creatinine clearance* Hepatic function: bilirubin (total and direct bilirubin), Alkaline Phosphatase, AST, ALT, LDH, Gamma-GT Albumin Prothrombin time Glucose Ferritin Urea Sodium Potassium Calcium Magnesium Phosphorus

*Only collected at baseline and at transplant visit.
Source: FDA generated table.

Concomitant medications
From visit 2 to visit 7, Information on previous and concomitant medications received by all patients enrolled was recorded.

Statistical Analysis Plan

The primary efficacy variable was the number and proportion of patients with primary or late graft rejection. The proportion of patients with primary or late graft rejection in the two treatment groups was estimated with their 95% Clopper-Pearson Cis and compared using an exact two-sided binomial test with α=0.05

The effect of pre-conditioning treatments on the following clinical and laboratory manifestations of thalassemia and transplant-related outcomes were evaluated as secondary endpoints.

- Overall survival (OS): defined as the time interval from date of transplant to date of death for any reason. In the absence of death, survival time was censored at the last date of follow-up when the patient was known to be alive. OS estimates were calculated using the Kaplan and Meier product limit estimator and survival estimates were compared with the log-rank test (two sided; α=0.05).

- Thalassemia-free survival (TFS): TFS was defined as the time from date of transplant to date of graft rejection or death to any cause, whichever came first. Subjects without graft rejection and still alive were censored at the last date known to be thalassemia-free. TFS estimates were calculated using the Kaplan and Meier product limit estimator and cumulative incidences were compared with the log-rank test (two sided; α=0.05).

- Transplant-related mortality: defined as the number of patients who died due to transplant-related reasons, at day 100 and at 1 year post-treatment in the two arms. Transplant-related mortality in the two arms was estimated with their 95% Clopper- Pearson Cis and were compared using an exact two-sided binomial test with α=0.05.

- Engraftment: Absolute neutrophils count (ANC) engraftment (3 consecutive days with ANC $\geq$ 500/mm^3) and platelet engraftment (>20 $\times$ 10^9/L at the first day of at least three consecutive days, in the absence of platelet transfusions in the prior 7 days); at day 30 pot-transplant were presented using descriptive statistics. Overall engraftment occurrence, defined as occurrence of both neutrophils and platelets engraftment, was also calculated.

- Time to recovery of ANC and platelet counts were presented as descriptive statistics.Time to recovery of ANC: defined as the number of days from the date of transplant until the first of three consecutive days with ANC values $\geq$ 0.5 x10^9/L. Time to recovery of platelets: defined as the number of days from the date of transplant until the first of seven consecutive days with a platelets count > 20 x10^9/L without platelets transfusion support.

Safety variables

Adverse events were assigned to Preferred Terms (PTs) and System Organ Class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.

The number and percentage of subjects with at least one AE, at least one SAE, at least one ADR , at least one mild, one moderate or one severe AE, at least one AE leading to study discontinuation and at least one fatal AE - were presented overall and by treatment arm. The proportion of patients with at least one event was estimated for each typology of AE, with 95% Clopper-Pearson CIs.

Summary statistics for all laboratory values were presented by parameter and visit. Summary statistics for the differences between values at day 30 post-transplant and transplant visit were presented for each hematology parameter. Shift analyses were performed, according to normal ranges classification, for each hematology parameter comparing abnormalities at day 30 post-transplant and at transplant visit.

The number and percentage (with 95% Clopper-Pearson CIs) of subjects who developed acute GvHD was presented by overall and by visit (day 30, day 90 and day 180 post-transplant). The number and percentage of subjects who developed any chronic GvHD was also presented overall and by visit (day 90 and day 180 post-transplant).

Sample Size
No formal sample size calculation was conducted for RETALCLASS3. All eligible patients with thalassemia class 3, transplanted with HLA identical, sibling-matched donors and treated according to Protocol 26M and with Protocol 26 at the two investigational sites over the treatment period were enrolled.

6 Review of Efficacy

6.1 The proposed indication is to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic progenitor cell transplantation for patients with class 3 β-thalassemia

6.1.1 Methods

The review strategy has been described in Section 5.2.

The efficacy of Tepadina for the proposed indication was based on data from RETALCLASS3 and a review of efficacy data from the published literature. The details of the protocol design for RETALCLASS3were described in Section 5.3.1. Patients were eligible for the protocol if they underwent allogeneic bone marrow transplantation from an HLA-identical sibling donor for class 3 β-thalassemia and treated according to Protocol 26M (a conditioning regimen with busulfan, cyclophosphamide and Tepadina, preceded by preconditioning with hydroxyurea, azathioprine and fludarabine). The control arm were patients treated with standard Protocol 26 (a conditioning regimen with busulfan and cyclophosphamide only, preceded by pre-conditioning with hydroxyurea, azathioprine and fludarabine). The primary efficacy variable was the number and proportion of patients with graft rejection (primary or late).

Reviewer Comment*: *Graft rejection is an appropriate primary efficacy endpoint for Class 3 thalassemia patients undergoing HLA identical, sibling-matched allogenic hematopoietic progenitor cell transplant.
Although the use of historical controls as the comparison group may result in selection bias and may reduce the internal validity of historically controlled studies, the use of this design in this circumstance is justifiable because 1) enrollment of sufficient numbers of patients in a randomized control trial (RCT) was impractical due to the rarity of B thalassemia major, and 2) a RCT could not be blinded and may be potentially unethical due to the widespread use and reported success rates of Tepadina for this indication in class 3 thalassemia patients.

6.1.2 Demographics.

The Efficacy Population consisted of all 76 patients included in the FAS of RETALCLASS3. The FAS was made up of all the transplanted subjects who provided informed consent or assent for the retrospective collection of data, and met the study inclusion/exclusion criteria. Table 9 shows the demographic characteristics of the Efficacy Population. Information on race/ethnicity was not collected in RETALCLASS3.

Table 9: Demographics by Treatment Arm, RETALCLASS3 (FAS, N= 76)

Demographic variable		Protocol 26 (N = 51)	Protocol 26M (N = 25)	p-value
Age at transplant [years], mean (SD)		10.1 (3.4)	10.4 (2.7)	0.6889**
Height [cm], mean (SD)		130.1 (12.6)	131.5 (14.3)	0.6769**
Weight [kg], mean (SD)		26.9 (8.0)	29.2 (8.4)	0.2560**
Gender [N, (%)]	Male	22 (43.1)	15 (60.0)	0.1670*
	Female	29 (56.9)	10 (40.0)	
CMV result [N, (%)]	Positive	48 (94.1)	24 (96.0)	1.0000***
	Negative	3 (5.9)	1 (4.0)	
History of splenectomy [N, (%)]	Yes	20 (39.2)	4 (16.0)	0.0408*
	No	31 (60.8)	21 (84.0)	
History of liver fibrosis [N, (%)]	Yes	51 (100.0)	25 (100.0)	-
Sex donor match [N, (%)]	Yes	29 (56.9)	15 (60.0)	0.7947*
	No	22 (43.1)	10 (40.0)	
Cell dose during transplantation, mean (SD)		4.5 (1.9)	4.4 (1.7)	0.7340**

CMV: cytomegalovirus, N: number of patients, SD: standard deviation
*: Chi square, **: t-test, ***: Fisher Exact test
Source: RETALCLASS3 CSR T-Table 11.2.1.1. Data verified by FDA

Reviewer Comment*: *A potential concern for this historically controlled study is selection bias in the choice of the control population. Controls were patients with class 3 thalassemia, transplanted with marrow from HLA-identical sibling donors with conditioning according to the Standard Protocol 26 at the two study sites. Additional information regarding the stepwise strategies used to select controls at each site was provided by the Applicant at the request of the FDA. This showed that a systematic process without bias was used to select the control population from thalassemia class 3 patients aged ≤ 17 years who presented for first allogeneic bone marrow transplantation at the two study sites.

The demographics of the study population show that subjects with the conditioning regimen including Tepadina (Protocol 26M) and those treated according to the Standard Protocol 26 (historical control group) were generally similar at baseline except for "history of splenectomy," which affected statistically significantly more patients treated with Protocol 26 than Protocol 26M (p-value: 0.0408).

6.1.3 Subject Disposition

Between May 27, 2004 and June 3, 2013, 76 class 3 thalassemia patients ≤ 17 years received conditioning and first BMT from genotypically HLA-matched sibling donors according to the according to standard Protocol 26 and the modified treatment Protocol (Protocol 26M) in 2 study centers in Italy, 51 patients in center 1 and 25 in center 2.

Overall, adherence was good. Eight patients (10.5%) discontinued the study prematurely due to deaths. Only one patient (1.31%) was lost to follow up.

6.1.4 Protocol Deviations

Since RETALCLASS3 was a retrospective study, only protocol deviations related to any visit performed out of schedule were documented. Overall, the number of patients with protocol deviations was highest at 365 days post-transplantation with 95.7% (44 of 46 patients remaining in the study) and lowest at 90 days post transplantation with 81.6% (58 of 71 patients in the study).

6.1.5 Primary Efficacy Endpoints

The primary efficacy endpoint for RETALCLASS3 was the number and proportion of patients with primary or late graft rejection. Primary graft rejection was defined as the presence of <15% donor cells or failure to achieve an absolute neutrophil count (ANC) >500 mm^3 by day 28 post-transplant. Late graft rejection was defined as a loss of donor derived hematopoietic cells in bone marrow and peripheral blood (<15%) after initial graft function and return to erythrocyte transfusion dependence.

Overall, no patient treated with Protocol 26M experienced primary or late graft rejection. In comparison, 13 patients (25.5%) treated according to Protocol 26 experienced graft rejection ($p < 0.01$) (Table 10).

Table 10: Number and Proportion of patients with graft rejection by Protocol type (FAS)

Protocol type	N	%	Clopper-Pearson CI 95%		p-value
			Lower	Upper	
Protocol 26 (N=51)	13	25.5	0.1	0.4	0.0036
Protocol 26M (N=25)	0	0	0	0	

CI: confidence interval; N= number of patients
Source: RETALCLASS3 CSR, Table 11.4.1.1. Data verified by FDA

Reviewer Comment*: *There is a statistically significant difference in the primary efficacy end point between patients treated according to the Tepadina containing regimen (Protocol 26M) and those treated without Tepadina (Protocol 26). Although no formal sample size calculation was performed a priori, a post-hoc assessment was performed to reject a statistically non-significant difference in graft rejection. This showed that the study had 79% power to reject a statistically non-significant difference in graft rejection between the two treatment groups. I agree with the FDA statistician's conclusion that the primary efficacy effect, as measured by number and proportion of patients with graft rejection, is robust.

6.1.6 Subpopulations

The samples size in the efficacy population for RETALCLASS3 was too small for any meaningful subgroup analysis.

6.1.7 Analysis of the Secondary Efficacy Endpoints

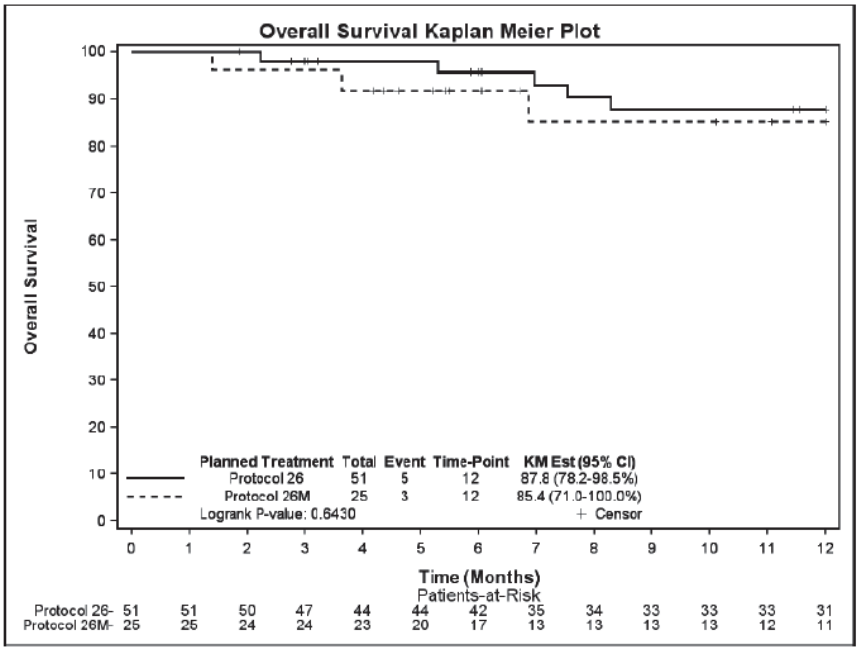
The secondary efficacy variables of interest in RETALCLASS3 were:-

- Overall survival (OS);
- Thalassemia-free survival;
- Transplant-related mortality (TRM) at day 100 and at 1 year post-treatment;
- Absolute ANC count engraftment (3 consecutive days with ANC ≥ 500/mm3) and platelet engraftment (>20 × 109/L at the first day of at least three consecutive days, in the absence of platelet transfusions in the prior 7 days);
- Time to recovery of ANC and platelet counts.

Overall survival

At one year post-transplantation, OS was 85.4% (95% CI: [71.0, 100]) in the Tepadina-treated patients (Protocol 26M) and 87.8% (95% CI: [78.2, 98.5]) in the historical control patients (Protocol 26).

Figure 6: Overall survival by treatment group (Protocol 26 vs Protocol 26M) FAS, N = 76

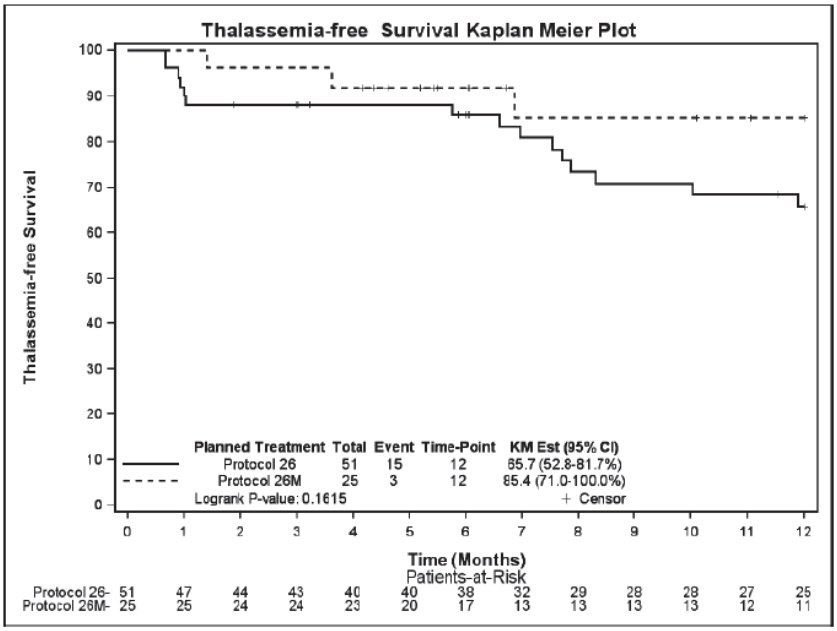


Source: RETALCLASS3 CSR, Figure 11.4.1

Thalassemia free survival

As shown in the figure below, TFS at 12 months were higher for patients treated with Protocol 26M than for patients treated with Protocol 26 (85.4% vs 65.7%) however this difference was not statistically significant (p = 0.16).

Figure 7: Thalassemia-free survival by treatment group (FAS, N = 76)

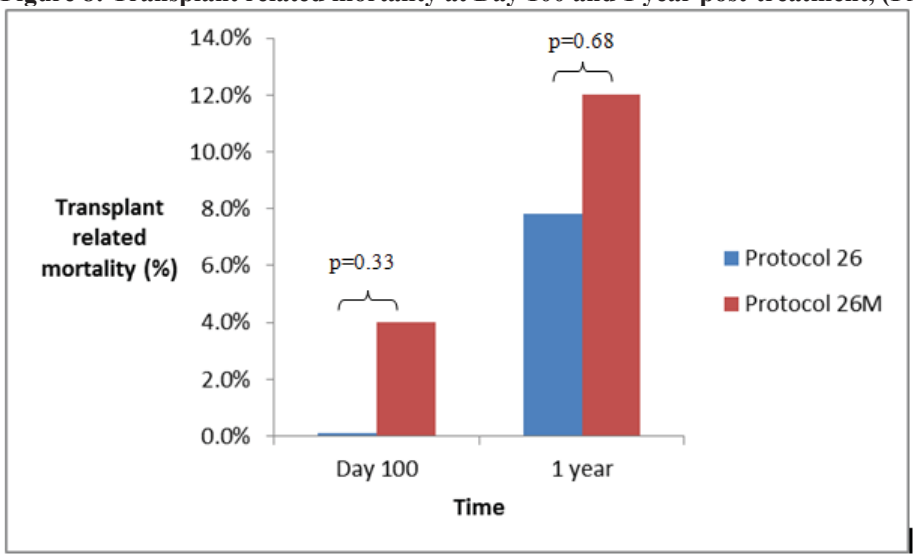


Source: RETALCLASS3 CSR, Figure 11.4.2

Transplant related mortality

Overall, there were eight deaths (3 in the 26M group and 5 in the 26 group) reported in the study population. Seven of these were categorized by the applicant as transplant related deaths. TRM was defined as the number of patients who died due to transplant-related reasons. At Day 100, no patient in the Protocol 26 group died due to TRM compared to 1 patient (4.0%) in the Protocol 26M group (p=0.3289). At 1 year post treatment, TRM was 4 (7.8%) and 3 patients (12.0%) in the Protocol 26 versus Protocol 26M group (p=0.6777). (Figure X).

Figure 8: Transplant related mortality at Day 100 and 1 year post-treatment, (FAS)



Source: FDA analysis

Neutrophils and Platelets Engraftment

Overall engraftment was 92.3% in the Tepadina-treated patients (Protocol 26M) and, and 86.3% in the historical control group (Table 11).

Table 11: Neutrophil and Platelet Engraftment by treatment Protocol (FAS, N=76)

Engraftment	Protocol 26M (N=25)		Protocol 26 (N = 51)	
	N		N	%
Neutrophils engraftment	25	100.0	45	88.2
Platelets engraftment	23	92.0	45	88.2
Overall engraftment	23	92.3	44	86.3

Source: RETALCLASS3 CSR, Table 14. 2.2.4

Engraftment and Time to Recovery of ANC and Platelet Count

All (100%) patients treated with TEPADINA engrafted and 88% of patients in the control group engrafted. Among patients who engrafted, the mean time to recovery of absolute neutrophil count and mean time to recovery of platelet count for patients treated with Tepadina in Protocol 26M and those treated historically with Protocol 26 was 21.0 ± 5.5 days versus 21.8 ± 4.2 days and 27.8 ± 9.6 days versus 28.4 ± 23.0 days, respectively (Table 12).

Table 12: Time (days) to recovery of ANC and platelets (FAS, N = 76)

	Mean (SD)	Median (Q1 – Q3)	Min - Max
Time to recovery of ANC (days)			
Protocol 26M (n = 25)	21.0 (5.5)	21.0 (18.0 – 23.0)	16.0 – 30.0
Protocol 26 (n = 45*)	21.8 (4.2)	20.0 (18.0 – 23.0)	14.0 – 42.0
Time recovery of platelets (days)			
Protocol 26M (n = 23**)	27.8 (9.6)	26.0 (20.0 – 34.0)	13.0 – 50.0
Protocol 26 (n = 45*)	28.4 (23.0)	23.0 (17.0 – 33.0)	12.0 – 160.0

Max: maximum, min: minimum; N = number of subjects, SD = standard deviation; Q: quartile
*Time to ANC and platelet recovery data missing for 6 patients;
**Time to platelet data missing for 2 patients
Source: FDA statistician analysis

Reviewer Comment*: *The mean time to recovery of ANC and platelet counts was similar in patients treated with Tepadina in Protocol 26M and those treated historically with Protocol 26. I agree with the FDA statisticians assessment that because the control patients used in RETALCLASS3 were not treated within the same time frame as the patients treated with Tepadina, time to event data should not be considered in the efficacy assessment of Tepadina for this indication and will not be included in the Tepadina label.

Please note that the sponsor's dataset contained incorrect analysis values for Days to recovery for ANC and for Platelet counts. Correct values were reflected in T-Table 11.4.2.3 of the Applicant's RETALCLASS3CTR and have been confirmed by the FDA statistician.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant provided no analysis of efficacy by Tepadina dose. The recommended dose of Tepadina by the Applicant for the indication of thalassemia in pediatric patients is (b) (4) (b) (4)

***Reviewer Comment*:**
The recommended Tepadina dose (b) (4) *was the only dose evaluated in RETALCLASS3. The doses of Tepadina used in the reviewed scientific literature ranged between 8 and 10 mg/kg/day. FDA did not identify any differences in efficacy outcomes by dose from these previous publications however; the total number of applicable studies reviewed was too small for any meaningful analysis by dose.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects
Not Applicable. Treatment with Tepadina is restricted to one day.

6.1.10 Additional Efficacy Issues
Tepadina should not be administered concurrently with cyclophosphamide when both drugs are present in the same conditioning treatment. This is because concurrent administration of Tepadina with cyclophosphamide in patients reduces the conversion of cyclophosphamide to the active metabolite, 4-hydroxycyclophosphamide, which may potentially reduce the therapeutic benefit of cyclophosphamide.

Reviewer Comment*: *A table is needed in the label for Tepadina to clearly display the timing of administration of Tepadina and cyclophosphamide when both drugs are present in the same conditioning treatment.

6.1.11 Applicants' Literature Review & Meta-analysis
The Applicant presented results from a *systematic literature review* of studies that evaluated the use of thiotepa as a conditioning treatment prior to allogeneic hematopoietic stem cell transplantation in patients with thalassemia and a *meta-analysis* assessing the incidence of graft rejection following allogeneic BMT using different conditioning regimens. The primary efficacy variable for the meta-analysis was the number and proportion of patients with graft rejection. The secondary efficacy variables included OS, TFS, TRM, engraftment, time to recovery of ANC and time to recovery of platelet count.

The primary search for the literature review was conducted using the terms "thiotepa"[All Fields] AND "thalassemia" [All Fields]. Sixteen publications including both retrospective and prospective studies were identified. Case report studies, publications from the same author, publications where efficacy data in thalassemia patients could not be extrapolated and publications in Chinese language were excluded. Nine publications met their criteria for inclusion and a total of 579 patients with thalassemia were included in the meta-analysis.

A summary of the study characteristics of the selected publications is shown in Table 13 below.

Table 13: Study Characteristics

Study	Study design	Number (Male/Female)	Patient Population	Conditioning regimen (drug code plus dose)	Cumulative dose	Thiotepa regimen		
						Infusion Dose (mg/kg)	Total dose (mg/kg)	Application day
Bernardo, 2012	Prospective	60 (32/28)	Thalassemia major	TT-TREO-FLU: n=60	TREO: 42 FLU: 160	8	8	-7
Choudhary, 2013	Consecutive cohort	40 (23/17)	Thalassemia major	TREO-TT-FLU: n=28 BU-CYC-ATG: n=12	TREO: 42 FLU: 160 BU: 14 CYC: 200 ATG: 90	8	8	-6
Gaziev, 2008	Prospective	16 (9/7)	Thalassemia recurrence after graft failure	BU-TT-CYC-ATG: n=16	BU: 14 CYC: 200 ATG: 10/12.5	10	10	-6
La Nasa, 2002	Consecutive cohort	32 (21/11)	Thalassemia major	BU-CYC: n=4 BU-TT-CYC: n=28	BU: 14 CYC: 120/160/200	5	10	-6
Li, 2012	Prospective	82 (56/26)	Thalassemia major	CYC-BU-TT-FLU: n=82	BU: x CYC: 120 FLU: 200	10	10	-5
Lisini, 2008	Retrospective	106 (61/45)	ß-thalassemia	BU-TT-FLU: n=91 BU-TT-CYC: n=12 TT-TREO-FLU: n=3	TREO: 42/FLU: 40 BU: 16/FLU: 160 CYC: 120	5	10	-4
Locatelli, 2003	Retrospective	44 (19/25)[1]	ß-thalassemia, Sickle cell disease	BU-CYC-TT: n=9 BU-FLU-TT: n=7 BU-CYC: n=16	FLU: x BU: x CYC: x	6/8/10	6/8/10	NA
Mathews, 2013	Retrospective	362 (227/135)[2]	Transfusion-dependent ß-thalassemia	BU-CYC: n=139 TT-FLU-TREO: n=50	BU: x CYC: x TREO: 42 FLU: 120	8	8	-6
Sodani, 2010	Prospective	22 (12/10)	Thalassemia major	BU-FLU-TT-CYC-ATG: n=22	FLU: 150 BU: 14 CYC: 200 ATG: 12.5	NA	10	NA

[1] Only 32 patients with ß-thalassemia were included in the meta-analysis
[2] Only 189 class 3 patients were included in the meta-analysis
ATG=antithymocyte globulin; BU=busulfan; CYC= cyclophosphamide; FLU= fludarabine; NA=not available; TREO=treosulfan; TT=thiotepa; x=variable dose or dose unknown

Source: Copied from RETALCLASS3 ISE, Table 5 (Module 5.3.5.3)

To test the pooling assumptions, the Applicant quantitatively measured study heterogeneity by Cochrane Q and I^2 statistics and assessed graphically using a Forest plot. None of these tests were statistically significant.

Results of Meta-analysis

Primary efficacy analyses: The global estimate of graft rejection in treatment regimens containing thiotepa from the meta-analysis using a fixed-effect model was 9.3%, 95% CI [6.7% to 12.5%]. The random-effect model calculated a global estimate of 9.6% with a 95% CI ranging from 6.6% to 13.1%. These results with the respective 95% CIs are shown in Table 14.

Table 14: Meta-Analysis of the Proportion of Patients with Graft Rejection

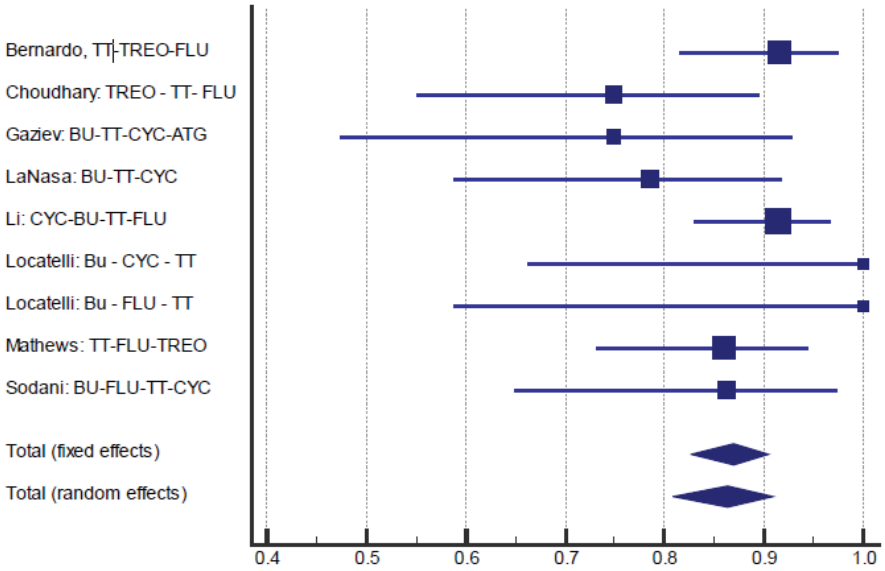
Study	N	Proportion (%)	95% CI
Bernardo, TT-TREO-FLU	60	8.333	2.761, 18.386
Choudhary: TREO - TT- FLU	28	7.143	0.877, 23.503
Gaziev: BU-TT-CYC-ATG	16	6.250	0.158, 30.232
LaNasa: BU-TT-CYC	28	7.143	0.877, 23.503
Li: CYC-BU-TT-FLU	82	3.659	0.761, 10.322
Lisini: BU - TT - FLU	91	9.890	4.623, 17.946
Lisini: BU - TT - CYC	12	16.667	2.086, 48.414
Lisini: TT - TREO - FLU	3	33.333	0.840, 90.570
Locatelli: Bu - CYC - TT	9	11.111	0.281, 48.250
Locatelli: Bu - FLU - TT	7	0.000	0.000, 40.962
Mathews: TT-FLU-TREO	50	8.000	2.223, 19.234
Sodani: BU-FLU-TT-CYC	22	27.273	10.729, 50.222
Total (fixed effects)	408	9.302	6.700, 12.493
Total (random effects)	408	9.640	6.625, 13.149

ATG=antithymocyte globulin; BU=busulfan; CYC= cyclophosphamide; FLU= fludarabine; TREO=treosulfan; TT=thiotepa

Source: Copied from RETALCLASS3 ISE, Table 9 (Module 5.3.5.3)

Secondary Efficacy Analyses: The meta-analysis using a fixed-effect model resulted in a global estimate of OS at 36 months of 86.9%, with a 95% CI ranging from 82.6% to 90.4%. The random-effect model resulted in a global estimate of 86.3% with a 95% CI ranging from 80.9% to 91.0%. The results are shown as a Forest plot in Figure 9.

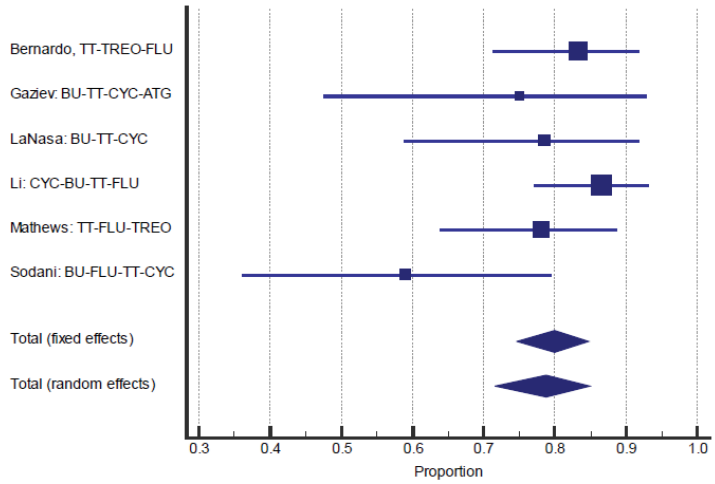
Figure 9: Forest Plot for Overall survival at 36 months



Source: Copied from RETALCLASS3 ISE, Figure 6 (Module 5.3.5.3)

Thalassemia Free Survival (TFS): TFS was defined as the number of patients alive and without thalassemia after 36 months. The meta-analysis using a fixed-effect model calculated a global estimate of TFS at 36 months of 80.0%, with a 95% CI ranging from 74.6% to 84.6%. The random-effect model calculated a global estimate of 78.7% with a 95% CI ranging from 71.7% to 84.9%. The results are shown as a Forest plot in Figure 10.

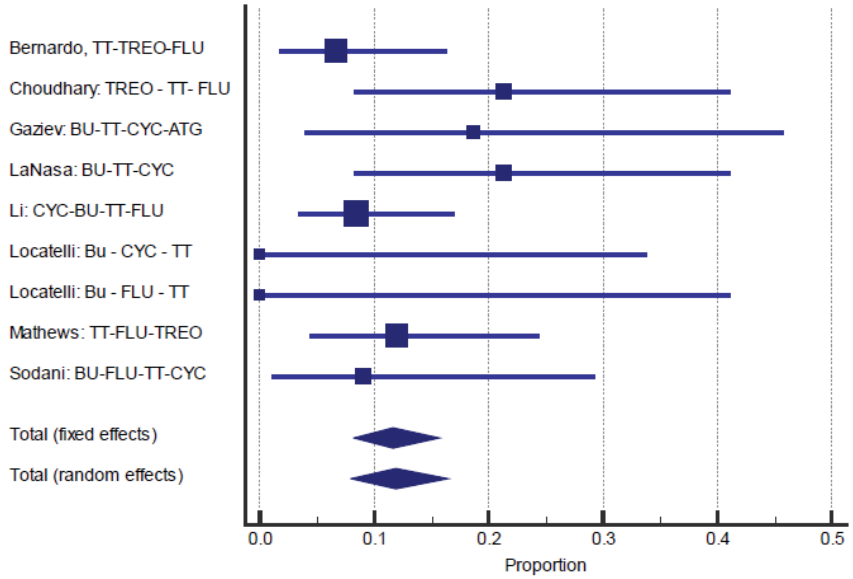
Figure 10: Forest Plot for Thalassemia-Free Survival at 36 Months



Source: Copied from RETALCLASS3 ISE, Figure 8 (Module 5.3.5.3)

Transplant-Related Mortality (TRM): For the secondary endpoint of TRM, the meta-analysis using a fixed-effect model calculated a global estimate of TRM of 11.6%, with a 95% CI ranging from 8.2% to 15.7%. The random-effect model calculated a global estimate of 11.9% with a 95% CI ranging from 8.0% to 16.4%. The results as a Forest plot are shown in Figure 11.

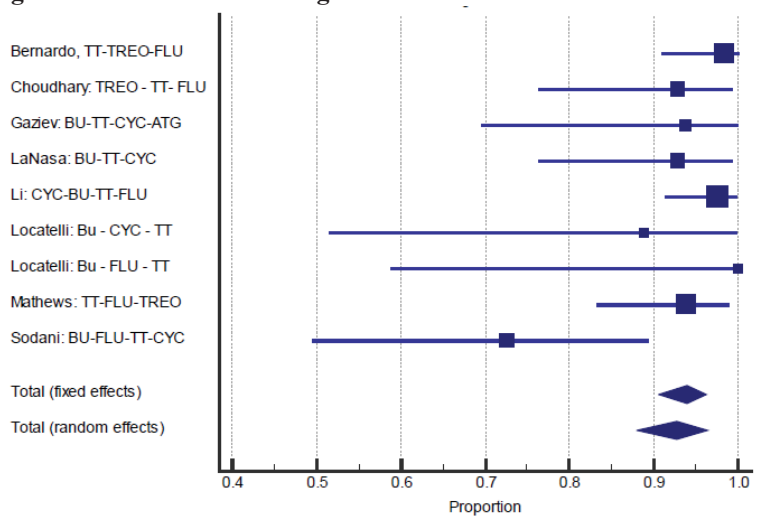
Figure 11: Forest Plot for Transplant Related Mortality



Source: Copied from RETALCLASS3 ISE, Figure 10 (Module 5.3.5.3)

Engraftment: The meta-analysis using a fixed-effect model calculated a global estimate of engraftment of 93.9%, with a 95% CI ranging from 90.6% to 96.3%. The random-effect model calculated a global estimate of 92.8% with a 95% CI ranging from 88.0% to 96.4%. The results as a Forest plot are shown in Figure 12.

Figure 12: Forest Plot for Engraftment



Source: Copied from RETALCLASS3 ISE, Figure 12 (Module 5.3.5.3)

Time to Recovery of ANC and Platelets Count: The weighted mean time to recovery for ANC was 17.6 days (SD: 4.51 days) and the mean time to recovery for platelet count was 24.6 days (SD: 11.97 days). Table 15 displays the reported mean times to ANC and platelets count recovery, as reported in the selected publications.

Table 15: Time to Recovery of ANC and Platelet Count

	Time to Recovery (days and range or SD)	
Conditioning regimen	**ANC**	**Platelet**
Bernardo: TT-TREO-FLU	20 (11-30)	20 (11-36)
Choudhary: TREO-TT- FLU	15 (12-23)	21 (14-34)
Gaziev: BU-TT-CYC-ATG	15 (10-24)	18 (12-60)
La Nasa: BU-TT-CYC	16 (11-26)	30 (16-60)
Li: CYC-BU-TT-FLU	19 (11-30)	16 (8-56)
Lisini: all	NA	NA
Locatelli: all	23 (12-60)	39 (19-92)
Mathews: TT-FLU-TREO	16.1 ± 3.2	18.8 ± 8.0
Sodani: BU-FLU-TT-CYC-ATG	13 (11-17)	12 (9-17)
Weighted mean (SD)	**17.6 (4.51)**	**24.6 (11.97)**

SD= Standard deviation
Source: Copied from RETALCLASS3 ISE, Table 18 (Module 5.3.5.3)

Reviewer Comment: I agree with the FDA statistician's assessment that results of the applicants meta-analysis should not be considered in the evaluation of the efficacy of Tepadina as a conditioning regimen because:

1. ***The literature meta-analysis was not prospectively planned;***
2. ***The follow up times varied across studies; and***
3. ***Not all studies used in the meta-analysis included patients with transplants from HLA-identical sibling donors.***

6.1.12 FDA Literature Review

Methodology

FDA searched the Medline (PubMed) database using a broad search strategy to identify studies evaluating the efficacy of thiotepa as conditioning treatment before allogeneic HSCT in thalassemia. The primary search was conducted using the terms:

("thiotepa"[All Fields]) AND ("graft rejection"[All Fields]) – 36 studies identified
("thiotepa"[All Fields]) AND ("graft failure"[All Fields]) – 51 studies identified
("thiotepa"[All Fields]) AND ("thalassemia"[All Fields] – 17 studies identified

The following types of publications were excluded:

- Publications in languages other than English
- Publications where thiotepa was not used as a conditioning regimen before hematopoietic stem cell transplantation in thalassemia patients
- Publications evaluating the use of thiotepa for non-hematological conditions
- Publications where the safety of thiotepa cannot be extrapolated
- Publications involving the use of thiotepa in non-human models
- Case report studies
- Publications from the same author

One hundred and four publications were identified by the primary search, including both retrospective and prospective studies. Six publications met the criteria for inclusion in the literature review and are summarized below.

1. **Choudhary D, Sharma SK, Gupta N, Kharya G, Pavecha P, Handoo A, Setia R, Katewa S. Treosulfan-thiotepa-fludarabine-based conditioning regimen for allogeneic transplantation in patients with thalassemia major: a single-center experience from north India. Biol Blood Marrow Transplant. (Choudhary, Sharma et al. 2013)**

This prospective study evaluated the safety and efficacy of the treosulfan-based conditioning regimen -treosulfan/thiotepa/fludarabine, (treo/thio/flu) in 28 consecutive patients with thalassemia major who underwent HLA-matched allogeneic HSCT between February 2010 and September 2012 at a single center in New Delhi, India; and to compared these results retrospectively with those in the patients treated earlier with the conventional conditioning regimen consisting of busulfan, cyclophosphamide, and anti-thymocyte globulin (Bu/Cy/ATG) at the same center.

Twenty-eight patients with thalassemia major and a median age of 9.6 years (range 2-18 years) who received HLA-matched allogeneic HSCT using a treosulfan-based conditioning regimen - treosulfan/thiotepa/fludarabine, (treo/thio/flu) were classified according to the Pesaro classification scheme based on liver size, adequacy of chelation, and hepatic fibrosis. Seven patients were in Pesaro class 2, and 21 patients were in Pesaro class 3. Data for 12 patients who underwent HSCT using a busulfan/cyclophosphamide/ATG-based regimen were also analyzed retrospectively and compared with the patients receiving the treosulfan/thiotepa/fludarabine-based protocol with a median age of 7.2 years (range, 2-11 years). Patients in the treo/thio/flu group received i.v. thiotepa 8 mg/kg on day -6, treosulfan 14 g/m^2/day on day -5 to day -3, and fludarabine 40 mg/m^2/day on day -5 to day -2. Patients in the Bu/Cy/ATG group (n=12) received oral busulfan 3.5 mg/kg/day on day -9 to day -6, cyclophosphamide 50 mg/kg/day on day -5 to day -2, and ATG 30 mg/kg/day on day -4 to

day -2. All patients received cyclosporine for 9 to 12 months post-HSCT, with trough plasma cyclosporine levels maintained at 200 - 350 ng/mL.

Efficacy Results: The median duration of follow-up in the treosulfan /thiotepa/fludarabine group was 387 days (range 37 to 930 days). Neutrophil and platelet engraftment occurred at a median of 15 days (range, 12-23 days) and 21 days (range, 14-34 days), respectively. Secondary graft rejection occurred in 2 patients on Days +369 and +414, and six deaths occurred in this group for a cumulative incidence of TRM of 21.4% (95% CI, 4%-35.8%) in the treosulfan /thiotepa/fludarabine group. Thalassemia-free survival and overall survival were 71.4% and 78.5%, respectively. Median chimerism was 100% (range 31% to 100%) in 18 of the 20 evaluable patients at the last follow-up. Fourteen of these patients achieved sustained full-donor chimerism, and 4 patients had mixed chimerism. In the retrospectively analyzed group of patients who received the busulfan/cyclophosphamide/ATG-based conditioning regimen, 2 patients experienced graft rejection (on days +154 and +210) but there was no TRM in this group. The thalassemia free survival and overall survival rates were 83.3% and 100%, respectively. Median chimerism in 8 of the 10 evaluable patients in this group at last follow-up was 100% (range, 61%-100%). Six patients achieved sustained full-donor chimerism, and 2 patients had mixed chimerism. There were no significant differences in the incidence of acute or chronic GVHD, or the incidence of veno-occlusive disease (VOD) between the treo/thio/flu and the Bu/Cy/ATG groups.

Efficacy Conclusions: This relatively small study did not demonstrate any significant differences in the incidence of graft failure, acute GVHD, chronic GVHD, VOD or TRM between the treo/thio/flu and Bu/Cy/ATG groups, although a trend toward higher TRM was seen in the treo/thio/flu group.

2. **Li C, Wu X, Feng X, He Y, Liu H, Pei F, Liao J, He L, Shi L, Li N, Liu Q, Liu S, Chen G, Su Q, Ren Y, Wang Y, Tan W. A novel conditioning regimen improves outcomes in β-thalassemia major patients using unrelated donor peripheral blood stem cell transplantation. (Li, Wu et al. 2012)**

The goal of this prospective study was to evaluate the effectiveness of a conditioning regimen consisting of intravenous busulfan (Bu), cyclophosphamide (Cy), fludarabine (Flu), and thiotepa (TT) (the NF-08-TM HSCT protocol) for allogeneic peripheral blood stem cell transplantation (PBSCT) in children with β-thalassemia major (TM), and to compare the outcomes of this regimen in children undergoing un-related donor -peripheral blood stem cell transplantation (UD-PBSCT) versus children undergoing hematopoietic stem cell transplantation from a well-matched sibling donor (MSD-HBSCT).

Between December 1, 2008 and June 31, 2011, 100 consecutive patients with TM were enrolled in the NF-08-TM protocol, and categorized into 3 groups for which the doses of chemotherapy were adjusted based on the patient's age, ferritin level, and liver size. Because the numbers of patients in group I (n = 9) and in group III (n = 9) were small, the study focused 82 patients in group II who received a uniform conditioning with 55 mg/kg/day Cy (day -10 to day -9); 40 mg/m^2/day Flu (day -8 to day -4); 10 mg/kg/day TT (day -5); and intravenous Bu (day -8 to day -6) at a dose dependent on the age of the patient. All patients received 3 mg/kg azathioprine and 30 mg/kg hydroxyurea daily beginning at day -45 before transplantation. This group included 52 patients with allogeneic PBSCT from unrelated donors (UD-PBSCT) with well-matched human leukocyte antigens and 30 with HSCT from matched sibling donors (MSD-HBSCT). On day 0, patients in the UD-PBSCT group

received granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood stem cells (PBSCs), whereas patients in the MSD-HSCT group received bone marrow (BM, n= 14), BM with pre-cryopreserved cord blood (BM + CB, n= 12), or PBSCs (n= 4). The median follow-up time was 24 months (range 12 to 39 months).

Efficacy Results: Eighty patients had successful engraftment, with >95% donor-derived cells by day +28 and became transfusion-independent. Two MSD-HSCT patients died before engraftment. There were no significant differences in ANC engraftment time between the MSD HSCT and UD PBSCT groups (17.5 days vs 19.0 days, p=0.230). The MSD HSCT group had a shorter duration of ANC <500/mm3 than the UD PBSCT group (18.0 days vs 22.0 days, p=0.010). Platelet engraftment time was similar for the 2 groups (17.0 days vs 15.5 days, p=0.344). Two patients rejected the graft in the MSD HSCT group and one patient rejected his graft during the second month after transplant in the UD PBSCT group (p=0.259).

One patient in the MSD HSCT group died during the conditioning treatment. An additional 6 patients died post- transplants, with a median time to death of 3 months after transplantation (range 1 to 6 months). The estimated 3-year OS was 90.0% in the MSD HSCT group and 92.3% in the UD PBSCT group (p=0.678). The estimated 3-year TFS was 83.3% for the MSD HSCT group and 90.4% in the UD PBSCT group (p=0.309). TRM was similar between the 2 groups (10.0% vs 7.7% for MSD HSCT and UD PBSCT, respectively [p= 0.678].

Efficacy Conclusions: There were no significant differences in efficacy outcomes between β-thalassemia patients who received UD-PBSCT and those who received MSD-HSCT when the NF-08-TM HSCT protocol - a conditioning regimen consisting of intravenous busulfan, cyclophosphamide, fludarabine, and thiotepa - was used.

3. **Sodani P, Isgrò A, Gaziev J, Polchi P, Paciaroni K, Marziali M, Simone MD, Roveda A, Montuoro A, Alfieri C, De Angelis G, Gallucci C, Erer B, Isacchi G, Zinno F, Adorno G, Lanti A, Faulkner L, Testi M, Andreani M, Lucarelli G. Purified T-depleted, CD34+ peripheral blood and bone marrow cell transplantation from haploidentical mother to child with thalassemia. (Sodani, Isgro et al. 2010)**

The objective of this study was to perform primary HSCT from a mismatched mother to thalassemic patient without an HLA-identical donor and to evaluate the use of haploidentical CD3+/CD19+-depleted marrow graft combined with CD34+ selected mobilized PBSCs and CD3+ marrow cells added back at the time of infusion.

Twenty-two children with thalassemia major, ranging in age from 3 to 14 years, received transplants from haploidentical donors (20 mothers and 2 brothers). For conditioning, all patients received 60 mg/kg hydroxyurea and 3 mg/kg azathioprine from Day -59 to -11; 30 mg/m^2 fludarabine from Day -17 to -11; 14 mg/kg busulfan starting on Day -10; and 200 mg/kg cyclophosphamide, 10 mg/kg thiotepa, and 12.5 mg/kg ATG daily from Days -5 to -2. Fourteen patients received CD34+-mobilized peripheral blood and bone marrow progenitor cells; 8 patients received marrow graft-selected PBSCs CD34+ and bone marrow CD3/CD19-depleted cells. T-cell dose was adjusted to 2 x 10^5/kg by fresh marrow cell add back at the time of transplantation. Both groups received cyclosporine for GVHD prophylaxis for 2 months after transplantation.

Efficacy Results: All patients showed donor chimerism by day 14 after HSCT. Fourteen patients showed full chimerism with functioning grafts at a median follow-up of 40 months; none of these patients developed acute or chronic GVHD. Graft rejection with complete autologous reconstitution and return to pre-transplantation clinical status occurred in six patients. In the patients who showed allogeneic reconstitution, the median time for granulocyte recovery was 13 days (range, 11-17 days), and the median time for a self-sustained platelet recovery was 12 days (range, 9-17 days). Three patients showed early mixed chimerism (MC) at 14, 38, and 42 months post- transplantation. Two patients died from transplantation-related causes (cerebral Epstein-Barr virus lymphoma or cytomegalovirus pneumonia).

Efficacy Conclusions: The findings from this study demonstrate the feasibility of maternal haploidentical hematopoietic stem cell transplantation in patients with thalassemia who lack a matched related donor. The conditioning regimen (including thiotepa) was relatively well-tolerated and effective for eradicating the hematopoietic system in patients with thalassemia.

4. Bernardo ME, Zecca M, Piras E, Vacca A, Giorgiani G, Cugno C, Caocci G, Comoli P, Mastronuzzi A, Merli P, La Nasa G, Locatelli F. Treosulfan-based conditioning regimen for allogeneic haematopoietic stem cell transplantation in patients with thalassemia major. (Bernardo, Zecca et al. 2008)

The aim of this phase I-II prospective, non-randomized, clinical trial was to assess the safety, tolerability and efficacy of a treosulfan-based conditioning regimen in young patients with thalassemia undergoing HSCT.

Twenty young (median age 13 years) patients with thalassemia major, transplanted between November 2005 and September 2007 in 2 centers were enrolled in this study. Seven patients were assigned to risk class 1 of the Pesaro classification, 4 to class 2, and 9 to class 3. All patients received the same conditioning regimen consisting of IV thiotepa (8 mg/kg on day -7), treosulfan (14 g/m^2/d from days -6 to -4), and fludarabine (40 mg/m^2/d from days -6 to -3). Three patients were transplanted from an HLA-identical sibling, and the remaining 17 received the allograft from an unrelated donor (UD). Bone marrow was used as the stem cell source in all patients. GVHD prophylaxis varied according to the stem cell source and type of donor.

Efficacy Results: All patients engrafted**.** Secondary graft failure occurred in two patients after transient engraftment of donor cells at day 36 and 270 post- HSCT, respectively. The overall cumulative incidence of graft failure was 11% (95% CI, 3–43). Nineteen patients were alive, at a median follow-up of 20 months (range 8–28). Seventeen were transfusion-independent with sustained donor engraftment of which fourteen achieved sustained full donor chimerism. The 2-year Overall Survival (OS) and Transfusion Free Survival (TFS) were 95% (95% CI, 85–100%) and 85% (95% CI, 66–100%), respectively. There were no observed differences in outcomes for patients by Pesaro risk classification or donor type.

Efficacy Conclusions: These results demonstrate the effectiveness of the combination of thiotepa/treosulfan/fludarabine as a myeloablative regimen for allogeneic HSCT in patients with thalassemia major patients regardless of risk class or the type of donor used.

5. **Mathews V, George B, Viswabandya A, Abraham A, Ahmed R, Ganapule A, et al. Improved Clinical Outcomes of High Risk B Thalassemia Major Patients Undergoing a HLA Matched Related Allogeneic Stem Cell Transplant with a Treosulfan Based Conditioning Regimen and Peripheral Blood Stem Cell Grafts. (Mathews, George et al. 2013)**

In this retrospective study, anonymous data from patients with transfusion-dependent β-thalassemia major who underwent an allogeneic SCT at a hospital in India were evaluated. The clinical outcomes of patients who received a treosulfan based conditioning regimen (consisting of thiotepa 8 mg/kg on day -6, fludarabaine 30 mg/m^2/day from day-5 to -2 and treosulfan 14 gm/m^2/days from day-5 to -3 (TreoFluT) was compared to the outcomes for patients who received the conventional conditioning regiment consisting of a combination of busulfan and cyclophosphamide (BuCy).

Three hundred and sixty-two patients (median age 7±4.4 years) with transfusion-dependent β-thalassemia underwent an allogeneic SCT; 358 (98.8%) of these were from related donors, of which 348 (97.2%) were HLA-identical. There were 16 (4.4%), 144 (39.8%) and 202 (55.8%) transplants in Lucarelli classes 1, 2 and 3, respectively. Eighty-two (40.5%) of the class 3 patients were classified as high risk (Class 3HR) - age ≥7 years and liver size ≥5 cm. Busulfan and cyclophosphamide was used as the conditioning regimen for 139 (68.8%) of the class 3 patients whilst TreoFluT was used in 50 (24.7%) patients. In the class 3 HR patients, 54 (65.8%) were conditioned with BuCy and 24 (29.2%) were conditioning with TreoFluT.

Efficacy Results: The proportion of patients who engrafted post-transplant was higher with the TreoFluT based conditioning regimen with borderline statistical significance in the class 3HR subset (78% vs 96%; p=0.055). Time to achievement of a platelet count >20 X10^9/L was significantly shorter with the TreoFluT conditioning regimen for Class 3 patients and the Class 3HR subset. Among the Class 3 patients, graft rejection occurred in 16 patients (12%) and 4 patients (8%) in the busulfan plus cyclophosphamide and treosulfan plus fludarabine regimens, respectively (p=0.599). Among the HR class 3 subset, graft rejection occurred in 7 patients (13%) and 2 patients (8%) for the BuCy and treosulfan plus fludarabine regimens, respectively (p=0.713).

After excluding patients who had early TRM (<100 days) the median follow up for this study was 42 months (range: 3–254). The 3 year OS and EFS estimate for the entire Class 3 cohort was 67.4 ± 3.5% and 58.9 ± 3.7% respectively. The TreoFluT regimen was associated with a significant improvement in OS compared to the BuCy regimen 63.6±4.2 vs 87.4±4.8; p=0.011, and EFS 57.3±4.3 vs 78.8±6.0 respectively (p=0.041), for Class 3 patients. OS and EFS were also significantly higher in Class 3HR subset conditioned with the TreoFluT regimen (39.4±6.8 vs 86.6±7.3; p=0.002) and (32.4±6.5 vs 77.8±8.8; p=0.003) respectively.

Efficacy Conclusions: These results suggest that in a very high risk group of β-thalassemia major patients undergoing an allogeneic SCT, the treosulfan, fludarabine and thiotepa conditioning regimen is associated with improved overall and event-free survival compared to the conventional regimen of busulfan and cyclophosphamide.

6. **La Nasa G, Caocci G, Argiolu F, Giardini C, Locatelli F, Vacca A, Orofino MG, Piras E, Addari MC, Ledda A, Contu L. Unrelated donor stem cell transplantation in adult patients with thalassemia. Bone Marrow Transplant. (La Nasa, Caocci et al. 2005)**

This study evaluated the outcomes of BMT in high-risk adult thalassemia patients, transplanted from unrelated donors (UD) selected by high-resolution HLA molecular typing at 4 bone marrow transplant (BMT) centers in Italy. From November 1992 to August 2003, twenty-seven consecutive Lucarelli risk class 3 adult thalassemia major patients (median age 22 years [range 17–37]) received a BMT from an UD selected by high-resolution HLA molecular typing. In 15 patients, the conditioning regimen used consisted of busulphan (BU, 14 mg/kg), thiotepa (TT, 10 mg/kg) and Cyclophosphamide (CY, 120– 160 mg/kg). Due to a high incidence of death in the first group of transplanted patients, the conditioning regimen in the remaining patients was changed: BU at 14 mg/kg followed by CY at 120 or 160 mg/kg. All patients received Cyclosporine-A and short-term Methotrexate for graft-versus-host disease (GVHD) prophylaxis. Three patients also received ATG to reduce the risk of both graft rejection and GVHD.

Efficacy Results: Transplantation was successful in 19 patients (70%) with complete, donor-derived, hematological and immunological reconstitution. The median time to granulocyte recovery and to self-sustained platelet recovery was 17 days (range 7–46 days) and 28 days (range 14–86 days) respectively. Eight patients died at a median of 153 days (range 17–470) post transplantation from transplant-related causes. Six out of the 8 deaths occurred in patients conditioned with BU-TT-CY; 2 were in patients who had received the combination BU-CY. The median follow-up of surviving patients is 43 months (range 16–137). The event-free survival and the cumulative incidence of TRM in the 27 patients studied as 70% and 30% respectively.

Ten patients (37%) developed grade II–IV acute GVHD; 4 of these were grades III–IV acute GVHD. Among the 22 patients at risk, six (27%) developed chronic GVHD. In the 16 evaluable patients with a donor identical for at least one extended haplotype, the incidence of grade II–IV acute GVHD was 31% (5/16). By contrast, among the nine recipients who did not share extended haplotypes with the donor, five patients (56%) experienced grade II–IV acute GVHD.

Efficacy conclusions: These results demonstrate that UD-BMT in adult class 3 thalassemia patients, with donors selected through high-resolution molecular typing is feasible and may offer a success rate similar to that historically reported in patients, with similar prognostic characteristics, transplanted from an HLA identical sibling. Albeit not statistically significant, a higher number of deaths were observed in adult patients conditioned with the regimen including thiotepa.

Reviewer Comment: In all studies reviewed, the efficacy of thiotepa as a conditioning treatment for myeloablation prior to allogeneic HSCT was demonstrated.

6.2 Other Indications

The current thiotepa label has indications for the following cancers:
Thiotepa for Injection, USP has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

- Adenocarcinoma of the breast
- Adenocarcinoma of the ovary
- For controlling intracavitary effusions secondary to diffuse of localized neoplastic diseases of various serosal cavities
- For the treatment of superficial papillary carcinoma of the urinary bladder

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

The dosage and administration instructions in the current label are as follows:

- Intravenous administration: Thiotepa may be given by rapid IV administration in doses of 0.3 mg/kg to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.
- Intracavitary administration: The dosage recommended is 0.6 mg/kg to 0.8 mg/kg. Administration is usually through the same tubing which is used to remove fluid from the cavity involved.
- Intravesical Administration: Patients with papillary carcinoma of the bladder are dehydrated for 8 to 12 hours prior to treatment. Then 60 mg of thiotepa in 30 to 60 mL of Sodium Chloride Injection is instilled into the bladder by catheter. For maximum effect, the solution should be retained for 2 hours. If the patient finds it impossible to retain 60 mL for 2 hours, the dose may be given in a volume of 30 ml. If desired, the patient may be positioned every 15 minutes for maximum area contact. The usual course of treatment is once a week for 4 weeks. The course may be repeated if necessary, but second and third courses must be given with caution since bone-marrow depression may be increased. Deaths have occurred after intravesical administration, caused by bone-marrow depression from systemically absorbed drug.

***Reviewer Comment*:**
A consult was sought from the FDA's division of oncology Products 1 (DOP1) regarding:

- ***The indication of thiotepa for the treatment of treatment of adenocarcinomas of the breast or ovary, and for the treatment of superficial papillary carcinoma of the urinary bladder.***
- ***The continued applicability of the doses described under the intravenous, intracavitary and intravesical routes of administration in the current label for thiotepa.***

DOP1 indicated that although thiotepa for IV administration is not used in current standard clinical practice for the treatment of adenocarcinomas of the breast or ovary, and thiotepa for IP administration is only rarely used in clinical practice for the treatment of adenocarcinoma of the ovary; there is no reason, related to safety, that the indication should be deleted from the new PI. Thiotepa is also still used in the treatment of urothelial cancer and there is no reason, related to safety, for a change in the indication for the treatment of urothelial cancer. DOP1 also indicated that there is insufficient information to warrant modification to the instructions for intravesical administration and there does not appear to be data in the literature to negate the prescribed dosing regimens for intravenous and intracavitary administration in the current label.

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of Tepadina in this application was based on safety data presented in RETALCLASS3 and ADN009. Details of the protocol design of both studies were described in Section 5.3.

Additional safety information was sought from a systematic review of the published literature. Since there was no comparative group data for study ADN009, only safety data from RETALCLASS3 is recommended for inclusion in the Tepadina label. The safety information from RETALCLASS3, study ADN009 and the available published literature are reported herein.

7.1.2 Categorization of Adverse Events

Adverse events for study RETALCLASS3 and for ADN009 were reported down to the preferred term (PT) and categorized into System Organ Class (SOC) according using MedDRA Version 18.0. Treatment emergent adverse events (TEAE) were defined as AE that began after the start of infusion of the first dose of study drug. For ADN009, the AE observation period was defined from the start of Tepadina infusion up to 30 days post-transplant for all subjects. For REALCLASS3, the AE observation period was defined from the start of Tepadina infusion up to 30 days post-transplant for the Tepadina group and from the start of the conditioning regimen up to 30 days post-transplant for the control group. The applicant did not pre-specify any adverse events of special interest.

7.1.3 Pooling of Data.

Because the methodology and follow up periods for RETALCLASS3 and study ADN009 were different, safety data from these studies were analyzed separately by the FDA (not pooled) - to avoid the probability of unexplained variables affecting the sensitivity of adverse events in the pooled data (Simpsons Paradox) (Chuang-Stein and Beltangady 2011, Hernan, Clayton et al. 2011). Table 16 below shows the planned scheduled visits for ADN009 and RETALCLASS3.

Table 16: Visit Designations for ADN009 & RETALCLASS3

ADN009			RETALCLASS3		
Visit	**Description**	**Visit No.**	**Visit**	**Description**	**Visit No.**
Screening	Eligibility assessment & demographic data	1	Baseline	Eligibility assessment & demographic data	1
Day 1 - 1st thiotepa infusion	Day 1 - 1st thiotepa infusion	2	Day -6	Day 1 - 1st thiotepa infusion	
Day 1 - 2nd thiotepa infusion	Day 1 - 2nd thiotepa infusion	3		Day 1 - 2nd thiotepa infusion	
Day 2	24 hrs after the start of the 2nd thiotepa infusion	4			
Day 7	Optional	5			
Pre-transplant	Lab tests from Day 3 until transplantation	7			
	Day of transplant		transplant	Day of transplant	2
Post-transplant	Lab tests until Day 30 after transplantation	8			
			Day 30	30 days post-transplant	3
			Day 60	60 days post-transplant	4
			Day 90	90 days post-transplant	5
			Day 180	180 days post-transplant	6
			Day 365	365 days post-transplant	7

Source: Copied from Table 2, Section 1.1. Tepadina ISS document

7.2 Adequacy of Safety Assessments

7.2.1 Safety Population

Safety data were evaluated for all patients in RETALCLASS3 and ADN009 who received at least one dose of Tepadina. Twelve subjects with a median age of 3.5 years (range: 1-14 years), including 4 females, were enrolled from 2 clinical centers in Italy in ADN009. Seventy–six subjects with a mean age of 10.4 years, including 10 females, received Tepadina in RETALCLASS3. The demographic characteristics of all patients enrolled in ADN009 and ADN010 are shown separately in the tables 17 and 18 below.

Table 17: Demographics, Study ADN009 (FAS, N=12)

		Total (N=12)
Age	Mean, years	5.5
	SD	4.6
	Median, years	3.5
	Min; Max	1.0; 14.0
Sex	Female, [N, (%)]	4 (33.3)
	Male, [N, (%)]	8 (66.7)

Height, cm	Mean (Range)	111.2 (82.0 -162.0)
Weight, kg	Mean (Range)	20.2 (10.0-45.0)

Source: FDA analysis
Abbreviations: Max=maximum, Min=minimum, SD= standard deviation.

Table 18: Demographics, RETALCLASS3 (FAS, N= 76)

		Protocol 26M N=25	Protocol 26 N=51	p-value
Age at transplant, years	Mean (SD)	10.4 (2.7)	10.1 (3.4)	0.69
Sex	Female, [N, (%)]	10 (40.0)	29 (56.9)	0.17
	Male [N, (%)]	15 (60.0)	22 (43.1)	
Height, cm	Mean [SD]	131.5 (14.3)	130.1 (12.6)	0.68
Weight, kg	Mean [SD]	26.9 (8.0)	29.2 (8.4)	0.26
History of splenectomy	[N, (%)]	4 (16.0)	20 (39.2)	0.04
History of liver fibrosis [N, (%)]	[N, (%)]	25 (100.0)	51 (100.0)	-
CMV result	[N, (%)]	24 (96.0)	48 (94.1)	1.00

Abbreviations: CMV: cytomegalovirus, SD: standard deviation
*: Chi square, **: t-test, ***: Fisher Exact test
FDA generated table
Data Source: RETALCLASS3 Clinical trial report, T-Table 11.2.1.1

Reviewer comment: Although Study ADN010 was not a randomized study; the baseline demographic characteristics of subjects in both treatment groups were generally similar. Majority of the patients in both groups had a positive test serology result for CMV. The entire study population consisted of children. No safety data for adults was provided.

7.2.2 Explorations for Dose Toxicity Relationship
No formal evaluation of dose-response or AEs by dose was conducted.

Review Comment: Only a single dose level of Tepadina was evaluated in RETALCLASS3 and in Study ADN009; therefore an assessment of dose-toxicity for Tepadina cannot be conducted.

7.2.3 Special Animal and/or In Vitro Testing
There is no new nonclinical information about thiotepa in this submission that warrants special clinical testing.

7.2.4 Routine Clinical Testing
The schedule of safety evaluations for each protocol was described in Section 5.3.

For ADN009, follow-up safety information including hematological assessments was collected from the day of transplant up to 30 days after transplantation. For AND010, clinical safety

evaluations were abstracted at the transplant phase and on Post-transplant Days 30, 60, 90, 180 and 365.

Reviewer comment: Initially, for ADN009, only data from Post- transplant Days 1, 2 and 30 were provided. Similarly for RETALCLASS3, only laboratory data at the transplant phase and on post-transplant Days 30, 60, 90, 180 and 365 was provided by the Applicant. This schedule of safety evaluations was found to be inadequate for assessing the toxicity of Tepadina in patients in the immediate post-transplant period since myelosuppression is a known pharmacologic class effect of alkylating agents especially in the 1st 30 days post transplantation. At the request of FDA, the applicant submitted a revised LB data file with all laboratory tests performed from both study groups from baseline of conditioning (transplant Day -10) through 30 days after transplantation for each subject in Protocols ADN009 and ADN010 within 4 months from the date of filing.

Concomitant Medications

A summary of concomitant medications received by ≥ 20% of patients of either Protocol group is shown in table 19. The 'selective immunosuppressant' antithymocyte globulin was administered to 15 (29.4%) of patients in the Protocol 26 group.

Table 19: Number of patients with concomitant medications (occurrence in ≥ 20% of patients), RETALCLASS3 FAS, N = 76

ATC 2	Medication Class	Protocol 26 (N = 51)	Protocol 26M (N = 25)
		N (%)	
A02	H2-Receptor antagonists	24 (47.1)	19 (76.0)
	Proton pump inhibitors	39 (76.5)	8 (32.0)
A07	Antibiotics	23 (45.1)	18 (72.0)
B01	Other antithrombotic agents	27 (52.9)	1 (4.0)
B02	Vitamin K	45 (88.2)	23 (92.0)
C03	Sulfonamides, plain	30 (58.8)	24 (96.0)
C08	Dihydropyridinederivates	15 (29.4)	8 (32.0)
C09	ACE inhibitors, plain	7 (13.7)	6 (24.0)
H02	Glucocorticoids	34 (66.7)	22 (88.0)
J01	Carbapenems	10 (19.6)	6 (24.0)
	Combinations of penicillins, incl. beta-lactamase inhibitors	25 (49.0)	9 (36.0)
	Combinations of sulphonamides and trimethoprim, incl. derivates	25 (49.0)	16 (64.0)
	Glycopeptideantibacterials	11 (21.6)	2 (8.0)
	Other aminoglycosides	19 (37.3)	4 (16.0)
	Third-generation cephalosporins	45 (88.2)	15 (60.0)
J02	Antibiotics	38 (74.5)	15 (60.0)
	Triazole derivatives	23 (45.1)	9 (36.0)
J05	Nucleosides and nucleotides excl. reverse transcriptase inhibitors	47 (92.2)	24 (96.0)
L01	Alkyl sulfonates	46 (90.2)	21 (84.0)
	Nitrogen mustard analogues	51 (100.0)	25 (100.0)
	Other antineoplastic agents	15 (29.4)	4 (16.0)
	Purine analogues	5 (9.8)	12 (48.0)
L04	Calcineurin inhibitors	50 (98.0)	25 (100.0)
	Other immunosuppressants	51 (100.0)	25 (100.0)
	Selective immunosuppressants	15 (29.4)	0 (0.0)
M04	Preparations inhibiting uric acid production	28 (54.9)	8 (32.0)
N03	Barbiturates and derivatives	7 (13.7)	6 (24.0)
	Fatty and acid derivatives	9 817.7)	9 (36.0)
N05	Benzodiazepine derivatives	16 (31.4)	0 (0.0)

Source: Copied from RETALCLASS3 CTR T-Table 11.2.3.1)

7.2.5 Metabolic, Clearance, and Interaction Workup

The results of the studies of human pharmacokinetics and pharmacodynamics relevant to safety were summarized in Section 4.3

Thiotepa is an immunosuppressive chemotherapeutic agent therefore, live virus and bacterial vaccines must not be administered to a patients receiving Tepadina and at least 3 months must elapse between discontinuation of therapy and vaccination. Thiotepa appears to be metabolized via CYP2B6 and CYP3A4 in the liver. The primary objective of Study ADN009 was originally planned to assess the effect of moderate hepatic impairment on the pharmacokinetics of Tepadina in pediatric patients with Child-Pugh score A vs. patients with Child-Pugh score B undergoing allogeneic HSCT. However, this was prematurely terminated due to difficulty enrolling patients with Child-Pugh B liver impairment and the study subsequently was focused on the general and cardiac safety of Tepadina. Since thiotepa has not been studied in patients with hepatic impairment, and thiotepa is primarily metabolized by the liver, use of Tepadina in patients is not recommended by this reviewer.

Studies in renally impaired patients have not been conducted.

No new general safety or cardiac concerns were raised for Tepadina in the pediatric patients in Study ADN009.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Myelosuppression is a known pharmacologic class effect of alkylating agents and is the main anticipated safety issue for Tepadina earmarked for detailed review. The severity and consequences of myelosuppression in thalassemia patients in ADN009 and RETALCLASS3 will be evaluated. Other expected regimen related toxicities for alkylating agents include: gastrointestinal, and CNS toxicity, veno-occlusive disease, pulmonary damage and renal toxicity.
In the context of use as a conditioning regimen for hematopoietic stem cell transplantation, graft-versus-host disease (GVHD) can be expected and will be specifically evaluated as a safety outcome.

7.3 Major Safety Results

7.3.1 Deaths

Study ADN009

There were no reported deaths in study ADN009.

RETALCLASS3

Eight deaths (3 in Protocol 26M, 5 in Protocol 26) were reported in RETALCLASS3. Deaths caused by AEs with onset between the start of conditioning through day 30 post-transplant were captured as fatal AEs by the applicant. Two fatal AE's (Table 19) were reported under Protocol 26M. No fatal AE's patients were reported under Protocol 26. There were no significant differences between Protocol 26M and Protocol 26 with respect to the incidence of transplant related mortality at day 100 and at 1 year post transplant (Table 20).

Table 20: Cause of death by treatment group, RETALCLASS3

Subject ID	Cause of Death		Fatal AE?
	Protocol 26	Protocol 26M	
(b) (6)		Grade 4 GvHD	Yes
		Gut infection complicated with paralytic ileus and hemorrhagic pneumonia	Yes
		Unknown	Unknown
	GvHD and sudden cardio-circulatory arrest		No
	Pneumonia		No
	Graft failure/rejection and lung aspergillosis		No
	Cardiac arrest during post-transplant splenectomy due to severe refractory thrombocytopenia		No
	Infection		No

Source: FDA Analysis

Table 21: Transplant related mortality at day 100 and 1 year post transplant (FAS, N=76)

	N	%	Clopper-Pearson CI 95%		p-value
			Lower	Upper	
Mortality at day 100					
Protocol 26 (N = 51)	0	0.0	0.0	0.1	0.3289
Protocol 26M (N = 25)	1	4.0	0.0	0.2	
Mortality at year 1					
Protocol 26 (N = 51)	4	7.8	0.0	0.2	0.6777
Protocol 26M (N = 25)	3	12.0	0.0	0.3	

CI: confidence interval, N: number of patients
Source: RETALCLASS3 Clinical trial report, Table 14.2.2.3

Below is a summary of the 3 deaths that occurred under Protocol 26M.

Case 1: Patient (b) (6) was a 9 year old male with a history of growth retardation, hepatic fibrosis at the liver biopsy, hepatomegaly, and infection. He received two Tepadina infusions (dose infused: 90 mg each) on (b) (6), according to Protocol 26M, followed by bone marrow transplantation on (b) (6). On (b) (6), he experienced a severe seizure and developed subarachnoid hemorrhage. He had another seizure described as moderate on (b) (6). He developed GVHD on (b) (6), and died at 42 days post transplantation on (b) (6), due to Grade 4 GvHD. In the opinion of the investigator, the moderate seizure was considered not related to the treatment. However, the severe seizure and subarachnoid hemorrhage were possibly related to treatment.

Review Comment: This reviewer agrees that the events of seizures and subarachnoid hemorrhage were serious and were possibly related to Tepadina treatment. This potential risk should be reflected in the Prescribing Information for Tepadina.

Case 2: Patient (b) (6) was a 9 year old female with a history of hepatic fibrosis, hepatomegaly, and splenomegaly and positive CMV at baseline. She received a bone marrow transplant on (b) (6), and received two Tepadina infusions (dose infused: 120 mg each) on (b) (6) according to Protocol 26M. On (b) (6), she developed moderate veno-occlusive disease, which resolved on (b) (6). On (b) (6) she was diagnosed with moderate pneumonia, which resolved on June 6. She died on (b) (6), (109 days post transplantation) due to a gut infection complicated by paralytic ileus and hemorrhagic pneumonia due to CMV/Adenovirus. In the opinion of the investigator, these events were serious. Pneumonia was considered not related while veno-occlusive disease was considered to be possibly related to treatment.

Review Comment: This reviewer agrees that the event of veno-occlusive disease was at least possibly related to Tepadina ***treatment. This potential risk should be reflected in the Prescribing Information for Tepadina.***

Case 3: Patient (b) (6) was 12 year old male with a history of hepatomegaly, hepatic fibrosis and splenomegaly. He received a bone marrow transplant on (b) (6), and was treated received two Tepadina infusions (dose infused: 150mg each) on (b) (6), according to Protocol 26M. He died on (b) (6), following discharge to his home country. The cause of death is unknown but was determined to be related to bone marrow transplant.

Review Comment: This reviewer is unable to comment on this case in the absence of any information on the cause of death for study subject (b) (6)***.***

7.3.2 Nonfatal Serious Adverse Events

This section provides a summary of non-fatal Serious Adverse Events (SAE) reported under RETALCLASS3 and ADN009 by the applicant.

ADN009

SAEs were reported for 2 patients (16.7%) enrolled in Study ADN009. Both of these SAEs were assessed by the Applicant as not related to the study treatment. Narratives of these 2 SAEs are summarized below.

Patient (b) (6) was a 2 year old female with a history of B lymphoblastic leukemia/lymphoma, NOS. She also had a history of infection, unspecified from (b) (6); and adenovirus infection, from (b) (6). She received HSCT on (b) (6). Her conditioning regimen included busulphan 16.5 mg IV (b) (6) and melphalan 84 mg IV on (b) (6) and Tepadina 70 mg IV on (b) (6) and (b) (6). On (b) (6), she experienced sepsis which resolved on (b) (6). This event was categorized as serious, life-threatening, and a possible role of Tepadina in causing the reported event could not be definitively ruled out by the applicant.

Review Comment: Sepsis is a known class toxicity of alkylating agents. This adverse event was likely related to hematopoietic depression induced by the treatment with busulfan, melphalan and/or Tepadina. I agree that a possible role of Tepadina in causing the event of Sepsis in this patient cannot be ruled out.

Patient (b) (6) was a 14 year old female with a history of B lymphoblastic leukemia/lymphoma. She received HSCT on (b) (6). Her conditioning regimen included fludarabine, treosulfan, and ATG Fresenius. She was treated with Tepadina (225 mg; intravenously x 2 doses) on (b) (6). On (b) (6) she was diagnosed with veno-occlusive liver disease. This event was still ongoing at 4 weeks after the end of the study and the outcome was documented as recovering/resolving. In the opinion of the Applicant, the event was serious, severe, definitely related to treosulfan and not related to Tepadina.

Review Comment: Veno-occlusive liver disease is a known class toxicity of alkylating agents. A possible role of treatment in causing this event cannot be ruled out by this reviewer.

RETALCLASS3

Table 21 shows the number and proportion of subjects with reported SAEs by SOC/PT for subjects enrolled in the RETALCLASS3 study. Overall, SAEs occurred in 16 patients (21.1%): 12 patients (23.5%) in the Protocol 26 group and 4 patients (16.0%) in the Protocol 26M group. These SAEs were predominantly assessed to be not related to treatment.

Table 22: Serious AEs by SOC and PT, RETALCLASS3

	Protocol 26M (N = 25)		Protocol 26 (N = 51)	
SOC	Number of subjects	Proportion (%)	Number of subjects	Proportion (%)
Infections and infestations	2	8.0	2	3.9
Herpes zoster	1	4.0	0	0.0
Pneumonia	1	4.0	0	0.0
Broncho-pulmonary aspergillosis	0	0.0	1	2.0
Sepsis	0	0.0	1	2.0
Gastrointestinal disorders	1	4.0	5	9.8
Gastrointestinal hemorrhage	1	4.0	2	3.9
Ascites	0	0.0	1	2.0
Diarrhea	0	0.0	1	2.0
Mouth hemorrhage	0	0.0	1	2.0
Nervous system disorders	1	4.0	2	3.9
Subarachnoid hemorrhage	1	4.0	0	0.0
Seizure	1	4.0	1	2.0
Loss of consciousness	0	0.0	1	2.0
Vascular disorders	1	4.0	1	2.0
Veno-occlusive disease	1	4.0	1	2.0
Blood and lymphatic system disorders	0	0.0	1	2.0

Thrombocytopenia	0	0.0	1	2.0
General disorders & admin site conditions	0	0.0	3	5.9
Chest pain	0	0.0	1	2.0
Multi-organ failure	0	0.0	1	2.0
Pyrexia	0	0.0	1	2.0
Injury, poisoning & procedural complications	0	0.0	4	7.8
Toxicity to various agents	0	0.0	1	2.0
Fall	0	0.0	1	2.0
Infusion related reaction	0	0.0	2	3.9
Renal and urinary disorders	0	0.0	4	7.8
Acute kidney injury	0	0.0	1	2.0
Cystitis hemorrhagic	0	0.0	2	3.9
Hematuria	0	0.0	1	2.0
Respiratory, thoracic, mediastinal disorders	0	0.0	3	5.9
Dyspnea	0	0.0	2	3.9
Idiopathic pneumonia syndrome	0	0.0	1	2.0
Pleural effusion	0	0.0	1	2.0
Pulmonary edema	0	0.0	1	2.0

Source: FDA analysis

SAEs considered by the Applicant to be at least possibly related to treatment in the Protocol 26M group are displayed in Table 22 below. Three SAE's in the Protocol 26M group were considered to be related to study treatment.

Table 23: Related SAEs, Protocol 26M, RETALCLASS3

	Protocol 26M (N = 25)		**Protocol 26 (N = 51)**	
SOC	*Number of subjects*	*Proportion (%)*	*Number of subjects*	*Proportion (%)*
Gastrointestinal disorders	1	4.0	0	0.0
GI hemorrhage	1	4.0	0	0.0
Injury, poisoning & procedural complications	0	0.0	1	2.0
Toxicity to various agents	0	0.0	1	2.0
Nervous system disorders	1	4.0	1	0.0
Seizure	1	4.0	0	0.0
Subarachnoid hemorrhage	1	4.0	0	0.0
Renal and urinary disorders	0	0.0	0	2.0
Acute kidney injury	0	0.0	1	2.0
Vascular disorders	1	4.0	0	0.0
Veno-occlusive disease	1	4.0	0	0.0

Source: FDA analysis

Review Comment: SAEs were documented 12 patients (23.5%) in the Protocol 26 group and 4 patients (16.0%) of the Protocol 26M group in RETALCLASS3. The most frequently reported (8%) SAE among subjects in the Protocol 26M group belonged to the "Infections and infestation" category. SAEs considered by the applicant to be at least possibly related to treatment in the Protocol 26M group belonged to the Gastrointestinal, Nervous system and Vascular disorders SOC categories.

Narratives of the nonfatal serious adverse events (Protocol 26M)
Summarized below are narratives of the nonfatal serious adverse events reported in the Protocol 26M group of RETALCLASS3.

Patient (b) (6) was a 16-year-old female with a medical history of hepatic fibrosis, hepatomegaly, splenomegaly and other comorbidities who received a bone marrow transplant on (b) (6). She received two IV Tepadina infusions (190 mg each) on (b) (6), for preconditioning according to Protocol 26M. On (b) (6) she was diagnosed with moderate herpes zoster infection which resolved on (b) (6). The applicant categorized this event as serous and not related to Tepadina treatment.

Review Comment: I agree that this event was serious. This event could however possibly be related to immunosuppression resulting from the conditioning treatment (including Tepadina) received pre-transplant.

Patient (b) (6) was a 9 year old female patient with a history of hepatic fibrosis, hepatomegaly and splenomegaly. She received a bone marrow transplant on (b) (6), and was given 2 doses of IV Tepadina infusions (190 mg each) for preconditioning according to Protocol 26M on (b) (6). On day 15 post-transplant, she had an episode of severe gastrointestinal hemorrhage which resolved on (b) (6). This event was categorized as serious and possibly related to treatment by the Applicant.

Review Comment: I agree that the event of gastrointestinal hemorrhage was at least possibly related to treatment with Tepadina. This potential risk should be reflected in the Prescribing Information.

Two other serious and fatal adverse events occurred in Patient (b) (6) (veno-occlusive disease and pneumonia) and Patient (b) (6) (severe seizure and subarachnoid hemorrhage). Narratives of these patients were provided in Section 7.3.1 above.

7.3.3 Dropouts and/or Discontinuations

This section provides a summary of dropouts and/or discontinuations that occurred under RETALCLASS3 and ADN009.

Nine patients (11.8%) discontinued the RETALCLASS3 study before the end of follow-up period. Eight (88.9%) of these discontinuations were due to death (3 from Protocol 26M and 5 from Protocol 26). One patient (11.1%) from Protocol 26 was lost to follow up. The applicant did not provide a reason for the loss to follow up in this patient. There were no early withdrawals due to adverse events.

Twelve patients met eligibility criteria and were enrolled in Study ADN009. There were no dropouts or discontinuations in this study.

7.3.4 Significant Adverse Events

Graft-versus-host Disease

The occurrence and severity of acute and chronic graft-versus-host disease (GVHD) was assessed in patients enrolled in in Study ADN009 and RETALCLASS3 by the Applicant and by the FDA.

ADN009: GVHD of the skin was reported for 2 patients in ADN009; one of these was assessed to be related to study treatment by the Applicant; neither was categorized as serious.

RETALCLASS3: Grade 1-4 acute GvHD occurred in 14/25 patients (56.0%) of the Protocol 26M group and in 20/51 (39.2%) of patients in the Protocol 26 group from Day 30 to Day 90. Grade 2-4 acute GvHD, occurred in 7/25 (28.0%) of patients in the Protocol 26M group and 13/51 (25.5%) in the Protocol 26 group. Table 23 shows the cumulative prevalence and severity of acute GVHD at 30, 60 and 90 days post-transplant for patients by treatment group.

Table 24: Cumulative prevalence of acute GVHD at 30, 60 & 90 days post-transplant, RETALCLASS3 (FAS, N=76)

	30 days post-transplant	
GVHD severity	**Protocol 26M (n=25)**	**Protocol 26 (n=51)**
	Number of occurrences (%)	**Number of occurrences (%)**
1	4(16.0)	8(15.7)
2	5(20.0)	7(13.7)
3	0	0
4	1(4.0)	1(2.0)
Total	10 (40.0)	16 (31.4)

	60 days post-transplant	
	Protocol 26M (n=24)	**Protocol 26 (n=51)**
1	7(28.0)	7 (13.7)
2	5(20.0)	11(21.6)
3	1(4.0)	1(2.0)
4	1(4.0)	1(2.0)
Total	14 (56.0)	20 (39.2)

	90 days post-transplant	
	Protocol 26M (n=23)	**Protocol 26 (n=49)**
1	7(28.0)	7 (13.7)
2	4 (13.0)	11 (21.6)
3	2(8.0)	1 (2.0)
4	1 (4.0)	1 (2.0)
Total	14 (56.0)	20 (39.2)

FDA generated table
Data Source: RETALCLASS3 Updated Clinical Trial Reported, Table 12.5.3.2

At one year post-transplantation, 8/23 (34.8 %) patients in Protocol 26M had developed chronic GvHD (4/23 patients [17.4%] had extensive disease); compared to 7/49 (14.3%) patients with chronic GvHD in the Protocol 26 group of which 3/49 (6.1%) had extensive disease. Table 24 shows the reported prevalence and severity of chronic GVHD at 90, 180 and 365 days post-transplant for patients treated according to Protocol 26M & Protocol 26 in RETALCLASS3.

Table 25: Cumulative prevalence of chronic GVHD at 90, 180 and 365 days post-transplant, RETALCLASS3 (FAS, N=76)

	90 days post-transplant	
	Protocol 26M (n=23)	**Protocol 26 (n=49)**
Chronic GVHD severity	**Number of occurrences (%)**	**Number of occurrences (%)**
Limited	4 (17.4)	1 (2.0)
Extensive	1 (4.3)	2 (4.1)
Total	5 (21.7)	3 (6.1)

	180 days post-transplant	
	Protocol 26M (n=17)	**Protocol 26 (n=11)**
Limited	6 (26.1)	4 (8.2)
Extensive	1 (4.3)	3 (6.1)
Total	7 (30.4)	7 (14.3)

	365 days post-transplant	
	Protocol 26M (n=13)	**Protocol 26 (n=33)**
Limited	4 (17.4)	4 (8.2)
Extensive	4 (17.4)	3 (6.1)
Total	8 (34.8)	7 (14.3)

FDA generated table
Data Source: RETALCLASS3 Updated Clinical Trial Reported, T-Table 12.5.4.1

Review Comment: There were no significant differences in the occurrence or severity of acute GVHD at 30, 60 and 90 days post-transplant in patients treated according to Protocol 26M and Protocol 26 in RETALCLASS3. However, there was a higher prevalence of chronic GVHD occurred in patients who received Protocol 26M compared to those treated according to Protocol 26 across all the time points evaluated. At one year post-transplantation, any chronic GvHD was reported in 34.8 % of patients treated with the Tepadina containing regimen compared to 14.3% in the control group.

The higher prevalence of chronic GVD in the Tepadina group is not surprising, given the absence of graft rejection in this group compared to the 25.5 % incidence of graft rejection (primary or late) in the control (Protocol 26) group. Also, for acute GvHD prophylaxis, all patients in the Protocol 26M and Protocol 26 arms received cyclosporine and other immunosuppressants and all but one patient in the Protocol 26 group also received calcinuerin inhibitors. However the selective immunosuppressant antithymocyte globulin was used in 29.4% of patients in the Protocol 26 group versus none of those in the Protocol 26M group, and likely accounts for part of the lower prevalence of GVHD in the control group.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This section provides a summary of common adverse events reported under RETALCLASS3 and Study ADN009 by the applicant.

ADN009

Table 25 shows a summary of all adverse events reported under Study ADN009. A TEAE was defined as any event not present prior to the initiation of the treatments or any event already present that worsened in either intensity or frequency following exposure to the treatments. All 12 patients enrolled in this study were included in the safety set and all patients received the two scheduled Tepadina infusions. No adverse event lead to treatment discontinuation in this study. Table 26 shows TEAE displayed by SOC and PT.

Table 26: Summary of all AEs, Study ADN009 (Safety population, N=12)

Patients with:	n	%
Any adverse events	11	9.7
At least one TEAE	10	83.3
At least one serious TEAE	2	16.7
At least one Severe TEAE	6	50.0
At least one TEAE related to study drug	9	75.0
Any AE leading to treatment discontinuation	0	0

Source: FDA analysis

Table 27: TEAEs by SOC/PT, Study ADN009 (Safety population, N=12)

TEAEs by SOC/PT	Events	# subjects	Proportion (%)
Blood and lymphatic system disorders	1	1	8.3
Febrile neutropenia	1	1	
General disorders & administration site conditions	14	9	75
Pyrexia	8	6	
Mucosal inflammation	6	6	
Hepatobiliary disorders	2	1	8.3
Hyperbilirubinemia	1	1	
Veno-occlusive liver disease	1	1	
Immune system disorders	2	2	16.7
Graft-versus-host disease in skin	2	2	
Infections and infestations	8	4	33.3
Adenovirus infection	1	1	
Anorectal infection bacterial	1	1	
Clostridium difficile infection	1	1	
Eye infection viral	1	1	
Febrile neutropenia	1	1	
Fungal infection	1	1	
Herpes virus infection	1	1	
Sepsis	1	1	
Nervous system disorders	2	2	16.7
Posterior reversible encephalopathy syndrome	1	1	
Seizure	1	1	

Respiratory, thoracic and mediastinal disorders			8.3
Respiratory tract infection	1	1	

Source: FDA analysis

Reviewer Comment: The most common TEAE reported for Study ADN009 were mucosal inflammation and pyrexia which belong to the "General disorders and administration site conditions" SOC group. Infections and infestations were also common. Although the sample size for study ADN009 is small, these adverse events are consistent with the known myelosuppression effect of thiotepa and other conditioning agents used during the transplant process and also consistent with findings from study ADN010.

RETALCLASS3

At least one adverse event was reported by all 25 patients (100%) and 51 (100%) of subjects treated according to Protocol 26M and Protocol 26. All adverse events reported under Protocol 26M and Protocol 26 are displayed by SOC in decreasing order of frequency in the Table 27. The most common AEs for patients of both Protocol groups belonged to the "Infections and infestations" SOC group. Cytomegalovirus infection (reactivation) was the most common infection in both treatment groups. The second most common adverse event by SOC for both Protocols was "gastrointestinal disorders".

Table 28: Most Frequent AE's by SOC (FAS set, N = 76)

	Protocol 26M (N = 25)		*Protocol 26 (N = 51)*	
SOC	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*
Infections and infestations	31	72.0	87	80.4
Gastrointestinal disorders	24	68.0	45	51.0
Renal and urinary disorders	11	40.0	24	35.3
Hepatobiliary disorders	8	32.0	6	11.8
Skin and subcutaneous tissue disorders	3	12.0	14	23.5
Gen. disorders & administration site conditions	2	8.0	21	29.4
Nervous system disorders	4	8.0	7	13.7
Vascular disorders	2	8.0	1	2.0
Blood and lymphatic system disorders	0	0.0	19	33.3
Cardiac disorders	0	0.0	2	3.9
Injury, poisoning and procedural complications	0	0.0	24	37.3
Investigations	0	0.0	7	11.8
Respiratory, thoracic and mediastinal disorders	0	0.0	11	15.7

Source: FDA analysis

The most common (>10%) TEAE in the Protocol 26M group were cytomegalovirus infection, stomatitis, hepatic function abnormalities, hemorrhagic cystitis, diarrhea, hematuria and pseudomonas infection (Table 28).
Fifty-one out of 85 adverse events (60%) occurred in subjects treated with Protocol 26M and were considered possibly related to study treatment by the investigators (not shown in table). In

subjects treated according to Protocol 26, majority (234/243, 96.3%) of adverse events were considered not related to study treatment. Only 7/243 (2.9%) and 2/ 243 (0.8%) were considered possibly or probably related to treatment respectively. Information on the relatedness of 25 adverse events in the Protocol 26 group was missing and is excluded from these numbers.

Table 29: Most common TEAE (>3%) by PT for patients treated according to Protocol 26M and Protocol 26

	Protocol 26M (N = 25)		Protocol 26 (N = 51)	
AEs by PT	# of subjects	Proportion (%)	# of subjects	Proportion (%)
Cytomegalovirus infection	17	68.0	29	56.9
Stomatitis	15	60.0	12	23.5
Hepatic function abnormal	7	28.0	3	5.9
Cystitis hemorrhagic	6	24.0	9	17.6
Diarrhea	6	24.0	8	15.7
Hematuria	4	16.0	9	17.6
Pseudomonas infection	3	12.0	0	0.0
Candida infection	2	8.0	5	9.8
Acute kidney injury	1	4.0	1	2.0
Cholecystitis	1	4.0	0	0.0
Conjunctivitis	1	4.0	0	0.0
Dermatitis exfoliative	1	4.0	0	0.0
Gastrointestinal hemorrhage	1	4.0	2	3.9
Gastrointestinal inflammation	1	4.0	0	0.0
Hemorrhage intracranial	1	4.0	0	0.0
Herpes zoster	1	4.0	1	2.0
Hypertensive crisis	1	4.0	0	0.0
Mucosal inflammation	1	4.0	10	19.6
Pneumonia	1	4.0	1	2.0
Pyrexia	1	4.0	7	13.7
Rash maculo-papular	1	4.0	4	7.8
Rash pruritic	1	4.0	0	0.0
Seizure	1	4.0	1	2.0
Staphylococcal infection	1	4.0	4	7.8
Stenotrophomonas infection	1	4.0	0	0.0
Subarachnoid hemorrhage	1	4.0	0	0.0
Tonsillitis bacterial	1	4.0	0	0.0
Veno-occlusive disease	1	4.0	1	2.0
Vomiting	1	4.0	8	15.7

Source: FDA analysis

Reviewer Comment: Infections and infestations, particularly Cytomegalovirus infection/reactivation, was the most commonly reported adverse event in subjects enrolled under both protocols. This is not unexpected since majority of subjects in both Protocol 26 and 26M groups were positive for CMV at baseline [48 (94.1%) and 24 (96%) respectively]. The second most

common adverse event by SOC for both Protocols was "gastrointestinal disorders" of which the most frequent adverse event considered at least possibly related to Tepadina treatment was stomatitis. This adverse event should be reflected in the Prescribing Information for Tepadina.

Majority of adverse events were in general comparable between the treatment arms or occurred at higher proportions in the Protocol 26 group except for, hepatobiliary disorders occurred more frequently among patients treated with the Tepadina protocol. This is not surprising since Tepadina is mainly metabolized by the liver. Tepadina has however not been studied in patients with hepatic impairment. This potential risk should be reflected in the Prescribing Information.

A greater proportion of adverse events, particularly gastrointestinal AEs, were considered possibly related or related to Protocol 26M treatment compared to Protocol 26, however, due to the absence of information on the details of majority of AEs occurring in the Protocol 26 group, a meaningful comparison between the 2 protocols cannot be made by this reviewer.

7.4.2 Laboratory Findings

Originally, the Applicant evaluated blood chemistry and hematology parameters at baseline (start of pre-conditioning) and at the transplantation visit for both Study ADN009 & RETALCLASS3. Erythrocytes, leukocytes, neutrophils, hemoglobin and platelets were collected additionally at day 30 post-transplant. At the request of FDA, supplementary hematology and chemistry laboratory test data was collected from baseline through 30 days post-transplant to permit a more complete assessment of the toxicity of Tepadina for studies ADN009 and RETALCLASS3.

RETALCLASS3

Blood chemistry parameters

Below are summary statistics for the observed values at screening /baseline, on the transplant day, and at Day 30, and the change from baseline at these time points for blood chemistry parameters for RETALCLASS3 (Table 29). Only small changes from baseline were seen for most parameters, and no clinically relevant differences were seen between the Tepadina group and the control group.

Table 30: Median (Range) Change from Baseline to Transplant Day for Clinical Chemistry Tests, Safety Population- RETALCLASS3

	Control from RETALCLASS3 study N=51 Transplant Day	Thiotepa from RETALCLASS3 study N=25 Transplant Day
Creatinine (mg/dL)	-0.055 (-1.81, 0.20)	-0.085 (-0.31, 0.43)
Ferritin (µg/L)	0.000 (0.00, 315.51)	-92.10* (-92.10, -92.10)
Alanine aminotransferase (U/L)	-21.0 (-289, 100)	-22.5 (-216, 107)
Aspartate aminotransferase (U/L)	-20.0 (-213, 40)	-25.0 (-385, 85)
Gamma-glutamyl transferase (U/L)	-3.0 (-32, 18)	1.0 (-7, 108)
Glucose (mg/dL)	3.0 (-30, 127)	-6.0 (-33, 25)
Alkaline phosphatase (U/L)	54.5 (-252, 706)	278.0* (278, 278)
Bilirubin (mg/dL)	-0.875 (-4.53, 0.72)	-1.060 (-3.66, 0.790)
Direct bilirubin (mg/dL)	-0.175 (-0.60, 0.31)	-0.135 (-0.33, 0.73)
Lactate dehydrogenase (U/L)	-69.0 (-682, 79)	-118.0 (-634, -67)
Urea (mg/dL)	0.0 (-22, 16)	-5.5 (-29, 15)
Sodium (mEq/L)	-1.00 (-41.0, 18.0)	0.0 (-6, 5)
Potassium (mEq/L)	-0.500 (-2.60, 35.60)	-0.80 (-1.3, 0.0)
Magnesium	-0.0576 (-0.576, 0.400)	-0.2592 (-0.617, 0.387)

Implausible values have not been displayed in the table but are displayed in the listings. Calcium and phosphate values not included in the table because no results were available in the thiotepa group.
* n=1

Source: RETALCLASS3 ISS Table 19

Hematological parameters

Summary statistics for hematological parameters at baseline (pre-conditioning), Day -6 pre-transplant, transplantation, and Day 30 visit are shown by treatment group for the FAS in Table 30 below. Overall, the expected changes in line with conditioning treatment were seen for most parameters, and by 30 days post-transplant, most hematological parameters had normalized and were generally consistent with the underlying condition of the patients. Clinically relevant abnormal values were documented as AEs. No clinically relevant differences were seen between arms.

Table 31: Hematological parameters at baseline, Day -6 pre-transplant, transplantation, and Day 30 visit by treatment group, RETALCLASS3

	Protocol 26			Protocol 26M		
Parameter Visit	N	Mean	SD	N	Mean	SD
Erythrocytes (10^{12}/L)						
Pre-Conditioning Baseline	50	3.6	0.6	25	3.6	0.3
Day 6 before transplantation	47	3.9	0.4	25	3.2	0.3
Transplantation	51	3.2	0.5	25	2.9	0.2
Day 30 after transplantation	21	3.3	0.4	13	3.4	0.3
Lymphocytes (10^9/L)						
Pre-Conditioning Baseline	47	3.7	3.1	24	2.7	1.1
Day 6 before transplantation	43	0.7	0.8	16	0.5	0.3
Transplantation	51	0.2	0.4	20	0.1	0.3
Day 30 after transplantation	21	7.5	30.6	13	0.6	0.4
Monocytes (10^9/L)						
Pre-Conditioning Baseline	42	0.7	0.9	24	0.6	0.5
Day 6 before transplantation	43	0.3	0.4	15	0.2	0.2
Transplantation	51	1.1	7.3	19	0.0	0.0
Day 30 after transplantation	19	2.5	8.4	13	0.4	0.3
Neutrophils (ANC, 10^9/L)						
Pre-Conditioning Baseline	48	4.4	2.8	24	5.4	7.7
Day 6 before transplantation	43	1.2	1.3	16	0.5	0.4
Transplantation	50	1.4	1.2	21	0.9	1.0
Day 30 after transplantation	20	2.4	1.6	13	1.3	0.8
Eosinophils (10^9/L)						
Pre-Conditioning Baseline	42	0.3	0.2	24	0.3	0.3
Day 6 before transplantation	43	0.1	0.1	15	0.1	0.1
Transplantation	51	0.1	0.1	19	0.0	0.0
Day 30 after transplantation	19	0.1	0.1	13	0.0	0.0
Basophils (10^9/L)						
Pre-Conditioning Baseline	42	0.0	0.1	24	0.0	0.0
Day 6 before transplantation	43	0.0	0.0	15	0.0	0.0
Transplantation	51	2.0	14.6	19	0.0	0.0
Day 30 after transplantation	19	0.0	0.0	13	0.0	0.0
Leukocytes(10^9/L)						
Pre-Conditioning Baseline	49	8.7	5.5	25	8.0	5.9
Day 6 before transplantation	48	2.2	1.9	25	1.3	0.8
Transplantation	50	1.7	1.3	25	1.2	1.3
Day 30 after transplantation	19	4.0	2.6	13	2.2	1.2
Hemoglobin (g/dL)						
Pre-Conditioning Baseline	50	9.5	1.6	25	9.5	1.1
Day 6 before transplantation	48	11.2	1.4	25	9.1	0.9
Transplantation	51	9.2	1.7	25	8.4	0.7
Day 30 after transplantation	20	9.7	0.8	13	9.6	0.8
Platelets (10^9/L)						
Pre-Conditioning Baseline	50	402.2	250.0	25	301.6	165.9
Day 6 before transplantation	48	140.6	90.7	25	154.8	88.8
Transplantation	51	163.1	103.2	25	90.2	57.9
Day 30 after transplantation	21	51.6	44.8	13	33.6	39.1

Source: RETALCLASS3 Updated Clinical Trial report, T-Table 12.4.2.1

Demographic differences in Chemistry Tests

The Applicant examined summary statistics for clinical chemistry tests at screening/baseline, on the transplant day, and at Day 30, and the change from baseline at these time points by age (<2 years, 2-11 years, 12-16 years) and (<12 years, and 12-18 years) and gender (males and females). No clinically relevant differences were found between the age categories in either the Tepadina group or the control group, with the exception of median changes in alanine aminotransferase and aspartate aminotransferase in the control group, where a greater decrease was seen in the younger patients (-33 U/L in the <12 age group compared to -1.0 U/L in the 12-18 age group for alanine aminotransferase, and -25 U/L in the <12 age group compared to -7.0 U/L in the 12-18

age group). No clinically relevant differences were seen between males and females in either the Tepadina group or the historical control group.

Worst treatment emergent chemistry abnormalities

Table 31 shows the worst treatment emergent key chemistry abnormalities from baseline through Day 30 post transplantation for subjects in RETALCLASS3. No grade 4 abnormalities in chemistry laboratory test results were reported.

Table 32: Worst chemistry abnormalities from baseline through 30 days post transplantation, Safety population - RETALCLASS3

Laboratory Test (units)	Tepadina (N=25)			Control (N=51)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Creatinine (mg/dL)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.9%)	0 (0.0%)	1 (2.0%)
Aspartate Aminotransferase [AST], (U/L)	20 (80.0%)	4 (16.0%)	0 (0.0%)	45 (88.2%)	9 (17.6%)	0 (0.0%)
Alanine Aminotransferase [ALT], (U/L)	22 (88.0%)	6 (24.0%)	0 (0.0%)	49 (96.1%)	13 (25.5%)	1 (2.0%)
Bilirubin (mg/dL)	20 (80.0%)	4 (16.0%)	0 (0.0%)	39 (76.5%)	2 (3.9%)	0 (0.0%)

Source: Applicant's ISS Statistical Extra Analysis Table T1.1.2

Reviewer Comment: Some abnormalities in hematology and chemistry results due to regimen related toxicities can be expected in hematopoietic transplant recipients in the first 30 days post-transplant.

Overall, the proportion of patients with elevations in serum bilirubin in the Tepadina (80%) and control groups (76.5%) were similar; although a greater proportion of patients in the Tepadina group had severe (Grade 3) abnormalities in serum bilirubin levels. However, it is reassuring that no life threatening or grade 4 serum chemistry abnormalities occurred in the Tepadina group and the prevalence of Grades 3 & 4 abnormalities in serum AST and ALT was similar between the Tepadina and the control group in the safety population.

There were no renal toxicities or abnormalities in creatinine reported during the 30 day post-transplant observation period in the Tepadina group.

ADN009

Hematological parameters: Summary statistics for hematological parameters at by visit (screening, day 1, day 2, and day 30 after transplantation) were evaluated and pre-post differences compared to the screening visit are summarized in Table 32 below. No significant or unexpected changes in hematological parameters were observed.

Table 33: Pre-post differences of hematology parameters (safety set, N = 12)

Parameter	Post-transplant Visit Day	Mean change from screening	SD
Erythrocytes	Day 1	0.0	0.4
	Day 2	-0.2	0.4
	Day 30	-0.1	0.5
Lymphocytes	Day 1	-0.6	1.3
	Day 2	-1.0	1.7
	Day 30	-0.2	1.6
Monocytes	Day 1	0.1	0.2
	Day 2	-0.0	0.3
	Day 30	0.5	1.1
Neutrophils	Day 1	1.1	2.9
	Day 2	0.7	3.4
	Day 30	-0.1	1.8
Eosinophils	Day 1	-0.0	0.1
	Day 2	-0.0	0.2
	Day 30	-0.0	0.1
Basophils	Day 1	0.0	0.0
	Day 2	-0.0	0.1
	Day 30	0.0	0.1
Leukocytes	Day 1	0.6	3.4
	Day 2	-0.4	4.3
	Day 30	0.2	3.9
Hemoglobin	Day 1	0.2	1.2
	Day 2	-0.3	1.1
	Day 30	0.4	1.5
Platelets	Day 1	18.4	99.1
	Day 2	10.3	91.5
	Day 30	-85.0	180.7

SD= Standard deviation
Source data: Protocol AND009 Abbreviated Clinical Study Report Table 14.3.3.1

Worst treatment emergent chemistry abnormalities

Table 33 shows the worst treatment emergent key chemistry abnormalities for the 12 subjects enrolled in ADN009 from baseline through Day 30 it transplantation. No renal toxicities or abnormalities in creatinine were observed in the study ADN009. Majority of patients had evidence of hepatic dysfunction with increased AST or ALT however, most of these abnormalities were mild (grades 1 & 2). One patient had a grade 4 increase in bilirubin.

Table 34: Worst key chemistry Abnormalities from Baseline through 30 Days Post Transplantation, Study ADN009

Laboratory Test	Tepadina Safety Population (N=12)		
	All Grades	Grade 3	Grade 4
Creatinine (mg/dL)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Aspartate Aminotransferase U/L)	12 (100.0%)	1 (8.3%)	0 (0.0%)
Alanine Aminotransferase U/L)	11 (91.7%)	3 (25.0%)	0 (0.0%)
Bilirubin(mg/dL)	10 (83.3%)	1 (8.3%)	1 (8.3%)

Note: Table shows the number and percent of subjects with abnormal laboratory finding according to the CTCAE version 4 criteria. Only the worst abnormality is counted for each subject.
Data Source: RETALCLASS3 ISS Statistical Extra Analysis Table T1.1.1

Review Comment: Overall, the observed abnormalities in hematology and chemistry parameters in Study ADN009 were minimal and consistent with findings RETALCLASS3.

7.4.3 Vital Signs

ADN009: The applicant provided individual vital signs data at screening and at the end of first Tepadina infusion were for each of the 12 subjects enrolled in ADN009. FDA did not identify any trends in blood pressure, heart rate of body temperature in the data provided.

For RETALCLASS3, vital signs were assessed at baseline an at the transplant visit. At baseline, the mean values for systolic blood pressure and diastolic blood pressure for the FAS were 105.1 mmHg (SD 15.6) and 62.0 mmHg (SD 15.4) respectively. The mean pulse rate was 87.6 beats/min (SD 9.3) and the mean body temperature was 36.4°C (SD: 0.4) for the FAS. However, vital signs at the transplantation visit was only available for 2 patients in the Protocol 26M group and 1 patient in the Protocol 26 group, so no objective assessments of pre-post treatment differences in vital signs could be performed by the FDA.

7.4.4 Electrocardiograms (ECGs)

The applicant evaluated the cardiac safety of Tepadina and in particular its effects on the ventricular repolarization (QT/QTc interval) in pediatric patients in Study ADN009. Twelve-lead ECG tracings were collected before infusion, 3 hours after the end of the first and second Tepadina infusions, and 24 hours after the second infusion of Tepadina. Additional tracings were obtained on day 7 in patients with clinically-relevant observed alterations in ECG tracings.

No U-waves, arrhythmias, or other ECG abnormalities were reported in any patient. No relevant effects of Tepadina on QT/QTc intervals pre and post Tepadina infusion were reported (Table 34). Majority of patients with available data had QTc interval increases from baseline of less than 30 msec. All patients with available data had QTc interval increases from baseline less than 60 msec. The applicant concluded that Tepadina had no negative effect on the ventricular repolarization in the pediatric patients.

Table 35: Pre-post differences of ECG parameters, AND009 (safety set, N = 12)

Parameter Visit	Mean change from screening	SD
QT interval, single beat		
Day 1 (1st Thiotepa infusion)	-4.0	24.0
Day 1 (2nd Thiotepa infusion)	18.8	34.9
Day 2	7.4	33.7
QTcB interval, single beat		
Day 1 (1st Thiotepa infusion)	-6.0	21.9
Day 1 (2nd Thiotepa infusion)	-0.5	30.1
Day 2	-4.0	28.1
QTcF interval, single beat		
Day 1 (1st Thiotepa infusion)	0.0	0.0
Day 1 (2nd Thiotepa infusion)	22.8	20.6
Day 2	13.8	18.2
QTcL interval, single beat		
Day 1 (1st Thiotepa infusion)	0.0	0.0
Day 1 (2nd Thiotepa infusion)	18.0	17.5
Day 2	8.3	8.5

QT = QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle), QTc = corrected QC, QTcB = Bazett QT correction, QTcF = Fridericia QT correction, QTcL = Framingham QT correction, SD = standard deviation
Source: Copied from AND009 - Abbreviated Clinical Study Report - Table 14.3.4.3

The Interdisciplinary Review Team provided an assessment of the effect of Tepadina on the QTc interval in the review of this NDA. Major limitations in the design of the QT study including the small sample size, inadequate ECG assessment strategies and discrepancies between the ECG intervals in the clinical dataset and those in the paper ECG tracings were identified. Given these limitations, the IRT concluded that they are unable determine whether or not Tepadina has an effect on the QTc (Interdisciplinary Review Team for QT Studies Consultation dated 7/19/2016).

Review Comment: I agree that the available data is inadequate for determining the effect of Tepadina on cardiac conduction. No QT information should be included in the label for Tepadina.

7.4.5 Special Safety Studies/Clinical Trials

Performance Status

In ADN009, the applicant evaluated the general effect on Tepadina on performance status in study patients. No general effect on Tepadina on performance status was observed. A Lansky index of 100% (i.e. fully active, normal) was documented at screening and at the end of the first Tepadina infusion for most subjects.

7.4.6 Immunogenicity

There was clinical data on the immunogenicity of Tepadina in this submission.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

FDA was unable to conduct an analysis of adverse events by Tepadina dose because only a single dose level of Tepadina (10 mg/kg/day divided in two daily infusions) was evaluated in RETALCLASS3 and Study ADN009. In the reviewed scientific literature, the dose of thiotepa reported ranged between 8 and 10 mg/kg/day. The total number of eligible studies reviewed was too small for any meaningful analysis of safety by dose.

7.5.2 Time Dependency for Adverse Events

Given the short term administration of Tepadina in RETALCLASS3 and ADN009, there is insufficient information about time-dependency for adverse events.

7.5.3 Drug-Demographic Interactions

This section provides a summary of the analysis of TEAE by selected demographic variables (age and gender) for RETALCLASS3. The total number of subjects (N=12) enrolled in Study ADN009 was too small to permit any meaningful analysis of demographic differences in AEs.

TEAE by Age

FDA assessed TEAE in subjects treated according to Protocol 26M by age at transplantation in RETALCLASS3. Table 35 lists the adverse events for subjects treated according to Protocol 26M by age group (< 12 years versus ≥12 years) in decreasing order of risk difference between the older and younger age groups. Only adverse events with a risk difference of at least 10% between the 2 age categories are shown. The greatest risk difference between the two age groups was in the frequency of stomatitis which was higher in the younger age group (10/14; 71.4%) than in those aged ≥12 years (5/11; 45.5%). However when the grouped term of mucosal inflammation and stomatitis were assessed (results not shown in table), the risk difference between the age groups were much less (10/14 vs 6/11). Hepatic function abnormalities and hematuria occurred more frequently in the older age group (≥12 years).

Table 36: TEAE for patients treated according to Protocol 26M by age at transplantation

Preferred Term	*Age < 12 years (N = 14)*		*Age ≥12 years (N = 11)*		Risk Difference (%)
	n	(%)	n	(%)	
Stomatitis	10	71.43	5	45.45	25.97
Candida infection	2	14.29	0	0	14.29
Hepatic function abnormal	3	21.43	4	36.36	-14.94
Hematuria	1	7.14	3	27.27	-20.13

Source: FDA analysis

FDA further evaluated age differences in adverse events by study treatment. Table 36 shows adverse events by treatment arm for subjects < 12 years of age by preferred term (PT) only. Only adverse events with greater than 10% risk difference in adverse events by treatment group are displayed. Stomatitis was the most common AE and occurred at a higher frequency in the Tepadina (Protocol 26M) treatment group.

Table 37: TEAE by treatment arm for subjects <12 years at the time of transplantation

Preferred Term	Protocol 26M (N = 14)		Protocol 26 (N = 34)		Risk Difference (%)
	n	(%)	n	(%)	
Stomatitis	10	71.43	8	23.53	47.9
Hepatic function abnormal	3	21.43	2	5.88	15.55
Pseudomonas infection	2	14.29	0	0	14.29
Cytomegalovirus infection	11	71.43	25	58.82	12.61
Hematuria	1	7.14	7	17.65	-10.5
Mucosal inflammation	0	0	7	20.59	-20.59
Infusion related reaction	0	0	14	38.24	-38.24
Febrile neutropenia	0	0	15	41.18	-41.18

Source: FDA analysis

TEAE by gender

Table 37 shows adverse events (in decreasing order of risk difference) by gender between genders. Only TEAE with a difference in incidence of at least 10% are shown. Hepatic function abnormalities and stomatitis occurred more frequently in males versus females. Diarrhea and candida infections were more common in females.

Table 38: TEAE by gender events for patients treated according to Protocol 26M

Preferred Term	Males (n = 16)		Females (n = 10)		Risk Difference (%)
	n	(%)	n	(%)	
Stomatitis	10	62.5	5	50	12.5
Hepatic function abnormal	5	31.25	2	20	11.25
Acute kidney injury	0	0	1	10	-10
Cholecystitis	0	0	1	10	-10
Dermatitis exfoliative	0	0	1	10	-10
Gastrointestinal hemorrhage	0	0	1	10	-10
Gastrointestinal inflammation	0	0	1	10	-10
Hemorrhage intracranial	0	0	1	10	-10
Herpes zoster	0	0	1	10	-10
Hypertensive crisis	0	0	1	10	-10
Mucosal inflammation	0	0	1	10	-10
Pneumonia	0	0	1	10	-10
Stenotrophomonas infection	0	0	1	10	-10
Tonsillitis bacterial	0	0	1	10	-10

Venoocclusive disease	0	0	1	10	-10
Vomiting	0	0	1	10	-10
Diarrhea	3	18.75	3	30	-11.25
Candida infection	0	0	2	20	-20

Source: FDA analysis

Reviewer Comment: For patients who received the Tepadina containing regimen (Protocol 26M), the greatest risk difference in TEAE between subjects less than 12 years versus those 12 years or older was in the frequency of stomatitis (risk difference 25.9%). Stomatitis (oral mucositis) refers to inflammation and ulceration that occur in the mouth. Mucositis is a frequent complication in bone marrow transplantation(Gabriel, Shea et al. 2003). Some previous studies have identified age as a risk factor for chemotherapy-induced mucositis which may be related to the greater mitotic rate and to the presence of a greater number of receptors for the epidermal growth factor in younger patients (Pico, Avila-Garavito et al. 1998). In the RETALCLASS3 study population, there was a higher frequency of stomatitis in patients less than 12 years of age; however, this difference was not statistically significant and may not be clinically meaningful in view of the small number of patients evaluated in this group.

Although there were substantial differences in the risk for stomatitis and hepatic function abnormalities by gender, there is no biological basis for this difference so these findings are considered random by this reviewer.

7.5.4 Drug-Disease Interactions

All patients enrolled in RETALCLASS3 and ADN009 had Class 3 β-thalassemia. Among RETALCLASS3 patients', the frequency of history of splenectomy was significantly higher among patients treated with Protocol 26M than among those treated with Protocol 26 (p= 0.04).

Table 38 shows adverse events (by PT) in subjects treated according to Protocol 26M by history of splenectomy in decreasing order of risk difference between groups. Only adverse events with a risk difference of at least 10% are shown. There were substantial differences in the risk for hemorrhagic cystitis, conjunctivitis, maculo-papular rash and hematuria among patients who had a history of splenectomy; however, in the absence of any biological basis for this, these findings are considered random by this reviewer.

Table 39: Adverse Events by history of splenectomy, Protocol 26M

	Splenectomy Y (N = 4)		*N (N = 21)*		
PT	*Events*	*Proportion (%)*	*Events*	*Proportion (%)*	*RD (per hundred)*
Cystitis hemorrhagic	2	50	4	19.05	30.95
Conjunctivitis	1	25	0	0	25
Rash maculo-papular	1	25	0	0	25
Hematuria	1	25	3	14.29	10.71
Pseudomonas infection	0	0	3	14.29	-14.29
CMV infection	3	50	17	71.43	-21.43
Stomatitis	1	25	14	66.67	-41.67

Source: FDA analysis

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies with TEPADINA have been conducted.

Reviewer Comment: In vitro studies suggest that thiotepa is metabolized to its active metabolite TEPA by CYP3A4 and CYP2B6. Medications which are strong inhibitors or inducers of CYP3A4 and CYP2B6 are therefore likely to affect the efficacy and/or toxicity of Tepadina and should be avoided during treatment with Tepadina. This information should be included in the drug label.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There is insufficient follow-up in the healthy volunteer studies for a meaningful analysis of carcinogenicity risk.

7.6.2 Human Reproduction and Pregnancy Data

No clinical data on the use of Tepadina during pregnancy was submitted in this application.

FDA searched the Medline (PubMed) database for publications on effects of thiotepa on pregnancy. Two eligible studies were identified - One retrospective study (Lacher and Toner 1986) and one case report (Elberg, Brok et al. 1989). Lacher and Toner evaluated the menstrual cycle, pregnancies, and offspring before and after initial combined radiation and chemotherapy with thiotepa, vinblastine, vincristine, procarbazine, and prednisone (TVPP) in 34 women (aged 18 - 44 years; median 26.5 years) treated for Stage II and Stage III Hodgkin's disease. Seventeen pregnancies occurred in 12 women after therapy; 2 had 4 elective abortions; 10 delivered 12 children with normal physical development; 1 was still pregnant at the time of publication. The authors concluded that the ability to become pregnant and have normal children after intensive chemotherapy and radiotherapy was comparable to the patients' pretreatment record.

Elberg J reported a case of congenital bilateral eventration of the diaphragm in a pair of male twins. The mother was a 28 year old nurse, who between the eighth and tenth week of pregnancy, had been in contact with a patient treated intrapleurally with thiotepa. Exposure of the mother to thiotepa in the first trimester of pregnancy was thought to be a possible etiologic factor.

In pre-clinical studies, administration of thiotepa to pregnant rats and rabbits during organogenesis produced teratogenic effects at doses corresponding to the maximum recommended human daily dose on a mg/m^2 basis. Thiotepa was lethal to rabbit fetuses at approximately 2 times the maximum recommended human therapeutic dose based on body-surface area. It is unknown whether thiotepa is excreted in human milk. Due to the potential toxicity for breast-fed newborns/infants, breast-feeding is contraindicated during treatment with thiotepa.

Review Comment: The available evidence is insufficient to determine the safety of Tepadina use before or during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

No data on the effect of thiotepa on growth in pediatric patients was submitted for this application. The effect of Tepadina on pediatric growth is unknown.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no events in the ISS adverse events data file pertaining to an overdose of TEPADINA.

Review Comment: I agree with the applicant that since Tepadina is only administered in hospital under closely monitored conditions, the risk of overdose is minimal.

7.7 Additional Submissions / Safety Issues

7.7.1 Literature Review & Meta-analysis

The Applicant conducted a systematic review and meta-analysis using published literature on thalassemia major patients undergoing BMT following myeloablative conditioning treatment preceded by cytoreduction/immunosuppression.

A descriptive summary of design and quality of the studies included in the meta-analysis was provided and overall results were estimated in a pooled fashion using Forest plots. The safety variable chosen for the meta-analysis was the occurrence of acute and chronic GVHD and safety data were summarized by conditioning regimen and toxicity grade. Acute and chronic GVHD grade was not included in the meta-analysis.

Applicants Methodology

The primary search was conducted using the terms "thiotepa"[All Fields] AND “thalassemia” [All Fields]. Sixteen publications were identified by this search, including both retrospective and prospective studies. Nine studies (N= 576 patients) met the criteria for inclusion in the meta-analysis. A summary of the study characteristics is shown below (Table 39).

Table 40: Characteristics of studies included in Applicants meta-analysis

Study	Study design	Number (Male/Female)	Patient Population	Conditioning regimen (drug code plus dose)
Bernardo, 2012	Prospective	60 (32/28)	Thalassemia major	TT-TREO-FLU: n=60
Choudhary, 2013	Consecutive cohort	40 (23/17)	Thalassemia major	TREO-TT-FLU: n=28 BU-CYC-ATG: n=12
Gaziev, 2008	Prospective	16 (9/7)	Thalassemia recurrence after graft failure	BU-TT-CYC-ATG: n=16
La Nasa, 2002	Consecutive cohort	32 (21/11)	Thalassemia major	BU-CYC: n=4 BU-TT-CYC: n=28
Li, 2012	Prospective	82 (56/26)	Thalassemia major	CYC-BU-TT-FLU: n=82
Lisini, 2008	Retrospective	106 (61/45)	ß-thalassemia	BU-TT-FLU: n=91 BU-TT-CYC: n=12 TT-TREO-FLU: n=3
Locatelli, 2003	Retrospective	44 (19/25)[1]	ß-thalassemia, Sickle cell disease	BU-CYC-TT: n=9 BU-FLU-TT: n=7 BU-CYC: n=16
Mathews, 2013	Retrospective	362 (227/135)[2]	Transfusion-dependent ß-thalassemia	BU-CYC: n=139 TT-FLU-TREO: n=50
Sodani, 2010	Prospective	22 (12/10)	Thalassemia major	BU-FLU-TT-CYC-ATG: n=22

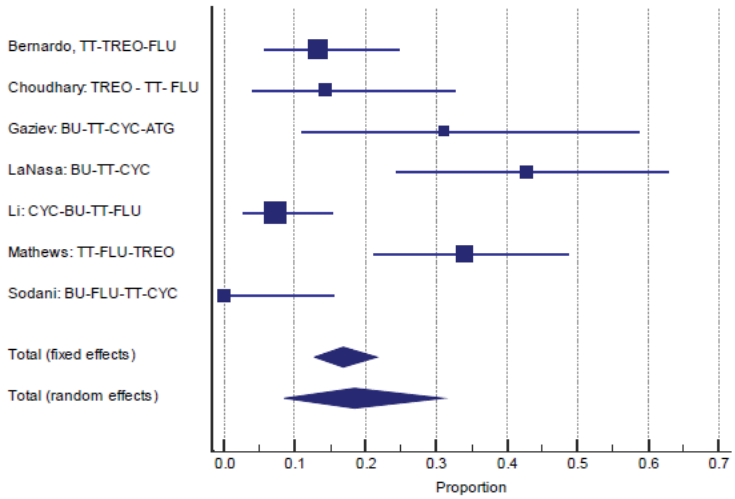
Source: Copied from Applicants ISS, Table 22.

To test the pooling assumptions, the Applicant quantitatively measured study heterogeneity by Cochrane Q and I^2 statistics. Both of the tests for acute and chronic GVHD were statistically significant ($p<0.005$), indicating differences in rates of acute and chronic GVHD between the manuscripts.

Results of Applicant's Meta-analysis

Acute GVHD: The fixed-effect model resulted in a global estimate of acute GVHD of 16.9% (95% CI 12.8% - 21.6%). The random-effect model resulted in a global estimate of 18.4% (95% CI: 8.5%- 31.0%). The meta-analysis results are shown in Figure 13.

Figure 13: Forest Plot for Acute GVHD

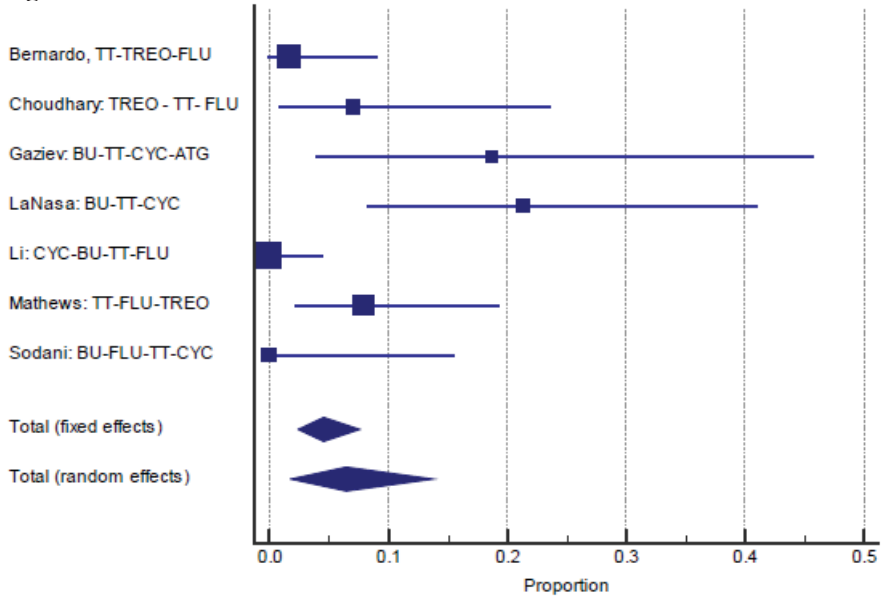


Source: Copied from Applicants ISS, Figure 1

Chronic GVHD

The meta-analysis using a fixed-effect model resulted in a global estimate of chronic GVHD of 4.5% (95% CI 2.4% - 7.6%). The random-effect model resulted in a global estimate of 6.4% (95% CI 1.7% - 13.8%). The meta-analysis results are shown in Figure 14.

Figure 14: Forest Plot for Chronic GVHD



Source: Copied from Applicants ISS, Figure 2

Review Comment: The Applicant also conducted a meta-analysis of the safety data from published literature to assess the incidence of acute and chronic GVHD as a safety parameter. Due to the unavailability of comparative data in all studies included in the applicant's meta- analysis, safety evidence from the meta-analysis is not recommended for inclusion in the Tepadina label.

FDA Methodology

FDA searched the Medline (PubMed) database using a broader search strategy to identify studies evaluating the safety of thiotepa as conditioning treatment before allogeneic hematopoietic stem cell transplantation (HSCT) in general and in thalassemia patients in particular. The primary search was conducted using the terms:

("thiotepa"[All Fields]) AND ("safety"[All Fields]) – 60 studies identified

("thiotepa"[All Fields]) AND ("thalassemia"[All Fields] – 17 studies identified

("safety "[All Fields]) AND ("thiotepa"[All Fields]) AND ("busulphan"[All Fields] OR "busulfan"[All Fields]) AND ("cyclophosphamide "[All Fields]) – 5 studies identified.

The following types of publications were excluded:

- Publications in languages other than English,

- Publications where thiotepa was not used as a conditioning regimen before hematopoietic stem cell transplantation in thalassemia patients
- Publications evaluating the use of thiotepa in non- malignant conditions and non-hematological patients.
- Publications where the safety of thiotepa cannot be extrapolated;
- Publications involving the use of thiotepa in non-human models.
- Case report studies
- Publications from the same author
- One study which used the same database used for this NDA application.

Eighty-two publications were identified by the primary search, including both retrospective and prospective studies. Seven publications met the criteria for inclusion in the literature review and are summarized below.

1. Vikram Mathews, Biju George, Auro Viswabandya, Aby Abraham, Rayaz Ahmed, Abhijeet Ganapule, Eunice Sindhuvi, Kavitha M. Lakshmi, Alok Srivastava. Improved Clinical Outcomes of High Risk b Thalassemia Major Patients Undergoing a HLA Matched Related Allogeneic Stem Cell Transplant with a Treosulfan Based Conditioning Regimen and Peripheral Blood Stem Cell Grafts. (Mathews, George et al. 2013)
This was a retrospective analysis of data from 362 patients with transfusion dependent β-thalassemia who underwent an allogeneic SCT from October, 1991, to February, 2012, at the Christian Medical College and Hospital in India. The clinical outcomes of patients who received a Treosulfan based conditioning regimen (consisting of thiotepa 8 mg/kg on day -6, fludarabine 30 mg/m^2/day from day-5 to -2 and treosulfan 14 gm/m^2 from day-5 to -3 (TreoFluT)) was compared to outcomes for patients who received the conventional conditioning regiment consisting of a combination of busulfan and cyclophosphamide (BuCy).

Three hundred and sixty-two patients (median age 7±4.4 years) with transfusion-dependent β-thalassemia underwent an allogeneic SCT at the study centers. Majority (98.8%) of these transplants were from related donors, and of the related donors 348 (97.2%) were HLA-identical. There were 16 (4.4%), 144 (39.8%) and 202 (55.8%) transplants in Lucarelli classes 1, 2 and 3, respectively. Of the 202 class 3 patients, 82 (40.5%) were classified as high risk (Class IIIHR: age ≥7 years and liver size ≥5 cm). Busulfan and cyclophosphamide was used as the conditioning regimen for 139 (68.8%) of the class 3 patients and Treosulfan, fludarabine and thiotepa conditioning regimen was used in 50 (24.7%) patients. Of the 82 class 3 HR patients, 54 (65.8%) were conditioned with BuCy and 24 (29.2%) were conditioning with TreoFluT.

Safety Results: There was a significantly lower incidence of sinusoidal obstruction syndrome (SOS) among Class 3 HR cases conditioned with theTreoFluT regimen compared to those conditioned with BuCy (78% to 30%; p=0.000). The lower incidence of SOS and other regimen related toxicity among Class IIIHR patients translated to a significantly lower day 100 treatment related mortality (TRM) among patient's conditioned with TreoFluT versus BuCy (13% vs. 46%; p-value-0.005). Use of a TreoFluT regimen was also associated with a significant improvement in OS and EFS among the Class III and Class IIIHR patients.

There was no significant difference in the incidence of acute or chronic GVHD among class 3 or class 3 HR cases conditioned with either regimen. Among class 3 patients conditioned with the TreoFluT who received either a BM or a PBSC graft, Grade 2 to 4 acute GVHD was seen in 3 (23%) vs. 10 (27%), respectively, while Grade 3 to 4 acute GVHD was seen in 0 vs. 3 (8.1%), respectively. Of the 3 patients who developed Grade 3 to 4 acute GVHD among those who received a PBSC graft, 1 patient responded to therapy and had complete resolution of GVHD while the other 2 succumbed to it. Among the 3 patients (12%) that developed chronic GVHD after the treosulfan, fludarabine and thiotepa conditioning regimen and PBSC graft, it was extensive in 1 patient while it was limited in the other 2 patients**.**

Safety Conclusions: These results suggest that in a very high risk group of β-thalassemia major patients undergoing an allogeneic SCT, the treosulfan, fludarabine and thiotepa conditioning regimen is associated with fewer safety risks, improved overall and event free survival compared to the conventional regimen of busulfan and cyclophosphamide.

2. Choudhary D, Sharma SK, Gupta N, Kharya G, Pavecha P, Handoo A, Setia R, Katewa S. Treosulfan-thiotepa-fludarabine-based conditioning regimen for allogeneic transplantation in patients with thalassemia major: a single-center experience from north India. Biol Blood Marrow Transplant. (Choudhary, Sharma et al. 2013)

This prospective study evaluated the safety and efficacy of the treosulfan-based conditioning regimen -treosulfan/thiotepa/fludarabine, (treo/thio/flu) in 28 consecutive patients with thalassemia major who underwent HLA-matched allogeneic HSCT between February 2010 and September 2012 at a single center in New Delhi, India; and compared these results retrospectively to patients treated earlier with the conventional conditioning regimen consisting of busulfan, cyclophosphamide, and anti-thymocyte globulin (Bu/Cy/ATG) at the same center.

Patients (median age was 9.6 years; range, 2-18 years) were classified according to the Pesaro classification scheme based on liver size, adequacy of chelation, and hepatic fibrosis. Seven patients were in Pesaro class 2, and 21 patients were in Pesaro class 3. Patients in the treo/thio/flu group (n=16) received i.v. thiotepa 8 mg/kg on day -6, treosulfan 14 g/m^2/day on day -5 to day -3, and fludarabine 40 mg/m^2/day on day -5 to day -2. Patients in the Bu/Cy/ATG group (n=12) received oral busulfan 3.5 mg/kg/day on day -9 to day -6, cyclophosphamide 50 mg/kg/day on day -5 to day -2, and ATG 30 mg/kg/day on day -4 to day -2. All patients received cyclosporine for 9 to 12 months post-HSCT, with trough plasma cyclosporine levels maintained at 200 to 350 ng/mL.

Safety Results: Nineteen patients developed World Health Organization (WHO) stage 1-3 oral mucositis (stage 3 in 2 patients). No renal, pulmonary, cardiac, or central nervous system toxicities were observed. Four patients developed grade II-IV acute GVHD, for a cumulative incidence of 14.3% (95% confidence interval [CI], 3.6%-26.2%). Three patients developed severe VOD. Six deaths occurred in the treo/thio/flu group for a cumulative incidence of TRM of 21.4% (95% CI, 4%-35.8%). Thalassemia-free survival and overall survival were 71.4% and 78.5%, respectively. The median duration of follow-up was 387 days (range, 37-930 days). There were no significant differences in the incidence of acute GVHD, chronic GVHD, TRM, and graft failure between the treo/thio/flu and Bu/Cy/ATG groups, although a trend toward higher TRM was seen in the treo/thio/flu group. The incidence of VOD did not differ in the 2 groups (p=0.82).

Safety Conclusions: This relatively small study did not demonstrate any safety advantage or safety risk for the –treosulfan, thiotepa and fludarabine conditioning regimen compared to the conventional busulfan, cyclophosphamide, and anti-thymocyte globulin conditioning regimen.

3. Li C, Wu X, Feng X, He Y, Liu H, Pei F, Liao J, He L, Shi L, Li N, Liu Q, Liu S, Chen G, Su Q, Ren Y, Wang Y, Tan W. A novel conditioning regimen improves outcomes in β-thalassemia major patients using unrelated donor peripheral blood stem cell transplantation. (Li, Wu et al. 2012)

The goal of this prospective study was to evaluate the effectiveness of a conditioning regimen consisting of intravenous busulfan (Bu), cyclophosphamide (Cy), fludarabine (Flu), and thiotepa (TT) [the NF-08-TM HSCT protocol] for allogeneic peripheral blood stem cell transplantation (PBSCT) in children with β-thalassemia major (TM), and to compare the outcomes of this regimen in children undergoing Un-related donor -peripheral blood stem cell transplantation (UD-PBSCT) Versus those obtained from well-matched sibling donor hematopoietic stem cell transplantation (MSD-HBSCT).

Between December 1, 2008, and June 31, 2011, 100 consecutive patients with TM were enrolled in the NF-08-TM protocol, and categorized into 3 groups for which the doses of chemotherapy were adjusted based on the patient's age, ferritin level, and liver size. Because the numbers of patients in group I (n = 9) and in group III (n = 9) were small, the study focused 82 patients in group II who received a uniform conditioning with 55 mg/kg/day Cy (day -10 to day -9); 40 mg/m^2/day Flu (day -8 to day -4); 10 mg/kg/day TT (day -5); and intravenous Bu (day -8 to day -6) at a dose dependent on the age of the patient. All patients received 3 mg/kg azathioprine and 30 mg/kg hydroxyurea daily beginning at day -45 before transplantation. On day 0, patients in the UD-PBSCT group received granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood stem cells (PBSCs), whereas patients in the MSD-HSCT group received bone marrow (BM, n= 14), BM with pre-cryopreserved cord blood (BM + CB, n= 12), or PBSCs (n= 4). The median follow-up time was 24 months (range 12 to 39 months).

Safety Results: Eighty of the 82 patients in group II had successful engraftment, with >95% donor-derived cells by day +28 and became transfusion-independent. Two MSD-HSCT patients died before engraftment. Of the 80 patients who successfully engrafted, 6 developed grades III-IV aGVHD. The incidences of grades III-IV aGVHD in the MSD-HSCT group versus the UD-PBSCT group was 3.6 vs 9.6% respectively, (p=0.328). Two 2 patients from the UD-PBSCT group died from GVHD. Extensive chronic GVHD was not diagnosed among any patient in the 2 study groups.

CMV reactivation occurred in 31 (38.8%) of the 82 patients. No patients died from CMV infection. Probable invasive fungal disease was diagnosed in 1 patient in the MSD-HSCT group and 5 patients in the UD-PBSCT group (p=0.328). The conditioning regimen was well tolerated with limited organ toxicity. There were 2 deaths, 1 before transplantation and the other before engraftment. The most frequently observed toxic effect was mucositis which occurred in 43/82 (53.8%) enrolled patients. VOD accompanied by elevated bilirubin (>2 mg/dL) was diagnosed in 5 cases, and 2 patients died from the comorbidity of VOD and infection.

Safety Conclusions: There were no significant differences in outcomes between β-thalassemia patients who received UD-PBSCT and those who received MSD-HSCT when the NF-08-TM protocol was used.

4. Bernardo ME, Piras E, Vacca A, Giorgiani G, Zecca M, Bertaina A, Pagliara D, Contoli B, Pinto RM, Caocci G, Mastronuzzi A, La Nasa G, Locatelli F. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. (Bernardo, Piras et al. 2012)

The study reported the final results from a study of the safety and efficacy of a treosulfan-based conditioning regimen used prior to HSCT in a cohort of 60 patients (48 children, 12 adults) with thalassemia major (TM). Twenty-seven pediatric patients were assigned to risk class 1 of the Pesaro classification, 17 to class 2, and 4 to class 3. All patients received the same conditioning regimen consisting of IV thiotepa (8 mg/kg on day -7), treosulfan (14 g/m^2/d from days -6 to -4), and fludarabine (40 mg/m^2/d from days -6 to -3). GVHD prophylaxis varied according to the stem cell source and type of donor. Twenty patients were transplanted from an HLA-identical sibling (matched family donor [MFD]) and the remaining 40 from an unrelated donor (UD).

Safety Results: All patients engrafted except one, who died on day +11. Eight patients developed grade II-IV acute GVHD. The cumulative incidence of grade II-IV and grade III-IV acute GVHD was 14% (95% CI, 6%-24%) and 7% (95% CI, 2%-15%), respectively. One child developed chronic GVHD (of limited extension); the cumulative incidence of cGVHD was 2% (95% CI, 0%-8%). Four patients died of transplantation-related complications (all within 4 months after HSCT). All patients who died had received transplantations from a UD and belonged to risk class 2 or 3.The cumulative incidence of transplantation-related mortality was 7% (95% CI, 3%-18%). No case of veno-occlusive disease was recorded. There were no difference in outcomes between patients belonging to risk class 1 or 2 and 3 adult patients**.**
Safety Conclusions: These results demonstrate the safety and efficacy of the thiotepa/ treosulfan/fludarabine combination as a preparative regimen in a cohort of thalassemia major patients regardless of risk class or the type of donor used.

5. Hongeng S, Pakakasama S, Chuansumrit A, Sirachainan N, Sura T, Ungkanont A, Chuncharunee S, Jootar S, Issaragisil S. Reduced intensity stem cell transplantation for treatment of class 3 Lucarelli severe thalassemia patients (Hongeng, Pakakasama et al. 2007)

In this study, investigators evaluated the use of reduced intensity stem cell transplantation (RIT) in Class 3 Lucarelli thalassemia patients with an intensive conditioning regimen. Eight patients with severe Class 3 Lucarelli thalassemia underwent RIT with peripheral blood stem cell. Six patients received T cell non-depleted PBSCs from HLA-identical siblings, one from an HLA mismatched sibling and one patient received purified CD341 cells from two HLA antigen mismatched maternal PBSCs. All eight patients received an intensive conditioning regiment pre-transplant consisting of busulfan, fludarabine, and antilymphocyte globulin. One patient also received thiotepa, and total lymphoid irradiation (TLI), while one only received TLI. All patients received hydroxyurea 20 mg/kg/day daily ≥3 months before RIT. Graft-versus-host disease (GvHD) prophylaxis included cyclosporine or tacrolimus and mycophenolate mofetil.

Safety Results: Initially, an engraftment of donor cells was observed in all eight patients, but subsequently only six of eight patients had stable full donor engraftment. There were no major toxic effects related to the regimen, other than fever. There were no serious infections except in

one patient who developed herpes zoster infection and cytomegalovirus (CMV) retinitis which resolved after treatment. Grade 1 and 2 acute GVHD occurred in 5 and one patients respectively. Four patients developed a limited stage of chronic GvHD. There were no deaths or Grade 3–4 acute GvHD in this study. The one year overall survival rate was 100%. The median of follow up time was 18 months (range 11–71 months).

Safety Conclusions: The intensive conditioning regimens used in this study (including thiotepa) were associated with minimal toxicity and resulted in stable full donor engraftment in the majority of the severe Class 3 Lucarelli thalassemia patients.

6. La Nasa G, Caocci G, Argiolu F, Giardini C, Locatelli F, Vacca A, Orofino MG, Piras E, Addari MC, Ledda A, Contu L. Unrelated donor stem cell transplantation in adult patients with thalassemia. (La Nasa, Caocci et al. 2005)

This study evaluated the outcomes of BMT in 27 high-risk adult thalassemia patients (median age 22 years), transplanted from unrelated donors (UD) selected by high-resolution HLA molecular typing. In 15 patients, the conditioning regimen used consisted of busulfan (BU, 14 mg/kg), thiotepa (TT, 10 mg/kg) and cyclophosphamide (CY, 120– 160 mg/kg). In 12 patients only busulfan (BU, 14 mg/kg) plus cyclophosphamide (CY, 120 or 160 mg/kg) was used as a conditioning regimen. All patients received cyclosporine-A and short-term methotrexate for graft-versus-host disease (GVHD) prophylaxis. Three patients also received anti-thymocyte globulin (ATG) to reduce the risk of both graft rejection and GVHD.

Safety Results: Nineteen patients (70%) were alive and transfusion-independent after a median follow-up of 43 months (range 16–137). Eight patients (30%) died at a median of 153 days (range 17–470) after transplantation from transplant-related causes. Six out of the 8 deaths occurred in patients conditioned with BU-TT-CY; 2 were in patients who had received the combination BU-CY. In the 16 evaluable patients with a donor identical for at least one extended haplotype, the incidence of grade II–IV acute GVHD was 31% (5/16). By contrast, among the nine recipients who did not share extended haplotypes with the donor, five patients (56%) experienced grade II–IV acute GVHD. Among the 22 patients at risk, six (27%) developed chronic GVHD.

Safety conclusions: These results suggest that suggest that UD-BMT in adult class 3 thalassemia patients, with donors selected through high-resolution molecular typing is feasible and may offer a success rate similar to that historically reported in patients, with similar prognostic characteristics, transplanted from an HLA identical sibling. A higher number of deaths were observed in patients conditioned with the protocol including TT.

7. Sodani P, Isgrò A, Gaziev J, Polchi P, Paciaroni K, Marziali M, et al. Purified T-Depleted, CD34+ Peripheral Blood and Bone Marrow Cell Transplantation from Haploidentical Mother to Child with Thalassemia. (Sodani, Isgro et al. 2010)

In this study, the outcomes of 22 children (3 to 14 years of age) with thalassemia major who received transplants from haploidentical donors (20 mothers and 2 brothers) were reported. For conditioning, all patients received 60 mg/kg hydroxyurea and 3 mg/kg azathioprine from Day -59 to -11; 30 mg/m^2 fludarabine from Day -17 to -11; 14 mg/kg busulfan starting on Day -10;

and 200 mg/kg cyclophosphamide, 10 mg/kg thiotepa, and 12.5 mg/kg ATG daily from Days -5 to -2. Fourteen patients received CD34+-mobilized peripheral blood and bone marrow progenitor cells; 8 patients received marrow graft-selected PBSCs CD34+ and bone marrow CD3/CD19-depleted cells. T-cell dose was adjusted to 2 x 10^5/kg by fresh marrow cell add back at the time of transplantation. Both groups received cyclosporine for GVHD prophylaxis for 2 months after transplantation.

Safety Results: Fourteen patients showed full chimerism with functioning grafts at a median follow-up of 40 months; none of these patients developed acute or chronic GVHD. Graft rejection with complete autologous reconstitution and return to pre-transplantation clinical status occurred in six patients. Two patients died from transplantation-related causes (cerebral Epstein-Barr virus lymphoma or cytomegalovirus pneumonia).

Safety Conclusions: The transplantation protocol employed in this study including pre-conditioning with thiotepa was relatively well-tolerated and effective for eradicating the hematopoietic system in patients with thalassemia.

8. Gaziev J, Sodani P, Lucarelli G, et al. Second Hematopoietic SCT in Patients with Thalassemia Recurrence Following Rejection of the First Graft (Gaziev, Sodani et al. 2008)

In this prospective study, the investigators evaluated results from a new treatment protocol for second transplantation in patients with thalassemia recurrence developed to decrease the high graft failure rate and increase thalassemia-free survival in this population. The study population consisted of 16 patients a median age of 9 years (range, 4–20) who had thalassemia recurrence following graft failure after the first graft, and who had an HLA-matched family donor, were eligible for a second transplantation. Most patients were in the class 3 risk group and the majority had severe iron overload at the time of the second transplant. The median interval between graft failure and second HSCT was 19.5 months (range, 5–204).

Study patients received second transplants using bone marrow (n=7) or PBSC (n=9) as a stem cell source after preparation with a new treatment protocol. The treatment protocol consisted of a preconditioning phase with an intensified preparation with 3 mg/kg of azathioprine and 30 mg/kg of hydroxyurea daily from day −45 pre-transplant, fludarabine 30 mg/m^2 from day −16 through day −12, followed by conditioning with BU 14 mg/kg total dose, thiotepa 10 mg/kg total dose, CY 200 mg/kg total dose and rabbit antithymocyte 12.5 or 10 mg/kg total dose. Continuous 24-hour infusions of 40 mg/kg of dexferoxamine via a central venous catheter were initiated on Day -45 and hypertransfusion with red blood cells (RBCs) was used to keep the level of hemoglobin between 14 and 15 g/100mL. During this time, patients received growth factors (twice weekly to maintain stem cell proliferation during hypertransfusion.

Safety Results: All but one patient had sustained engraftment with donor chimerism of 95–100%. One patient had primary graft failure. Five out of the 15 evaluable patients developed grades 2–4 acute GVHD. The cumulative incidence of grades 2–4 acute GVHD was 33%. Three out of 15 evaluable patients developed extensive chronic GVHD (20%). The patient who had graft failure developed moderate hepatic sinusoidal obstructive syndrome, which was resolved with supportive care. Two patients had grade 2 mucositis. Three patients developed

cyclosporine-A-related neurotoxicity with seizures. Asymptomatic CMV reactivation occurred in 11 (68%) patients. Five out of 13 patients (38%) had EBV reactivation in blood without developing lymphoproliferative disorders. One patient developed encephalitis on day 55. Seven patients had BK virus-related late hemorrhagic cystitis. There were 3 transplant-related deaths at 3 months, 6 months and 1 year post transplant due to cerebral bleeding, pneumonia and multi-organ failure respectively. All three deaths occurred in patients given PBSC.

Safety Conclusions: The intensified conditioning treatment protocol (including thiotepa) used in this study was relatively well tolerated with no significant increase in toxicity.

Review Comment: In all the literature reviewed, thiotepa was relatively well tolerated and no new safety issues related to the use of thiotepa as a conditioning regimen prior to HSCT in thalassemia patients was identified. One study (La Nasa, Caocci et al. 2005) reported a higher number of deaths in patients conditioned with busulphan, thiotepa and cyclophosphamide compared to those who received only busulphan and cyclophosphamide; however, this difference was not statistically significant and no meaningful conclusions can be drawn especially considering the overall small size (n=27) of this study.

8 Post-market Experience

The Applicant reported that for the period March 16, 2010, (the International Birth Date [IBD] of Tepadina) through March 31, 2015, (b) (4) vials of 15 mg and (b) (4) vials of 100 mg Tepadina were sold in Europe and in extra-EU countries. This equates to approximately 21,000 patients who have received Tepadina as part of a conditioning regimen before stem cell transplantation.

The following safety signals were identified in the 6th Periodic Safety Update Report (PSUR) for Tepadina covering the period 16 March 2012 to 31 March 2015 (data lock point):

- Pulmonary hypertension
- Toxic skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
- leukoencephalopathy
- hemorrhagic cystitis

9 Appendices

9.1 Advisory Committee Meeting

There was no advisory committee consulted for this application.

9.2 Labeling Recommendations

See final Label.

9.3 **References**

Angelucci, E. (2010). "Hematopoietic stem cell transplantation in thalassemia." Hematology Am Soc Hematol Educ Program **2010**: 456-462.

Bernardo, M. E., E. Piras, A. Vacca, G. Giorgiani, M. Zecca, A. Bertaina, D. Pagliara, B. Contoli, R. M. Pinto, G. Caocci, A. Mastronuzzi, G. La Nasa and F. Locatelli (2012). "Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan." Blood **120**(2): 473-476.

Bernardo, M. E., M. Zecca, E. Piras, A. Vacca, G. Giorgiani, C. Cugno, G. Caocci, P. Comoli, A. Mastronuzzi, P. Merli, G. La Nasa and F. Locatelli (2008). "Treosulfan-based conditioning regimen for allogeneic haematopoietic stem cell transplantation in patients with thalassaemia major." Br J Haematol **143**(4): 548-551.

Cao, A. and R. Galanello (2010). "Beta-thalassemia." Genet Med **12**(2): 61-76.

Choudhary, D., S. K. Sharma, N. Gupta, G. Kharya, P. Pavecha, A. Handoo, R. Setia and S. Katewa (2013). "Treosulfan-thiotepa-fludarabine-based conditioning regimen for allogeneic transplantation in patients with thalassemia major: a single-center experience from north India." Biol Blood Marrow Transplant **19**(3): 492-495.

Chuang-Stein, C. and M. Beltangady (2011). "Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies." Pharm Stat **10**(1): 3-7.

Elberg, J. J., K. E. Brok, S. A. Pedersen and K. E. Kock (1989). "Congenital bilateral eventration of the diaphragm in a pair of male twins." J Pediatr Surg **24**(11): 1140-1141.

Gabriel, D. A., T. Shea, O. Olajida, J. S. Serody and T. Comeau (2003). "The effect of oral mucositis on morbidity and mortality in bone marrow transplant." Semin Oncol **30**(6 Suppl 18): 76-83.

Gaziev, J., P. Sodani, G. Lucarelli, P. Polchi, S. Marktel, K. Paciaroni, M. Marziali, A. Isgro, M. D. Simone, A. Roveda, A. Montuoro, A. Lanti, C. Alfieri, G. De Angelis, C. Gallucci, F. Ciceri and M. G. Roncarolo (2008). "Second hematopoietic SCT in patients with thalassemia recurrence following rejection of the first graft." Bone Marrow Transplant **42**(6): 397-404.

Hernan, M. A., D. Clayton and N. Keiding (2011). "The Simpson's paradox unraveled." Int J Epidemiol **40**(3): 780-785.

Hongeng, S., S. Pakakasama, A. Chuansumrit, N. Sirachainan, T. Sura, A. Ungkanont, S. Chuncharunee, S. Jootar and S. Issaragisil (2007). "Reduced intensity stem cell transplantation for treatment of class 3 Lucarelli severe thalassemia patients." Am J Hematol **82**(12): 1095-1098.

La Nasa, G., G. Caocci, F. Argiolu, C. Giardini, F. Locatelli, A. Vacca, M. G. Orofino, E. Piras, M. C. Addari, A. Ledda and L. Contu (2005). "Unrelated donor stem cell transplantation in adult patients with thalassemia." Bone Marrow Transplant **36**(11): 971-975.

Lacher, M. J. and K. Toner (1986). "Pregnancies and menstrual function before and after combined radiation (RT) and chemotherapy (TVPP) for Hodgkin's disease." Cancer Invest **4**(2): 93-100.

Li, C., X. Wu, X. Feng, Y. He, H. Liu, F. Pei, J. Liao, L. He, L. Shi, N. Li, Q. Liu, S. Liu, G. Chen, Q. Su, Y. Ren, Y. Wang and W. Tan (2012). "A novel conditioning regimen improves outcomes in beta-thalassemia major patients using unrelated donor peripheral blood stem cell transplantation." Blood **120**(19): 3875-3881.

Lucarelli, G., R. A. Clift, M. Galimberti, P. Polchi, E. Angelucci, D. Baronciani, C. Giardini, M. Andreani, M. Manna, S. Nesci, F. Agostinelli, S. Rapa, M. Ripalti and F. Albertini (1996). "Marrow transplantation for patients with thalassemia: results in class 3 patients." Blood **87**(5): 2082-2088.

Lucarelli, G., M. Galimberti, P. Polchi, E. Angelucci, D. Baronciani, C. Giardini, P. Politi, S. M. Durazzi, P. Muretto and F. Albertini (1990). "Bone marrow transplantation in patients with thalassemia." N Engl J Med **322**(7): 417-421.

Lucarelli, G., M. Galimberti, P. Polchi, C. Giardini, P. Politi, D. Baronciani, E. Angelucci, F. Manenti, C. Delfini, G. Aureli and et al. (1987). "Marrow transplantation in patients with advanced thalassemia." N Engl J Med **316**(17): 1050-1055.

Mathews, V., B. George, A. Viswabandya, A. Abraham, R. Ahmed, A. Ganapule, E. Sindhuvi, K. M. Lakshmi and A. Srivastava (2013). "Improved clinical outcomes of high risk beta thalassemia major patients undergoing a HLA matched related allogeneic stem cell transplant with a treosulfan based conditioning regimen and peripheral blood stem cell grafts." PLoS One **8**(4): e61637.

Pico, J. L., A. Avila-Garavito and P. Naccache (1998). "Mucositis: Its Occurrence, Consequences, and Treatment in the Oncology Setting." Oncologist **3**(6): 446-451.

Sodani, P., A. Isgro, J. Gaziev, P. Polchi, K. Paciaroni, M. Marziali, M. D. Simone, A. Roveda, A. Montuoro, C. Alfieri, G. De Angelis, C. Gallucci, B. Erer, G. Isacchi, F. Zinno, G. Adorno, A. Lanti, L. Faulkner, M. Testi, M. Andreani and G. Lucarelli (2010). "Purified T-depleted, CD34+ peripheral blood and bone marrow cell transplantation from haploidentical mother to child with thalassemia." Blood **115**(6): 1296-1302.

Thomas, E. D., C. D. Buckner, J. E. Sanders, T. Papayannopoulou, C. Borgna-Pignatti, P. De Stefano, K. M. Sullivan, R. A. Clift and R. Storb (1982). "Marrow transplantation for thalassaemia." Lancet **2**(8292): 227-229.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROSANNA W SETSE
12/27/2016

DONNA PRZEPIORKA
12/27/2016

I agree with the primary reviewer's recommendation for approval of Tepadina for the indication “to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor (stem) cell transplantation (HSCT) for pediatric patients with class 3 beta-thalassemia. See the CDTL review for my recommendations regarding the additional indications.

Medical Officer Consult
Office of Hematology and Oncology Products
Division of Oncology Product 1

Requester
Donna Przepiorka, MD
CDER/OND/OHOP/DHP

Date Requested
July 15, 2016

Date Completed
October 06, 2016

NDA# and Corresponding Drug: NDA 208264: Thiotepa

Reason for Request
1. Should the indication "For the treatment of superficial papillary carcinoma of the urinary bladder" listed currently not be included in the new PI? If any should be deleted, please provide the rationale.

2. Are the doses described under "Intravesical Administration" still applicable? If these should be deleted or revised, please provide the rationale.

Background
For the consult of interest, the Applicant, Adienne, in its NDA208264, relies on data from ANDA 075547, and the drug Thioplex from NDA 020058, in support of it application and the proposed new indication.

Based on review of orange book and drugs@FDA, as the date of this consult, the table below summarizes the regulatory history of thiotepa.

Drug Name	Active Ingredient	Application ID	Company	Approval Date	Status	Reference Listed Drug (Y/N)
Thiotepa	Thiotepa	NDA011683	IMMUNEX	March 9, 1959	Discontinued	No.
Thioplex	Thiotepa	NDA020058	IMMUNEX	Dec 22, 1994	Discontinued	No
Thiotepa	**Thiotepa**	**ANDA075547**	**EUROHLTH INTL SARL**	**April 2, 2001**	**Active**	**Yes**
Thiotepa	Thiotepa	ANDA075730	TEVAPARENTEREAL	April 20, 2001	Discontinued	No
Thiotepa	Thiotepa	ANDA075698	FRESENIUS KABI USA	Sept 20, 2001	Discontinued	No

The current application holding the reference listed drug is ANDA075547.

Questions to DOP1

1. Should the indication "For the treatment of superficial papillary carcinoma of the urinary bladder" listed currently not be included in the new PI? If any should be deleted, please provide the rationale.

DOP1 Response:
Thiotepa is still used in the treatment of urothelial cancer and the indication should not be deleted.

Thiotepa has been deemed medically necessary per review submitted under ANDA075547, the application holding the reference list drug for thiotepa, by DOP1, dated August 15, 2013. In particular, DOP1, in that review, endorsed the medical necessity of thiotepa including the indication of:

For the treatment of superficial papillary carcinoma of the urinary bladder

2. Are the doses described under "Intravesical Administration" still applicable? If these should be deleted or revised, please provide the rationale.

DOP1 Response:
There is insufficient information to warrant such modification.

The package insert states that 60 mg of thiotepa in 30-60 mL of sodium chloride should be instilled into the bladder and retained for 2 hours. The usual course of treatment is once a week for 4 weeks. Additional 4 week courses of treatment should be given with caution.

At the present time, thiotepa 30 mg in 15 mL sterile water is used as a single instillation into the bladder following tumor resection. This is retained for 30 minutes. No evidence to support this dose was included in the submission.

Thiotepa is uncommonly used at a dose of 30-60 mg in 15-30 mL sterile water. If used at this dose, it is retained in the bladder for 2 hours and is given weekly for 4-8 weeks. This is similar to the approved dose and schedule.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES X XU
10/17/2016

VIRGINIA E MAHER
10/18/2016

GEOFFREY S KIM
10/18/2016

Medical Officer Review of Interoffice Consult
Division of Oncology Products-1

NDA #	208264
Drug(s)	Thiotepa 505(b)(2)
NDA Sponsor	Adienne
Primary Reviewer	Gwynn Ison, MD
Team Leader	Laleh Amiri, MD
Consult Due Date	9/1/16

Background:

The Sponsor Adienne has submitted a 505(b)(2) application for Thiotepa. The analytical bridge supports use of data generated for any thiotepa product in the US manufactured 1994 or later. The PI will be reformatted to PLR. The current Thiotepa label has indications for the following cancers:

Thiotepa for Injection, USP has been tried with varying results in the palliation of a wide variety of neoplastic diseases. However, the most consistent results have been seen in the following tumors:

1. **Adenocarcinoma of the breast**
2. **Adenocarcinoma of the ovary**
3. For controlling intracavitary effusions secondary to diffuse of localized neoplastic diseases of various serosal cavities
4. For the treatment of superficial papillary carcinoma of the urinary bladder.

While now largely superseded by other treatments, thiotepa has been effective against other lymphomas, such as lymphosarcoma and Hodgkin's disease.

The dosage and administration instructions in the current label are as follows:

- Intravenous administration: Thiotepa may be given by rapid IV administration in doses of 0.3 mg/kg to 0.4 mg/kg. Doses should be given at 1 to 4 week intervals.
- Intracavitary administration: The dosage recommended is 0.6 mg/kg to 0.8 mg/kg. Administration is usually through the same tubing which is used to remove fluid from the cavity involved.

DHP asks for input on the following 2 questions:

1) Should any of the indications listed currently not be included in the new PI? If any should be deleted, please provide the rationale.

DOP1 response: Although Thiotepa for IV administration is not used in current standard clinical practice for the treatment of adenocarcinomas of the breast or ovary, there is not a reason, related to safety, that either

indication should be deleted from the new PI. Likewise, although Thiotepa for IP administration is only rarely used in clinical practice for the treatment of adenocarcinoma of the ovary, there is no reason, related to safety, that the indication should be deleted from the new PI.

2) Are the doses described under "Intravenous administration", "Intracavitary Administration" and "Intravesical Administration" still applicable? If these should be deleted or revised, please provide the rationale.

DOP1 response:
There does not appear to be data in the literature to negate the prescribed dosing regimens for IV and IP administration (listed above) in the current label, however, we note that a recent literature review reveals that most current clinical trials using thiotepa for IV and IP administration have dosing recommendations based upon mg/m^2 dosing, rather than mg/kg dosing. For example:

1) Chahal et al. Neurol Sci, 2015. Sep 36 (9): 1691-3. Use of IV thiotepa for breast cancer-related leptomeningeal carcinomatosis. *Thiotepa was dosed at 40 mg/m^2 IV every 21 days.*

2) Yu et al, Beijing Da Xue Xue Bao 2011. Feb 12; 43(1): 151-6. Randomized clinical case-control trial for the comparison of docetaxel plus thiotepa vs. docetaxel plus capecitabine in patients with metastatic breast cancer. *Dosing for thiotepa was 60-65 mg/m^2 IV on Day 1 every 21 days.*

3) Song et al, Scientific Reports. 2015. 5, 16775. The prognostic values of CYP2B6 genetic polymorphisms and metastatic sites for advanced breast cancer patients treated with docetaxel and thiotepa. *Dosing for thiotepa is 30 mg/m^2 IV D1 and D8 every 21 days.*

4) Fuen et al. Gynecologic Oncol. 1998. Dec; 71(3): 410-5. IP thiotepa was assessed in a GOG study in combination with IP cisplatin (and IV cisplatin). *The IP thiotepa dose was 12 mg/m^2 IP every 4 weeks up to 6 cycles.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GWYNN ISON
08/31/2016

LALEH AMIRI KORDESTANI
08/31/2016