CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208264Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM TO STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #/ Serial No. #:	NDA 208264 / 002	
Supplement #:		
Drug Name:	Tepadina® (thiotepa) lyophilized powder for injection (15 mg/vial and 100 mg/vial)	
Indication(s):	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 for patients with class 3 β-thalassemia	
Applicant:	Adienne SA	
Date(s):	Submission date:	31 March 2016
	PDUFA date:	31 January 2017
Review Priority:	Standard	
Biometrics Division:	Division of Biometrics V	
Statistical Reviewer:	Che Smith, Ph.D.	
Concurring Reviewers:	Yuan Li Shen, Dr.P.H., Team Leader	
	Thomas Gwise, Ph.D., Deputy Division Director	
Medical Division:	Division of Hematology Products	
Clinical Team:	Rosanna Setse, M.D., Donna Przepiorka, M.D.	
Project Manager:	Charlene Wheeler	
Keywords:	Historical control, meta-analysis	

This addendum includes a correction to Table 4 of the statistical review, as well as a correction to a reviewer's comment related to the same table. Particularly, values for the median and range of Days to recovery for ANC and Days to recovery for Platelets are corrected in the table below. The correct values were verified by the reviewer and the comment has been edited to reflect the correct reference table from the Study 01 Clinical Study Report.

Table 1. Secondary efficacy results

Secondary Efficacy Endpoint	Protocol 26M (N = 25)	Protocol 26 (N = 51)
	Proportion % (95% CI)	**Proportion % (95% CI)**
Overall survival, 1 year	85.4 (71.0, 100)	87.8 (78.2, 98.5)
Thalassemia-free survival, 1 year	85.4 (71.0, 100)	65.7 (52.8, 98.5)
Transplant-related mortality, 1 year	12.0 (0, 30.0)	7.8 (0, 20.0)
Engraftment	92.0 (80.9, 100)	86.3 (76.2, 96.3)
	Median (Min – Max)	**Median (Min – Max)**
Days to recovery for ANC	21.0 (16.0 – 30.0)	20.0 (14.0 – 42.0)
Days to recovery for Platelets	26.0 (13.0 – 50.0)	23.0 (12.0 – 160.0)

Reviewer's comment:

- *The sponsor's dataset contained incorrect analysis values for Days to recovery for ANC and Days to recovery for Platelets. Correct values were reflected in the sponsor's Integrated Summary of Efficacy, as well as in Table 11.4.2.3 of the Study 01 Clinical Study Report. The values presented in Table 4 reflect the correct analysis values, as calculated by the reviewer.*

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/s/

CHE L SMITH
12/22/2016

YUAN L SHEN
12/22/2016

THOMAS E GWISE
01/13/2017

U.S. Department of Health and Human Services
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1 EXECUTIVE SUMMARY

This is an original New Drug Application (NDA) seeking the approval of TEPADINA® (thiotepa) lyophilized powder for injection (15 mg/vial and 100 mg/vial) to reduce the risk of graft rejection when used in conjunction with high-dose busulfan and cyclophosphamide as a preparative regimen for allogenic hematopoietic stem cell transplantation for patients with class 3 β-thalassemia.

The pivotal study supporting this application, RETALCLASS3 (AND-010) (hereafter referred to as Study 01), is a retrospective, observational study in class 3 thalassemia major patients undergoing bone marrow transplant following myeloablative conditioning treatment preceded by cytoreduction/immunosuppression. The study included patients treated on one of two protocols. On Protocol 26, patients were treated with a standard conditioning regimen containing busulfan and cyclophosphamide; these patients were considered historical controls in Study 01. On a modified protocol (Protocol 26M), a separate group of patients were treated on a similar conditioning regimen which also included thiotepa. This review considers Study 01 as a single-arm study of Protocol 26M patients, since there was not sufficient evidence to justify that the cohort of historical control patients were comparable to the treatment group.

None of the 25 patients treated on a conditioning regimen containing thiotepa experienced graft rejection after undergoing transplantation (0%; 95% CI: [0, 0.12]). Historically, the incidence of graft rejection among patients who received the same conditioning regimen without thiotepa was 25.5% (95% CI: [0.13, 0.37]). Overall survival for patients conditioned with thiotepa was 85.4% at 12 months after transplantation, and all surviving patients remained thalassemia-free. Transplant-related mortality was 4.0% at 100 days after transplant, and 12.0% at 12 months after transplant.

The sponsor submitted a literature meta-analysis of nine studies that included thalassemia major patients undergoing allogeneic HSCT following various conditioning treatments preceded by cytoreduction/immunosuppression to assess the incidence of graft rejection when the conditioning regimen contains thiotepa. However, differences in study designs, patient populations, and follow up times preclude comparisons of the meta-analysis results with Study 01 results.

Several statistical issues were identified which made interpretation of efficacy results difficult, including the retrospective design of Study 01, concerns about the comparability of the control cohort (Protocol 26) to treatment cohort (Protocol 26M), the comparability of the meta-analysis to Protocol 26 M, insufficient source data to support the secondary endpoints and inability to analyze results among certain demographic subgroups and generalize results to the greater patient population. Overall, the decision as to whether TEPADINA is safe and effective for the proposed indication is deferred to the clinical review team.

APPEARS THIS WAY ON ORIGINAL

2 INTRODUCTION

2.1 Overview

The sponsor is seeking approval of the use of TEPADINA® to prevent graft rejection in pediatric patients with class 3 β-thalassemia who underwent allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-identical sibling donor.

Thalassemia major is a hereditary hemolytic anemia; with more than 100,000 affected children born each year, it is one of the most common monogeneic hereditary diseases in the world. β-thalassemia major is the most severe form of thalassemia due to reduced or absent production of beta-globin gene leading to ineffective erythropoiesis & hemolytic anemia. Thalassemia is classified based on the presence of three risk factors: hepatomegaly >2 cm, hepatic fibrosis at liver biopsy, and history of irregular chelation. Currently, bone marrow transplantation is the only known cure. Patients with class 3 β-thalassemia are considered at high risk for both graft rejection and transplant-related mortality. Patients having a second allogeneic HSCT have a significant risk of graft failure, transplant-related mortality, and lower thalassemia-free survival especially in pediatric class 3 β-thalassemia.

Historically, pediatric β-thalassemia patients have been treated with a standard conditioning regimen (Protocol 26) containing busulfan and cyclophosphamide prior to undergoing allogeneic hematopoietic stem cell transplantation. The risk of graft rejection in these patients remains high and is highly predictive of thalassemia-free survival. A modified regimen, referred to as Protocol 26M, adds thiotepa. The information submitted by the sponsor seeks to show that, when compared to a historical control cohort treated on Protocol 26, the modified regimen may reduce the risk of graft rejection and improve other transplant-related outcomes in pediatric class 3 β-thalassemia patients.

To support this application, the sponsor submitted information from the clinical study RETALCLASS3 (ADN-010); hereafter, this study is referred to as Study 01. This review treats Study 01 as a single-arm trial since there is insufficient evidence to support the comparability of the treatment cohort to the historical control cohort. Table 1 summarizes the characteristics of Study 01.

Table 1. List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
RETALCLASS3 (ADN-010), referred to here as Study 01	Phase 2/3	One baseline visit before transplant, along with GvHD prophylaxis with cyclosporine, low dose methylprednisolone and a modified short course methotrexate	30, 60, 90, 180, and 365 days post-transplant	25 (51 historical control patients)	Pediatric patients with class 3 β-thalassemia who underwent allogeneic transplantation from an HLA-identical donor

2.2 Regulatory History

The proposed indication is a subset of a previously-approved indication of "conditioning treatment prior to hematopoietic stem cell transplantation" for which TEPADINA was granted an Orphan Drug Designation by the FDA in April 2007. In 2010, TEPADINA was approved as an orphan drug in the European Union (EU).

TEPADINA has been approved in the EU, Switzerland, Russia, Hong Kong, and Israel for the following indication: "in combination with other chemotherapy medicinal products: with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous hematopoietic progenitor cell transplantation (HPCT) in hematological diseases in adult and pediatric patients; when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumors in adult and pediatric patients."

Under PIND # 109219, the Agency held several pre-NDA meetings with the sponsor regarding the current proposed indication. In August 2013, a previous statistical reviewer expressed concerns about the small sample size of the treatment cohort and the non-randomized design of the pivotal study submitted for the application.

For the current proposed indication, TEPADINA was designated as a Fast Track development program by the Agency on July 28, 2014; on January 15, 2015, the Agency granted a request from the sponsor for a "rolling review" of submissions of portions of the application. In July 2015, the sponsor communicated to the Agency the postponement of submission of Module 5, corresponding Module 2 documents, and remaining Module 1 documents by April 29, 2016. On March 31, 2016, the sponsor submitted all remaining modules and documents.

2.3 Data Sources

Information from applicant study reports, data sets, and reference literature were reviewed.

The location of datasets for Study 01 is:
\\CDSESUB1\evsprod\NDA208264\0002\m5\datasets\adn010\analysis

3 STATISTICAL EVALUATION

This section includes results from Study 01, an observational, retrospective, case-series, multicenter, historical-controlled study in patients undergoing allogeneic HSCT for class 3 β-thalassemia.

3.1 Data and Analysis Quality

Data for the primary endpoint of Study 01, incidence of graft rejection, were submitted without source data to validate these outcomes.

Because of concerns over primary endpoint data, the Office of Scientific Investigation was asked to confirm validity of the data. The inspection was conducted in July 2016, and included an audit

of both sites at which patients from both protocols were treated. The inspection found that source documents for the raw data used to assess the primary study endpoint were verifiable at study sites, and that there was no under-reporting of adverse events or serious adverse events. Data for secondary efficacy endpoints were not validated in the inspection, so there remain concerns about the validity of secondary endpoint results.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 01 was an observational, retrospective, case-series, multicenter, historical-controlled study in patients undergoing bone marrow transplantation for thalassemia and microdrepanocytosis. The aim of the study was to evaluate the impact of Protocol 26M (thiotepa cohort)- a modified conditioning regimen with busulfan, cyclophosphamide, and thiotepa, preceded by pre-conditioning cytoreduction/immunesuppression with hydroxyurea, azathioprine, and fludarabine – as compared to Protocol 26 (historical control cohort) which includes a conditioning regimen with busulfan and cyclophosphamide only, preceded by pre-conditioning with hydroxyurea, azathioprine, and fludarabine.

For each cohort, treatment included a baseline visit, where eligible patients were evaluated for participation, the transplant phase, and 5 post-transplant follow-up visits, scheduled at 30, 60, 90, 180, and 365 days after transplant. At the follow-up visits, a ±7-day window from the planned visit was considered acceptable.

The primary objective of the study was to retrospectively assess the incidence of graft rejection following allogeneic hematopoietic stem cell transplantation from an HLA-identical sibling donor in class 3 thalassemia patients treated according to Protocol 26M (as defined above), in comparison with a control group of patients treated with a standard Protocol 26 (as defined above).

The secondary objective was to further evaluate the efficacy – in terms of overall survival (OS), incidence of transplant-related mortality (TRM), thalassemia-free survival (TFS), engraftment, and recovery of absolute neutrophils count and platelets count – and safety (non-hematological toxicity, incidence of acute and chronic GvHD, incidence of infectious complications) of Protocol 26M compared to Protocol 26.

There was no formal sample size calculation for Study 01. There were a total of 25 and 51 transplanted patients respectively treated with Protocol 26M and with Protocol 26. The treatment period for patients treated on Protocol 26M was between February 2007 and November 2012, and all were treated at the Mediterranean Institute of Hematology, Policlinic of Tor Vergata in Rome, Italy. Between March 1997 and September 2008, 51 patients were treated on Protocol 26 at the BMT Center of San Raffaele Hospital of Milan (n=25) and the International Center for Transplantation of the Mediterranean Institute of Hematology of Rome (n=26).

Reviewer's comment:

- *Regarding the analysis of the data, this reviewer questions whether the Protocol 26M and Protocol 26 groups are comparable since patients were not randomized and study periods differed. It is difficult to determine if subjects from the treatment cohort and the historical control cohort come from the same underlying patient population due to insufficient data collection lack of a pre-planned matching strategy.*

The primary objective of the study was to assess the incidence of graft rejection following allogeneic bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling donor in class 3 thalassemia patients treated according to Protocol 26M, in comparison with a control group .

The primary efficacy endpoint was the number and proportion of patients experiencing a graft rejection (either primary or late rejection) after transplantation. A 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 28 days 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.

Reviewer's comment:
The sponsor's submission did not include source data to confirm the incidence of graft rejection based on the above definition.
Secondary endpoints proposed by the sponsor evaluate the effect of pre-conditioning treatment and transplantation on clinical and laboratory manifestations of thalassemia and other transplant-related outcomes. These secondary endpoints include:

- Overall survival
- Thalassemia-free survival
- Transplant-related mortality
- Rate of neutrophils
- Rate of platelets
- Engraftment
- Time to recovery for ANC
- Time to recovery for platelets

Additional safety endpoints included:

- Non-hematological toxicity
- Incidence of acute and chronic GvHD
- Incidence of infectious complications

3.2.2 Statistical Methodologies

Study Population
All statistical analyses were performed on the Full Analysis Set (FAS), which included 25 patients in the Protocol 26M (thiotepa) cohort and 51 patients in the Protocol 26 (historical

control) cohort. All patients were transplanted, provided informed consent and assent for the retrospective collection of data, and fit the study's inclusion/exclusion criteria.

Primary and Key Secondary Efficacy Endpoints
The primary efficacy endpoint was the number and proportion of patients experiencing graft rejection (primary or late rejection) after transplantation.

Key secondary efficacy endpoints include:
Overall survival (OS): time from the date of transplant to the date of death for any reason. In the absence of death, survival time was censored at the last date of follow-up when the subject was known to be alive.

Thalassemia-free survival (TFS): time from the date of transplantation to either date of graft rejection or death due to any cause, whichever event happened first. Subjects without graft rejection and still alive were censored at the last date known to be thalassemia-free (date of thalassemia recurrence or date of last visit if no recurrence occurred).

Transplant-related mortality (TRM) incidence: number of patients who died due to transplant-related reasons, at day 100 and at 1 year post-treatment in the two cohorts. Information about cause of death and time of death was taken from the study termination case report forms.

Engraftment: Two different engraftment evaluations based on absolute neutrophils count (ANC) and platelets count were given at day 30 post-transplant.

Time to recovery of ANC: number of days from the date of transplant until the first of three consecutive days with ANC values $\geq 0.5 \times 10^9$/L.

Time to recovery of Platelets: number of days from the date of transplant until the first of seven consecutive days with a platelets count $> 20 \times 10^9$/L without platelets transfusion support.

Analysis Method for Primary and Key Secondary Endpoints
The proportion of patients experiencing graft rejection in the thiotepa and historical control cohorts were estimated with corresponding two-sided 95% Clopper-Pearson confidence intervals (CI). The Clopper-Pearson CI at two-sided significance level α for proportion θ is calculated using F distribution quantiles as follows:

$$\left(1+\frac{n-x}{[x+1]\ F\left[\frac{\alpha}{2};2(x+1),\ \ 2(n-x)\right]}\right)^{-1} < \theta < \left(1+\frac{n-x+1}{x\ F\left[1-\frac{\alpha}{2};2x,\ \ 2(n-x+1)\right]}\right)^{-1}$$

where x represents the number of events; n is the number of trials, and $F[k; d_1, d_2]$ is the $1-k$ quantile from an F distribution with d_1 and d_2 degrees of freedom[1]. The sponsor also compared groups using an exact two-sided binomial test with significance level $\alpha = 0.05$.

Reviewer's comment:

- *This review does not consider the thiotepa cohort to be comparable to the historical control cohort, as discussed in Section 5.1. Thus, no statistical tests or formal comparisons (i.e., p-value) between cohorts are made in this review.*

Overall survival and thalassemia-free survival estimates were calculated using the Kaplan and Meier product limit estimator and survival estimates were compared with the log-rank test (two-sided; $\alpha = 0.05$).

Reviewer's comment:

- *No formal comparisons of OS or TFS results are made in this review, since the cohorts are not considered comparable. Section 3.2.4 presents Kaplan-Meier plots that compare cohorts, but no log-rank test results are presented.*
- *In general, time to event endpoints cannot be evaluated based on a single arm trial.*

Transplant-related mortality was estimated with a corresponding 95% Clopper-Pearson CI. The sponsor compared estimates between cohorts using an exact two-sided binomial test with significance level $\alpha = 0.05$.

Reviewer's comment:

- *No formal comparisons of TRM estimates are made in this review, since the cohorts are not considered comparable. Section 3.2.4 presents the 95% CIs for each cohort, but no exact binomial test results are presented.*

The sponsor summarized engraftment results using descriptive statistics. Results for the overall engraftment occurrence, defined as occurrence of both neutrophils and platelets engraftment, are presented for the thiotepa cohort as well as the historical control cohort.

Time to Recovery for ANC/Platelets results were presented with descriptive statistics.

Reviewer's comment:

- *No testing hierarchy was pre-specified for the primary and key secondary efficacy endpoints. Additionally, the sponsor did not pre-specify methods for handling missing data.*

[1] Clopper, C and Pearson, E.S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika*. **26**: 404-413. DOI:10.2307/2685469.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 76 patients were treated on either a conditioning regimen that included thiotepa, Protocol 26M (N=25), or were treated on a standard (control) conditioning regimen that did not include thiotepa, Protocol 26 (N=51); all patients were treated at one of two centers in Italy. All patients underwent allogeneic transplantation; data were retrospectively identified, and the incidence of graft rejection was also available for all patients.

The primary analysis population was the Full Analysis Set (FAS), which included all transplanted subjects who provided informed consent or assent (together with corresponding parent / tutor consent) for retrospective collection of data. There were no other analysis populations defined.

Patient age at baseline ranged from 4 years to 16 years, and in both groups the median age at baseline was 10 years. The Protocol 26M group contained more males than females while the Protocol 26 group had more female patients. On average, patients on Protocol 26M were of similar height had a higher weight than Protocol 26 patients at baseline. All patients from the Protocol 26M group were treated at the study site in Rome, Italy; while patients identified for the Protocol 26 group were treated at either the Rome or Milan sites.

Table 2. Baseline Demographic Characteristics by Protocol

Variable	**Protocol 26** (N = 51)	**Protocol 26M** (N = 25)
Age, in years		
Mean (SD)	10.1 (3.37)	10.4 (2.74)
Median [Min, Max]	10 [4 – 16]	10 [5 – 16]
Gender [%, (N)]		
Female	56.9 (29)	40.0 (10)
Male	43.1 (22)	60.0 (15)
Height, in cm [Mean (SD)]	130.1 (12.58)	131.5 (14.25)
Weight, in kg [Mean (SD)]	26.9 (8.04)	29.2 (8.39)
Study Site [%, (N)]		
IT01	51.0 (26)	100 (25)
IT02	49.0 (25)	0 (0)

Reviewer's comment:

- *All Protocol 26M patients were treated at one center in Italy, so study results may not be generalizable to overall population.*
- *Limited baseline characteristics data were collected, so it is not clear whether the baseline characteristics are comparable between the two protocols.*

3.2.4 Results and Conclusions

Of the 25 patients treated on Protocol 26M, none experienced a graft rejection after one year [95% CI: (0, 0.137)]. Thirteen of the 51 historical control patients treated on Protocol 26 [25.5%; 95% CI: (0.143, 0.396)] experienced graft rejection within one year after transplantation. No formal statistical comparisons were made between the groups. Table 3 summarizes these results.

Table 3. Primary Efficacy Results: Number of patients experiencing graft rejection, by treatment group

Protocol Type	N	%	Clopper-Pearson 95% CI	
			Lower	Upper
Protocol 26 (N = 51)	13	25.5	0.143	0.396
Protocol 26M (N = 25)	0	0	0	0.137

Table 4. Secondary efficacy results

Secondary Efficacy Endpoint	Protocol 26M (N = 25)	Protocol 26 (N = 51)
	Proportion % (95% CI)	Proportion % (95% CI)
Overall survival, 1 year	85.4 (71.0, 100)	87.8 (78.2, 98.5)
Thalassemia-free survival, 1 year	85.4 (71.0, 100)	65.7 (52.8, 98.5)
Transplant-related mortality, 1 year	12.0 (0, 30.0)	7.8 (0, 20.0)
Engraftment	92.0 (80.9, 100)	86.3 (76.2, 96.3)
	Median (Min – Max)	Median (Min – Max)
Days to recovery for ANC	21.0 (16.0 – 23.0)	21.0 (14.0 – 42.0)
Days to recovery for Platelets	52.0 (26.0 – 101.0)	23.0 (12.0 – 320.0)

Secondary analyses of efficacy results include six outcomes. At one year post-transplantation, 85.4% thiotepa-treated patients had survived, and 87.8% of historical control patients survived. There were a total of 3 deaths in the treatment group, which all occurred within 7 months of transplantation, and 5 deaths among the historical control cohort which all occurred within 9 months of transplantation. Two of the three deaths in the treatment group were transplant-related, and all 5 deaths in the historical control cohort were transplant-related.

***Reviewer's comments*:**

- *Although some secondary endpoint data can be confirmed based on the sponsor's derived datasets, some data were not supported by source data and were not confirmed by OSI. Therefore, the validity of secondary endpoint data is unclear.*

Figure 1. Kaplan-Meier curve, Overall survival by treatment group

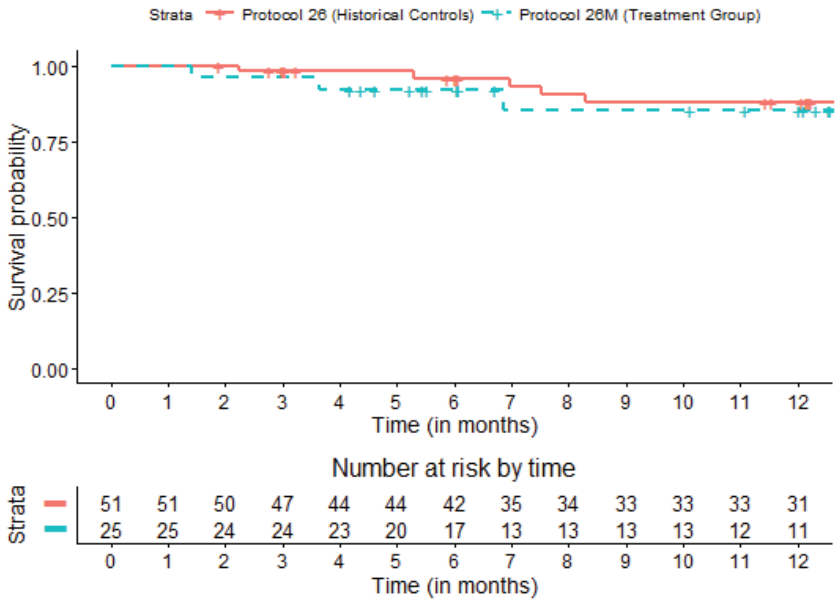


Figure 1 displays the Kaplan-Meier estimates of overall survival for the treatment group (Protocol 26M – thiotepa) and the historical control cohort (Protocol 26). At 12 months after transplantation, 85.4% of patients in the thiotepa cohort survived [95% CI: (71.0, 100)] and 87.8% of historical control patients survived [95% CI: (78.2, 98.5)].

Estimates of thalassemia-free survival by cohort are displayed in Figure 2. At 12 months after transplantation, 85.4% of patients in the thiotepa cohort were living and remained thalassemia-free [95% CI: (71.0, 100)] while 65.7% of historical control patients were alive and thalassemia-free [95% CI: (52.8, 98.5)].

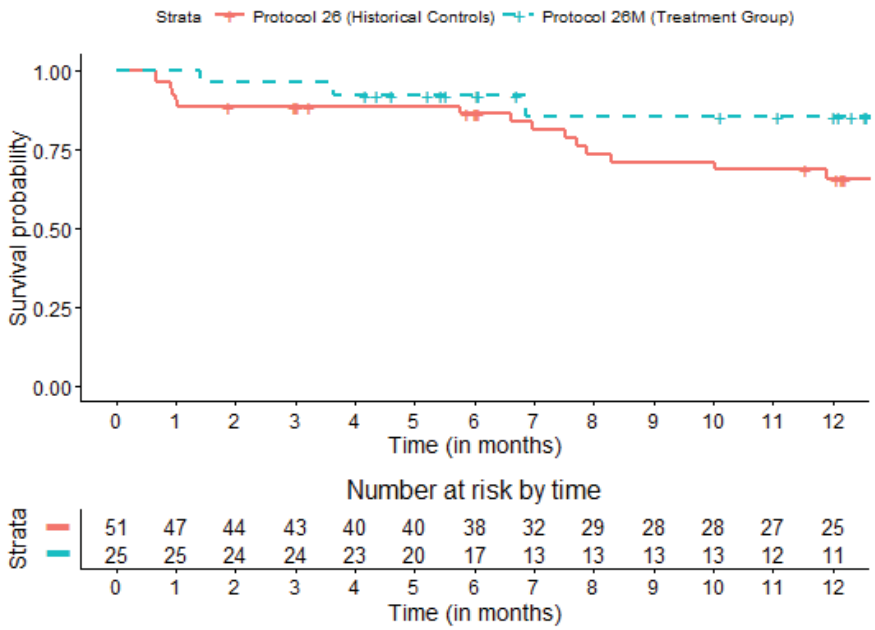
Overall engraftment in the treatment group was 92%, and 86.3% in the historical control cohort.

Days to recovery for ANC was available for all Protocol 26M patients and for 45 of 51 Protocol 26 patients. Days to recovery for Platelets was available for 23 of 25 Protocol 26M patients, and for 45 of 51 of Protocol 26 patients.

Reviewer's comments:

- *The sponsor's dataset contained incorrect analysis values for Days to recovery for ANC and Days to recovery for Platelets. Correct values were reflected in the sponsor's Integrated Summary of Efficacy, as well as in Table 14.2.2.5 of the Study 01 Clinical Study Report. The values presented in Table 4 reflect the correct analysis values, as calculated by the reviewer.*

Figure 2. Kaplan-Meier curve, Thalassemia-free survival by treatment group



3.3 Evaluation of Safety

Please refer to the clinical review for more information on the evaluation of the safety of TEPADINA for the proposed indication.

4 LITERATURE META-ANALYSIS

The applicant submitted a literature meta-analysis using published literature on thalassemia major patients undergoing bone marrow transplantation following myeloablative conditioning treatment preceded by cytoreduction/immunosuppression to assess the incidence of graft rejection for patients undergoing different conditioning regimens. Like Study 01, secondary objectives of the meta-analysis were to further evaluate efficacy in terms of overall survival, thalassemia-free survival, incidence of transplant-related mortality, engraftment, and time to recovery of ANC and platelet count.

4.1 Methodology and Description of Individual Studies

To identify studies included in the meta-analysis, the sponsor searched the Medline database using a broad search of studies that used thiotepa as a conditioning treatment before allogeneic HSCT in thalassemia major patients. The primary search used the terms “thiotepa” [All Fields] AND “thalassemia” [All Fields].

Sixteen publications were identified in the literature search, including some retrospective and prospective studies; case report studies, publications from the same author, publications where

efficacy data in thalassemia patients could not be extrapolated and publications in Chinese were excluded.

Nine publications met the criteria for inclusion in the meta-analysis, and are summarized in Table 5. In total, these studies included 579 patients with thalassemia. There was a mix of prospective, retrospective, and consecutive cohort designs; sample sizes also varied greatly across the nine studies. Three studies included cohorts of patients on a similar conditioning regimen as Protocol 26M (busulfan + thiotepa + cyclophosphamide), though dosing and order varied across studies; two studies add additional components to this regimen.

Table 5. Summary of literature meta-analysis study characteristics[1]

Study	Design	Sample Size	Patient Population	Conditioning regimen
Bernardo, 2012	Prospective	60	Thalassemia major	TT-TREO-FLU: n = 60
Choudhary, 2013	Consecutive cohort	40	Thalassemia major	TREO-TT-FLU: n = 28 BU-CYC-ATG: n = 12
Gaziev, 2008	Prospective	16	Thalassemia recurrence after graft failure	BU-TT-CYC-ATG: n = 16
La Nasa, 2002	Consecutive cohort	32	Thalassemia major	BU-CYC: n = 4 BU-TT-CYC: n = 28
Li, 2012	Prospective	82	Thalassemia major	CYC-BU-TT-FLU: n = 82
Lisini, 2008	Retrospective	106	β-thalassemia	BU-TT-FLU: n = 91 BU-TT-CYC: n = 12 TT-TREO-FLU: n = 3
Locatelli, 2003	Retrospective	44[2]	β-thalassemia, Sickle cell disease	BU-CYC-TT: n = 9 BU-FLU-TT: n = 7 BU-CYC: n = 16
Mathews, 2013	Retrospective	362[3]	Transfusion-dependent β-thalassemia	BU-CYC: n = 139 TT-FLU-TREO: n = 50
Sodani, 2010	Prospective	22	Thalassemia major	BU-FLU-TT-CYC-ATG: n = 22

[1]This table is derived from Table 5 of the Integrated Summary of Efficacy
[2]Only 32 patients with β-thalassemia were included in the meta-analysis
[3]Only 189 class 3 patients were included in the meta-analysis
ATG = antithymocyte globulin; BU = busulfan; CYC = cyclophosphamide; FLU = fludarabine; TREO = treosulfan; TT = thiotepa

The sponsor tested pooling assumptions by evaluating study heterogeneity using the Cochrane Q and I^2 statistics on the primary endpoint, and four of the secondary efficacy endpoints. Evidence of publication bias was measured quantitatively using the Deeks asymmetry test. These evaluations did not find any statistically significant results, indicating that there was no publication bias and that pooling the studies was valid.

Reviewer's comment:
The literature meta-analysis was not prospectively planned to be included for evaluation of the efficacy of a conditioning regimen that includes thiotepa.

As in Study 01, all analyses were conducted on the full analysis set. The primary endpoint of interest in the meta-analysis was the incidence of graft rejection (follow up times vary by study); secondary endpoints were overall survival (at 36 months), thalassemia-free survival (at 36 months), transplant-related mortality (follow up times vary by study); incidence of engraftment; and time to recovery of ANC and platelet counts.

Reviewer's comment:
In Study 01, incidence of graft rejection is calculated at one year post-transplantation. The post-transplant follow up times varied across studies, and nearly every study followed patients well beyond one year (12 months) beyond treatment/transplant. Overall, follow up times extended up to 110 months beyond treatment/transplant. In several studies, overall survival and thalassemia-free survival were measured at 3 years after treatment/transplant. Thus, measurements of the primary and secondary endpoints are not directly comparable to results found in Study 01, which measured endpoints at only 12 months post-transplantation.

4.2 Consideration of Meta-Analysis Results for this Review

While the meta-analysis provides useful historical information about the incidence of post-transplant graft rejection and other transplant-related outcomes in β-thalassemia and thalassemia major patients who were treated on conditioning regimens with and without thiotepa, some differences in study characteristics, patient populations, and follow up times make it difficult to make statistical inferences in comparison to the corresponding efficacy results of Study 01.

5 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Study 01 collected information on patients' age at baseline and gender; in this section, efficacy results are presented for these subgroups. There was no data collected on patient race or geographical region of residence.

5.1 Gender, Race, Age, and Geographic Region

Below, Table 9 displays primary efficacy results by treatment group and demographic subgroups, particularly age group (using the median, 10 years of age, as the cutoff) and gender. Overall, there was no evidence of a differential risk of graft rejection by age or gender, either in the thiotepa cohort or in the historical control cohort.

Secondary efficacy results by subgroups were not calculated due to the small sample sizes in each subgroup.

Table 6. Number of patients experiencing graft rejection, by treatment group and demographic subgroups

	Protocol 26M (N = 25)	Protocol 26 (N = 51)
Age, in years		
≤10	0 (0%)	8 (24.2%)
>10	0 (0%)	5 (27.8%)
Gender		
Female	0 (0%)	7 (24.1%)
Male	0 (0%)	6 (27.3%)

No conclusions regarding efficacy of TEPADINA to prevent graft rejection after transplantation by subgroup can be drawn due to the fact that there were no graft rejections in the Protocol 26M group. Overall, the small study sample size and lack of data on race/ethnicity and geographic region do not allow for in-depth analysis by subgroup.

5.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

6 SUMMARY AND CONCLUSIONS

6.1 Statistical Issues

During the review, several statistical issues were identified:

Study 01 has a retrospective study design with historical, unmatched controls. Thus, there is no evidence that the study's treatment arms are comparable. Particularly, the timelines of protocols 26M and 26 differ, and patients were not randomized or prospectively matched to validate formal statistical comparisons of results.

While source data for the primary efficacy endpoint, incidence of graft rejection, was verified, some secondary endpoint data was not validated.

Data were available from only two centers in Italy, which makes it difficult to generalize study results to a broader patient population.

A literature meta-analysis of nine studies that was included in the sponsor's application as supporting efficacy data presented the following concerns: (1) Primary and secondary endpoints were evaluated at a longer time interval from transplantation than in Study 01; (2) Not all studies used in the meta-analysis included patients with transplants from HLA-identical sibling donor pairs; and (3) The timing of follow up differs across studies. Therefore, meta-analysis results are not supportive of the results from Protocol 26M.

No information on patient race/ethnicity and geographic region were collected. This limits assessment of the consistency of results across relevant patient subgroups to describe the

potential effect of treatment among the patient population that is likely to be prescribed to TEPADINA.

This reviewer recommends that claims made based on historical controls or a literature meta-analysis should not be allowed since the pivotal trial did not prospectively plan for these comparisons.

6.2 Conclusions and Recommendations

Although there are concerns that patients treated on Protocol 26M cannot be formally compared to Protocol 26 patients, Study 01 has demonstrated the benefit of adding thiotepa to the pre-conditioning regimen of busulfan and cyclophosphamide to prevent graft rejection in Class 3 thalassemia patients undergoing allogeneic transplantation. Historically, the rate of graft rejection one year after transplantation in class 3 β-thalassemia patients not treated with thiotepa has ranged from 13% to 40%. None of the thiotepa-treated patients experienced post-transplantation graft rejection. Additionally, TEPADINA does not appear to negatively impact chances of overall survival, thalassemia-free survival, or transplant-related mortality in class 3 β-thalassemia patients; a lack of supporting source data prevents further interpretation of secondary efficacy outcomesSmall sample sizes in Protocol 26M and the historical control cohort limit the generalizability of the results of Study 01 to the intended patient population, and do not allow for assessment of differential treatment effects in patient subgroups.

In summary, the reviewer cannot make formal inferences on the treatment effect of TEPADINA in the thiotepa-treated cohort vs. the historical control cohort; however, this review confirms that there is evidence that TEPADINA reduces the rate of graft rejection in class 3 β-thalassemia patients undergoing allogeneic stem cell transplantation.

The final decision on the risk-benefit evaluation of thiotepa for reducing the rate of graft rejection in class 3 β-thalassemia patients undergoing allogeneic stem cell transplantation from an HLA-identical sibling donor is deferred to the clinical review team.

6.3 Labeling Recommendations

(b) (4)
(b) (4)
(b) (4) The reviewer recommends that no formal statistical comparisons are made between the cohorts (i.e., p-values). Additionally, the reviewer recommends that all results from the literature meta-analysis be excluded from the label since some study specifications do not allow for comparison with Protocol 26M and since efficacy outcomes were evaluated at different time points from Protocol 26M. Finally, the reviewer recommends exclusion of secondary endpoint results due to insufficient source data collection supporting results. The final label summarizes efficacy results from Protocol 26M without making formal comparisons between the thiotepa-treated cohort and the historical control cohort. The label also omits mention of the literature efficacy meta-analysis.

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/s/

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12/19/2016

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