

Application Type	Original BLA
STN	125685
CBER Received Date	April 5 <sup>th</sup> , 2019
PDUFA Goal Date	December 4 <sup>th</sup> , 2019
Division / Office	DCGT/OTAT
Committee Chair	Tom Finn
Clinical Reviewer	Winson Tang
Project Manager	Jean Gildner/ Adriane Fisher
Priority Review	Yes
Reviewer Name(s)	Cong Wang
Review Completion Date / Stamped Date	
Supervisory Concurrence	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	Enzyvant Therapeutics GmbH
Established Name	Allogeneic processed postnatal thymus tissue (RVT-802)
(Proposed) Trade Name	RETHYMIC
Pharmacologic Class	Allogeneic cultured postnatal thymus tissue product
Dosage Form(s) and Route(s) of Administration	Single administration by surgical implantation
Dosing Regimen	(b) (4) to 22,000 mm <sup>2</sup> of thymus tissue/recipient body surface area in m <sup>2</sup>
Indication(s) and Intended Population(s)	For the immune reconstitution of pediatric patients with congenital athymia

**TABLE OF CONTENTS**

<b>GLOSSARY .....</b>	<b>3</b>
<b>1. EXECUTIVE SUMMARY .....</b>	<b>4</b>
<b>2. CLINICAL AND REGULATORY BACKGROUND .....</b>	<b>5</b>
2.1 Disease or Health-Related Condition(s) Studied .....	5
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) .....	6
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission .....	6
<b>3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES.....</b>	<b>6</b>
3.1 Submission Quality and Completeness.....	6
<b>5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE     REVIEW.....</b>	<b>7</b>
5.1 Review Strategy .....	7
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review.....	7
5.3 Table of Studies/Clinical Trials .....	7
<b>6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS .....</b>	<b>8</b>
<b>7. INTEGRATED OVERVIEW OF EFFICACY .....</b>	<b>8</b>
7.1 Major Inclusion/Exclusion Criteria .....	9
7.2 Design Overview .....	9
7.3 Demographics and Baseline Characteristics .....	10
7.4 Analysis of Primary Endpoint .....	13
7.5 Analysis of Other Efficacy Endpoints.....	16
7.6 Subpopulations .....	17
7.7 Efficacy Conclusions .....	19
<b>8. INTEGRATED OVERVIEW OF SAFETY .....</b>	<b>19</b>
8.1 Deaths .....	20
8.2 Nonfatal Serious Adverse Events .....	20
8.3 Adverse Events of Special Interest (AESI) .....	22
<b>10. CONCLUSIONS .....</b>	<b>23</b>
10.1 Statistical Issues and Collective Evidence .....	23
10.2 Conclusions and Recommendations.....	24
<b>REFERENCES.....</b>	<b>24</b>

## Glossary

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of Special Interest
BLA	Biologics Licensure Application
BMT	Bone marrow transplantation
cDGA	complete DiGeorge anomaly
CI	Confidence interval
CMC	Chemistry, Manufacturing and Controls
CR	Complete Response
CSR	Clinical study report
DGS	DiGeorge syndrome
DUMC	Duke University Medical Center
EAS	Efficacy analysis set
EAS-cDGA	Analysis set of all EAS subjects except those with FOXN1 deficiency
FAS	Full analysis set
FDA	Food and Drug Administration
FOXN1	Forkhead box protein N1
GVHD	Graft Versus Host Disease
HCT	Hematopoietic cell transplantation
HIV	Human immunodeficient virus
Ig	Immunoglobulins
IND	Investigational new drug
KM	Kaplan-Meier
NA	Not applicable
PHA	Phytohemagglutinin
SCID	Severe combined immunodeficiency
SD	Standard Deviation
SAE	Serious adverse event
US	United States

## 1. Executive Summary

RETHYMIC is a tissue therapy. It is allogeneic cultured postnatal thymus tissue manufactured from tissue obtained from unrelated donors under the age of 9 months. This Biologics License Application (BLA) seeks licensure of RETHYMIC for the immune reconstitution of pediatric patients with congenital athymia.

T cell immunodeficiency associated with athymia is a life-threatening disorder that results in a patient's inability to develop naïve T cells and subsequently mount an appropriate immune response to infection. Without immune reconstitution, infants diagnosed with primary immunodeficiency due to athymia will die from infection within the first few years of life. T cell immunodeficiency due to athymia is associated with congenital disorders which prevent the development of a functional thymus; these congenital disorders include complete DiGeorge anomaly (cDGA) and forkhead box protein N1 (FOXP1) deficiency. Using a conservative estimate, the estimated birth prevalence of cDGA would be approximately 0.02 to 0.05 in 10,000 births. The FOXP1 (also known as nude severe combined immunodeficiency) is even rarer with an estimated incidence of less than 0.01 in 10,000 births (Dhalla, 2017;12).

The primary source of evidence to support this application is data pooled from 7 core, single-site, open-label, non-randomized clinical studies in subjects with congenital athymia (Studies 668-1, 668-2, 884[including 884-1], 931, 932, 950[including 950-1] and 25966). Two (2) additional IND 9836 protocols (Studies (b) (6) and 51692) and one non-IND protocol (Study 735) provided additional supporting data, though subjects treated in these studies were not included in the efficacy analysis set (EAS).

Ninety-three (93) subjects were treated by a single surgical implantation procedure at the dose range of (b) (4) to 22,000 mm<sup>2</sup> of thymus tissue per recipient body surface area in m<sup>2</sup> and 85 subjects were included in the EAS from the original BLA submission. The primary efficacy endpoint, the survival rate at Year 1, was 76.5% (95% CI: 65.9%, 84.1%) in the EAS estimated based on the Kaplan-Meier method. The supportive efficacy endpoint, the estimated survival rate at Year 2 was 75.2% (95% CI: 64.6%, 83.1%). Both lower limits of 95% CIs at Year 1 and Year 2 are greater than the pre-specified survival rate of 50% under the null hypothesis. The comparison rate of 50% was agreed to between the sponsor and FDA as the T cell immunodeficiency due to congenital athymia was fatal with almost all infants dying by the age of 2 years without therapeutic reconstitution of the immune system based on the natural history data. The median survival time for all subjects was yet to be reached as of the data cut-off date. No new death was observed for those subjects who survived to Year 9 post implantation and the first treated subject was censored at Year 24. Thus, the survival rate was 70.2% at Year 24 (95% CI: 58.7%, 79.1%) estimated based on the Kaplan-Meier method (Figure 1). In addition, all the Naïve CD3, CD4, CD8 cell counts, Total CD3, CD4, CD8 cell counts showed generally durable increases in these T cell indicators of thymic function as the study follow-up period progressed. The proliferative T cell response to Phytohemagglutinin (PHA) also increased through Year 2 post-implantation. Results of survival rate at Year 1 (and Year 2) were generally consistent among age, sex, race, cDGA phenotype and immunosuppression subgroups.

Twenty-seven (27) deaths occurred as of the data cutoff (July 16, 2018) after the administration of RVT-802 treatment. Of these, 23 subjects died within 2 years of implantation. This included 22 subjects who died during the study follow-up period and 1 subject who died within 2 years of treatment but after having prematurely discontinued the study due to physician's decision. The time to death ranged from 0 to 480 days (1.3 years) in subjects who died within 2 years of implantation and from 0 to 3116 days (8.5 years) in all subjects who died. During the 2 years after implantation, 443 serious adverse effects (SAEs) were reported in 79 subjects. The most frequently reported SAEs were infections and infestations (213 SAEs), which occurred in 67 subjects. In addition, 58 treatment-related SAEs were reported in 30 subjects within 2-year implantation. The most frequently reported treatment-related SAEs were blood and lymphatic system disorders (22 events), which occurred in 13 subjects.

The statistical analysis results provide evidence to support the safety and effectiveness of RETHYMIC for the proposed indication in this BLA.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

T cell immunodeficiency resulting from congenital athymia is a rare condition associated with genetic disorders such as cDGA and FOZN1 deficiency. DiGeorge syndrome (DGS) is a congenital disorder characterized by defects in organs derived from the third and fourth pharyngeal pouches and the intervening third pharyngeal arch. The parathyroid, thymus, and heart are derived from this region during the development of the human embryo and patients with DGS typically present with clinical features including congenital cardiac anomalies, a small thymus, and hypocalcemia secondary to hypoparathyroidism.

DGS is a clinically defined syndrome with diagnosis based on the presence of cardiac anomalies, hypocalcemia, and reduced numbers of circulating T cells.

Taken together with the estimate that approximately 55% of all DiGeorge anomalies are attributable to 22q11.2DS, the estimated birth prevalence of all DGS cases would be approximately 2 to 5 per 10,000 births. Complete DGA occurs in less than 1% of patients with DGS; using a conservative 1% estimate, the estimated birth prevalence of cDGA would be approximately 0.02 to 0.05 in 10,000 births. The FOZN1 is even rarer with an estimated incidence of less than 0.01 in 10,000 births (Dhalla, 2017;12). Without therapeutic reconstitution of the immune system, the T cell immunodeficiency due to congenital athymia in conditions such as cDGA or FOZN1 deficiency is fatal, with almost all infants dying by the age of 2 years, most frequently from infections.

## **2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)**

There are currently no approved therapies for the treatment of T cell immunodeficiency associated with congenital athymia. Patients can be treated with supportive care; however, the 2-year survival rate for untreated cDGA is only 6% with all patients dying by 3 years of age.

## **2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission**

Table 1 below summarizes the major regulatory activities associated with this BLA.

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Milestone
05/18/2001	IND 9836 submission
08/15/2003	Orphan Drug designation granted to RVT-802
04/13/2017	Breakthrough Therapy designation and Regenerative Medicine Advanced Therapy designation granted
05/01/2017	End-of-Phase 3 meeting
08/25/2017	Rare Pediatric Disease designation granted
10/30/2017	Orphan Drug designation transferred to Enzyvant Therapeutics GmbH
11/06/2017	Pre-BLA meeting
04/05/2019	BLA 125685 submission
06/04/2019	BLA filed. Filing letter issued to the applicant
07/26/2019	120-day safety update
12/04/2019	PDUFA action due date

(Source: FDA statistical reviewer's summary)

## **3. Submission Quality and Good Clinical Practices**

### **3.1 Submission Quality and Completeness**

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

## 5. Sources of Clinical Data and Other Information Considered in the Review

### 5.1 Review Strategy

The primary source of evidence to support the proposed product RVT-802 came from Studies 668-1, 668-2, 884 (including 884-1), 931, 932, 950 (including 950-1) and 25966. Two (2) additional IND 9836 protocols (Studies (b) (6) and 51692) and 1 non-IND protocol (Study 735) provided additional supporting data, though subjects treated in these studies were not included in the EAS. The integrated efficacy analysis including all subjects with athymia associated with cDGA or FOXN1 deficiency, who had no prior Hematopoietic cell transplantation (HCT) and who were treated with RVT-802 once by implantation (i.e., EAS) is the focus of this review memo.

### 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes the review of

- Clinical study reports and data sets submitted in modules 2 and 5 of BLA 125685/0.0
- Efficacy and safety 120-day update submitted in BLA 125685/2.0

### 5.3 Table of Studies/Clinical Trials

Table 2 summarizes the 10 studies included in the BLA submission. Results from core Studies 668-1, 668-2, 884 (including 884-1), 931, 932, 950 (including 950-1) and 25966 (ongoing) formed the primary evidence of the proposed product RVT-802 for the BLA application. All the studies were conducted at Duke University Medical Center (DUMC).

Table 2. Studies in the BLA application

Study code	Study design+ Study population	Study status	# of subjects implanted*
668-1 (core)	Phase 1, single-site, non-randomized, open-label, thymus transplantation for complete DiGeorge syndrome with typical/atypical cDGA, no immunosuppression planned	completed	14
668-2 (core)	Phase 2, single-site, non-randomized, open-label, thymus transplantation for complete DiGeorge syndrome with typical cDGA	completed	12
884 (core, including 884-1)	Phase 1, single-site, non-randomized, open-label, thymus transplantation with immunosuppression with typical cDGA and elevated T cell function/atypical cDGA	completed	12
931 (core)	Phase 1, single-site, non-randomized, open-label, thymus and parathyroid transplantation for complete DiGeorge	completed	5

	syndrome with typical/atypical cDGA and with hypoparathyroidism requiring calcium supplementation		
932 (core)	Phase 2, single-site, non-randomized, open-label, dose study of thymus transplantation in DiGeorge anomaly with typical cDGA without immune suppression	completed	7
950 (core, including 950-1)	Phase 1/2, single-site, non-randomized, open-label, thymus transplantation with immunosuppression with typical/atypical cDGA and with varying PHA responses pre-transplantation	completed	15
25966 (core)	Phase 1/2, single-site, non-randomized, open-label, thymus transplantation with typical/atypical cDGA with varying pre-treatment immune function	ongoing	24
(b) (6) (supportive)	Open-label, expanded access study to treat a single, pre-identified subject, thymus Transplantation for EBV Lymphoma	completed	1
51692 (supportive)	Single-site, non-randomized, open-label, expanded access study, thymus transplantation for immunodeficiency, hematologic malignancies, and autoimmune disease related to poor thymic function	ongoing	2
735↓ (supportive)	Single-site, non-randomized, open-label, thymic transplantation in partial DiGeorge syndrome	completed	1

\* Data cutoff date = July 16, 2018

↓ Non-IND protocol

(Source: FDA statistical reviewer's summary)

## 6. Discussion of Individual Studies/Clinical Trials

As the primary and secondary efficacy endpoints are similar across all 7 core studies and assessed by similar criteria, an integrated (pooled) analysis of efficacy is presented in Section 7. Safety data are presented in Section 8.

## 7. Integrated Overview of Efficacy

The review of efficacy in this section is intended to discuss integrated efficacy results combining all 7 core studies and 3 supportive studies.



## 7.1 Major Inclusion/Exclusion Criteria

- By the nature of the study, all subjects included in the EAS were under 2 years of age at the time of implantation.
- Diagnosis of congenital athymia based on flow cytometry documenting fewer than 50 naïve T cells  $\text{mm}^3$  in the peripheral blood or less than 5% of total T cells considered naïve in phenotype.
- Eligible subjects were required to have at least one of the following (criteria were similar across studies):
  - i. Congenital heart defect
  - ii. Hypoparathyroidism or hypocalcemia requiring replacement
  - iii. 22q11.2 hemizygosity or 10p13 hemizygosity
  - iv. CHARGE syndrome or CHD7 mutation
- In general, subjects were excluded if met any of the following criteria:
  - i. Heart surgery conducted or anticipated near the time of the projected RVT-802 implantation date
  - ii. Rejection by the surgeon or anesthesiologist as surgical candidate
  - iii. Lack of sufficient muscle tissue to accept an implant within the planned dose range
  - iv. Prior attempts at immune reconstitution, such as Bone marrow transplantation (BMT) or previous thymus transplantation
  - v. Human immunodeficient virus (HIV) infection
- FOXP1-deficient subjects were required to have a diagnosis of athymia and FOXP1 deficiency.

## 7.2 Design Overview

As described in Table 2, all studies were open-label, single-site, non-randomized clinical trials of RVT-802. Across studies, most screening procedures were conducted over a period of approximately 2 to 12 weeks prior to implantation. While more extended subject follow-up was planned in the original protocols, effective in the multi-protocol addendum dated July 31, 2017, protocol-specified assessments were collected only through the first 2 years post-implantation. In Studies 668-1, 668-2, 884 (including 884-1), 931, 932 and 950 (including 950-1), subjects were followed for adverse events (AEs) beyond 2 years post-implantation through the December 31, 2017 cut-off. In Study 25966, subjects were followed for AE reporting through 2 years post-implantation (or through July 16, 2018 whichever was sooner).

Subjects in Studies 931 and 932 could have received a single parental parathyroid transplant in addition to RVT-802. Except for subjects in Studies 668-1, 668-2, 932 and a subset of subjects in Study 25966, immunosuppressive therapy was administered before and after RVT-802 implantation. With the exception of Study 932, which included only subjects with the typical phenotype of cDGA, the core studies included both the typical and atypical phenotypes of cDGA. In addition, the EAS included 2 subjects with FOXP1 deficiency. One (1) subject with FOXP1 deficiency was enrolled in Study 668-2 (Subject (b) (6)) and another was enrolled in Study 884 (Subject (b) (6)).

### **Study Treatments or Agents Mandated by the Protocol**

RVT-802 was administered as a single surgical implantation procedure at the dose range of (b) (4) to 22,000 mm<sup>2</sup> of thymus tissue per recipient body surface area in m<sup>2</sup>.

### **Sites and Centers**

DUMC was the center that conducted all the studies during the past 25 years under the guidance of Dr. Louise Markert.

### **Surveillance/Monitoring**

There was no independent surveillance/monitoring board as this study was originally an academic program.

### **Endpoints**

Primary: Survival rate at Year 1

Supportive: Survival rate at Year 2

- Secondary: Number of Total CD3 T cells, Total CD4 T cells, Total CD8 T cells, Naïve CD3 T cells, Naïve CD4 T cells, Naïve CD8 T cells at Month 6, Year 1 and Year 2; Proliferative T cell responses to mitogens (PHA, ConA, Sol CD3, Insol CD3, TT, and Candida) at Year 1; TCR repertoire variability at Year 1; TREC/TREG at Year 1; Biopsy of Transplanted Thymus at Year 1.

[Note: In the original BLA 125685/Amendment 0.6 dated 05/10/2019, the applicant re-defined the primary efficacy endpoint as the survival rate at Year 1 and the survival rate at Year 2 would be a supportive endpoint. The reason for the modification is to make the primary efficacy endpoint consistent between the Clinical Study Report and the study protocol/SAP based on the agency's recommendation sent on 05/03/2019.](#)

Data on other flow cytometry parameters (double negative [DN; CD4-CD8-; DB Neg], TCR $\alpha\beta$ , TCR $\gamma\delta$ , B, and NK cells), serum immunoglobulins (Ig), isohemagglutinins, and B cell antibody responses to antigens were also collected as data permitted across the studies.

## **7.3 Demographics and Baseline Characteristics**

There were 3 analysis sets defined in the study:

- Efficacy Analysis Set (EAS): all subjects with athymia associated with cDGA or FOXP1 deficiency, who had no prior HCT and who were treated with RVT-802 once by implantation.
- Modified Efficacy Analysis Set (i.e., EAS-cDGA): all EAS subjects except those with FOXP1 deficiency.
- Full Analysis Set (FAS): all subjects who received RVT-802.

There were 93 subjects in the FAS, 85 subjects in the EAS and 83 subjects in the EAS-cDGA in this study.

The EAS included all subjects with congenital athymia associated with cDGA (N=83) or FOXP1 deficiency (N=2). Eight (8) additional subjects were included in the FAS and these subjects include 2 subjects with SCID, 3 subjects with cDGA who had received

prior HSCT, 1 cDGA subject who has received 2 prior fetal thymus transplants, 1 subject who had athymia of unknown origin and had received prior HSCT, and 1 subject who was considered to have partial DGA as the time of implantation but is now believed to have atypical cDGA.

Table 3 shows the demographic information for subjects in the FAS, EAS and EAS-cDGA, respectively. Subjects' sex, race and ethnicity information in these 3 analysis sets were similar. As for the age on the day of implantation, the mean results in the EAS and EAS-cDGA were less than the results in the FAS due to the fact that all subjects included in the EAS were under 2 years of age at the time of implantation, whereas some subjects in the FAS received prior treatments such as HSCT and then received the treatment of RVT-802 at older age.

Table 3. Pooled demographics for all analysis populations

	FAS N=93	EAS N=85	EAS-cDGA N=83
Age on the day of implantation (days)			
Mean (SD)	449.1 (963.48)	249.9 (152.05)	247.6 (152.66)
Median (min, max)	256 (33, 6163)	239 (33, 664)	215 (33, 664)
Sex n (%)			
Female	37 (39.8%)	33 (38.8%)	32 (38.6%)
Male	56 (60.2%)	52 (61.2%)	51 (61.4%)
Race n (%)			
White	67 (72.0%)	59 (69.4%)	58 (69.9%)
Black or African American	18 (19.4%)	18 (21.2%)	17 (20.5%)
Other	8 (8.6%)	8 (9.4%)	8 (9.6%)
Ethnicity n (%)			
Hispanic or Latino	19 (20.4%)	17 (20%)	17 (20.5%)
Other	74 (79.6%)	68 (80%)	66(79.5%)

(Source: FDA statistical reviewer's analysis)

Similarly, Table 4 shows the baseline characteristics for subjects in the FAS, EAS and EAS-cDGA, respectively. The mean age at enrollment was younger in the EAS and EAS-cDGA than that in the FAS due to the same reason above; The mean age at initial diagnosis was also younger in the EAS and EAS-cDGA because supportive study 51692 was included in the FAS but excluded from EAS, which included the expanded access use in other conditions (hematologic malignancy, immunodeficiency, severe autoimmune disease related to poor thymic function, prior HCT) among subjects with older ages at initial diagnosis.

Table 4. Pooled baseline characteristics for all analysis populations

	FAS N=93	EAS N=85	EAS-cDGA N=83
Age at enrollment (days)			
Mean (SD)	412.8 (955.4)	215.2 (148.5)	212.7 (148.8)
Median (min, max)	220 (23, 6124)	193 (23, 658)	187 (23, 658)
Age at initial diagnosis			
Mean (SD)	79.6 (151.01)	57.2 (89.4)	56.8 (89.8)
Median (min, max)	28 (0, 841)	26 (0, 537)	26 (0, 537)
Diagnosis n (%)*			
SCID	2 (2.2%)	0	0
FOXN1	2 (2.2%)	2 (2.4%)	0
Partial DiGeorge anomaly	1 (1.1%)	0	0
cDGA	87 (93.5%)	83 (97.6%)	83 (100%)
DiGeorge phenotype n (%)			
Typical cDGA	45 (48.4%)	43 (50.6%)	43 (51.8%)
Atypical cDGA	41 (44.1%)	39 (45.9%)	39 (47%)
Missing	7 (7.5%)	3 (3.5%)	1 (1.2%)

\* There was 1 subject in Study 950-1 (Subject (b) (6)) with athymia of an unknown etiology and, as such, no diagnosis was reported. Two (2) subjects with severe combined immunodeficiency (SCID) were in Study 51692 and 1 subject with partial DiGeorge anomaly was in Study 735. These subjects were all included in the FAS. The EAS only included subjects with congenital athymia associated with cDGA (N=83) or FOXN1 deficiency (N=2) and the efficacy conclusions were made based on the EAS. (Source: FDA statistical reviewer's analysis)

Note: In Study 25966, there was one data entry error for Subject (b) (6). The subject's age at enrollment was 243 days, however, the age at the initial diagnosis was 378 days (>243 days). In Enzyvant's response dated July 2019, they stated that "The DIAGDY entry of 378 for Subject (b) (6) is a data entry error. The initial diagnosis was on Day 12 of life (not Day 378). This data discrepancy has been corrected in the database and will be reflected in future data cuts." The results of age at initial diagnosis calculated by this statistical reviewer was based on the corrected data.

Table 5 shows the pooled subject disposition information in the FAS, EAS and EAS-cDGA, respectively. Among the 85 subjects in the EAS, 61 subjects (71.8%) were still alive and 24 subjects (28.2%) died at the data cutoff.

Table 5. Pooled subject disposition for all the analysis populations

	FAS N=93	EAS N=85	EAS-cDGA N=83
Completed at least 2 years follow-up	62*(66.7%)	56 (65.9%)	54 (65.1%)
Ongoing	8 (8.6%)	8 (9.4%)	8 (9.6%)
Withdrew prior to 2 years after implantation-Death	22 (23.7%)	21 (24.7%)	21 (25.3%)
Withdrew prior to 2 years follow-up-physician decision	2*(2.2%)	0	0
Withdrew prior to 2 years follow-up-parental decision	0	0	0
At the time of analysis data cutoff N (%)			
Alive	65 (69.9%)	61 (71.8%)	59 (71.1%)
Withdrew- death	25 (26.9%)	24 (28.2%)	24 (28.9%)
Withdrew-physician decision	3 (3.2%)	0	0
Withdrew-parental decision	0	0	0

\* In Study 932, Subject <sup>(b) (6)</sup> discontinued the study on Day 379 after implantation with RVT-802, however, this subject was still followed up for his vital status after the study discontinuation. Thus, this subject was taken into account in both categories of “Completed at least 2 years follow-up” and “Withdrew prior to 2 years follow-up.”  
(Source: FDA statistical reviewer’s analysis)

## 7.4 Analysis of Primary Endpoint

### Study hypotheses and Statistical method

The analysis of the primary efficacy endpoint was performed by testing  $H_0: \pi \leq 50\%$  v.s.  $H_1: \pi > 50\%$ , where  $\pi$  is the survival rate at Year 1 from transplant.

The Kaplan-Meier estimate of survival rate with 95% CI is shown in this section. The exact binomial test (significance level of two-sided 0.05) was also used to test the survival rate estimated as a proportion.

### Results

In the EAS of 85 subjects, 1 subject was censored at Year 1; among the remaining 84 subjects, 64 subjects (76.2%) were alive. The survival rate estimated using the Kaplan-Meier method at Year 1 was 76.5% (95% CI: 65.9%, 84.1%). The lower limit of 95% CI was well above pre-specified survival rate of 50% under the null hypothesis.

To access robustness of study results, the primary endpoint survival rate at Year 1 was analyzed in the FAS, EAS and EAS-cDGA, respectively (Table 6). The lower limits of 95% CIs for survival rate at Year 1 estimated using the Kaplan-Meier or estimated as a proportion were all well above the pre-specified rate of 50% under the null hypothesis

among all analysis population sets. The estimate of survival rate at Year 2 was also shown in Table 6.

Table 6. Survival rate results for all analysis populations

	FAS set (N=93)		EAS set (N=85)		EAS-cDGA set (N=83)	
	Year 1	Year 2#	Year 1	Year 2	Year 1	Year 2
Alive n	71	62	64	56	62	54
Dead n	21	23	20	21	20	21
Censored n	1	8	1	8	1	8
Alive + dead n	92	85	84	77	82	75
Survival rate estimated as a proportion	77.2%	72.9%	76.2%	72.7%	75.6%	72%
95% exact binomial CI	(67.2%, 85.3%)	(62.2%, 82%)	(65.7%, 84.8%)	(61.4%, 82.3%)	(64.9%, 84.4%)	(60.4%, 81.8%)
Two-sided p-value*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Survival rate estimated using KM method	77.4%	75.2%	76.5%	75.2%	76.5%	74.6%
95% CI	(67.5%, 84.6%)	(65.1%, 82.8%)	(65.9%, 84.1%)	(64.6%, 83.1%)	(65.2%, 83.7%)	(63.8%, 82.6%)

\* Based on an exact binomial test (significance level of two-sided 0.05) with survival rate of 50% under the null hypothesis

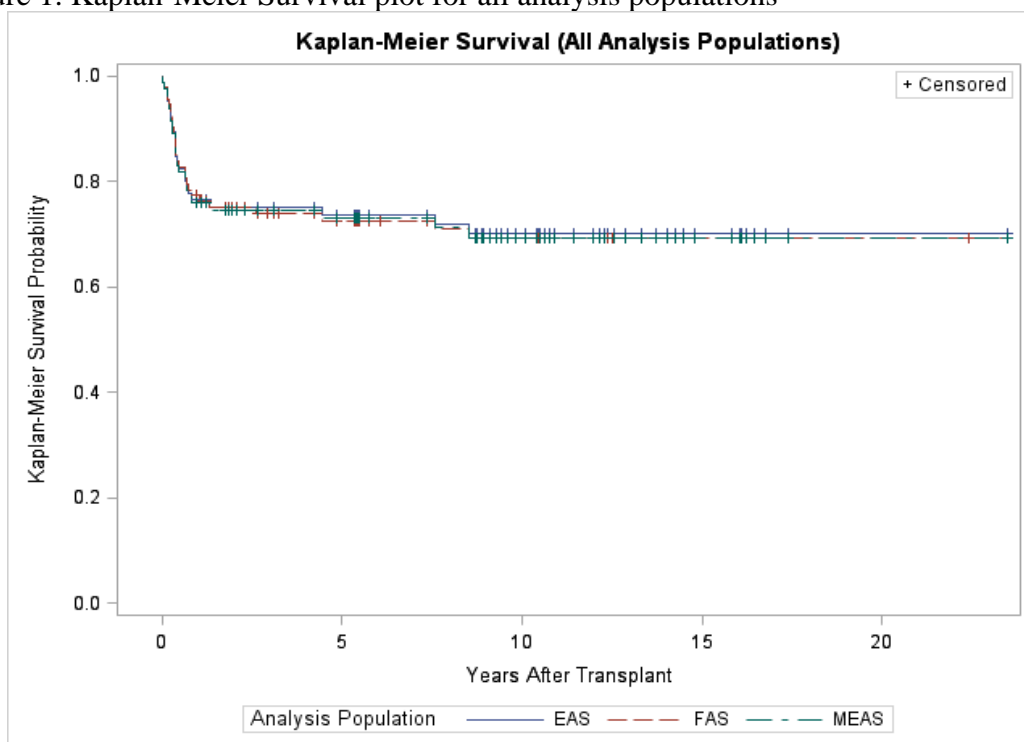
#Survival rate at Year 2 was presented as a supportive efficacy endpoint

(Source: FDA statistical reviewer's analysis)

Note: Based on the 120-day safety updated data, the survival rates at Year 1 and Year 2 estimated based on the Kaplan-Meier method were 76% (95% CI: 65.8%, 83.8%) and 75% (95% CI: 64.6%, 82.8%), respectively. The survival rates at Year 1 and Year 2 estimated as the proportion of {#alive subjects} among {#alive and dead subjects} at the specific time points were 76.1% (95% CI: 65.9%, 84.6%) and 74.1% (95% CI: 63.5%, 83%), respectively.

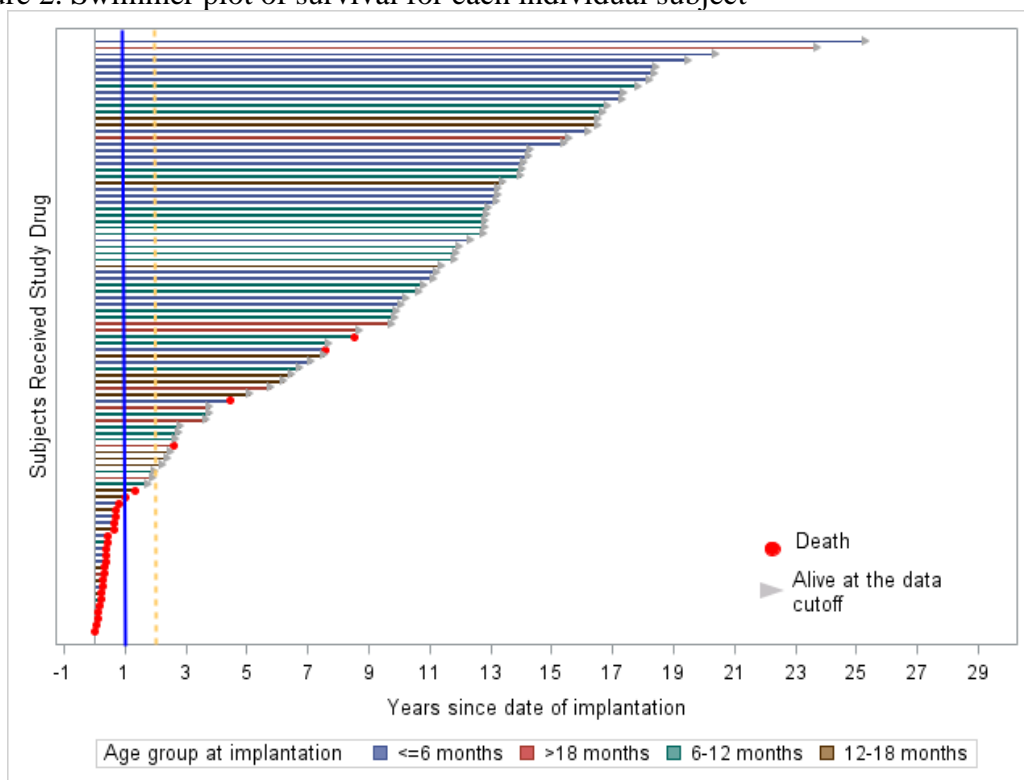
Figure 1 shows the Kaplan-Meier survival plot within 2-year follow-up in the FAS, EAS and EAS-cDGA respectively. Figure 2 shows the swimmer plot of survival in the EAS that gives detailed status for each individual subject. The majority of deaths occurred within the first year after implantation, which was prior to the development of thymic function.

Figure 1. Kaplan-Meier Survival plot for all analysis populations



(Source: FDA statistical reviewer's analysis)

Figure 2. Swimmer plot of survival for each individual subject



(Source: FDA statistical reviewer's analysis)

## 7.5 Analysis of Other Efficacy Endpoints

Other efficacy endpoints included naïve CD3, CD4 and CD8 cell counts, total CD3, CD4 and CD8 cell counts, number of T cell proliferative responses to PHA, RVT-802 biopsy, etc. Statistical analyses for other efficacy endpoints were descriptive.

Table 7 shows the naïve CD3, CD4, CD8, total CD3, CD4 and CD8 cell counts at 6-month intervals from baseline to 2 years post-implantation in the EAS. All the cell counts showed generally durable increases in these T cell indicators of thymic function as the study follow-up period progressed. For example, in the EAS, the median naïve CD3 cell counts (cells/mm<sup>3</sup>) were 1.29 (n=36) at baseline, 16 at month 6 (n=23), 124 at Year 1 (n=12) and 227 at Year 2 (n=7), respectively. However, it is unclear how the cell counts increase beyond the 2-year follow-up due to the lack of cell counts information after 2-year post-implantation.

Table 7. Descriptive statistics results of naïve CD3, CD4, CD8, total CD3, CD4 and CD8 cell counts in the EAS

Visit		CD3 (cells/mm <sup>3</sup> )		CD4 (cells/mm <sup>3</sup> )		CD8 (cells/mm <sup>3</sup> )	
		Naïve	Total	Naïve	Total	Naïve	Total
Baseline	N	33	85	57	75	51	72
	Mean (SD)	6.05 (17.01)	700.8 (1437.23)	3.39 (6.16)	266.9 (500.01)	5.35 (11.56)	265.23 (738.33)
	Median (min, max)	2 (0,98)	139 (0,7684)	1 (0,35.1)	111 (0,2458)	0.29 (0,45.94)	14.1 (0,4594)
Month 6	N	21	70	62	70	51	70
	Mean (SD)	41.05 (50.77)	506.1 (908.71)	66.49 (103.1)	370.5 (738.4)	19.89 (29.46)	69.53 (107.26)
	Median (min, max)	16 (0.52, 159)	346 (30, 7532)	23 (0,653)	251 (10,6187)	6.72 (0,163)	37.84 (1.42,651.16)
Month 12	N	10	49	39	50	36	49
	Mean (SD)	176.46 (151.96)	786 (435.6)	269.1 (207.33)	580 (355.44)	84.63 (81.17)	155.3 (124.5)
	Median (min, max)	124 (4,515.2)	731 (5, 1947)	261.8 (1,751)	526 (4,1780)	58.68 (0,304.3)	140 (1, 624.9)
Month 24	N	7	27	25	28	25	28
	Mean (SD)	295.3 (247.2)	775.4 (412.85)	281.9 (200.79)	564.9 (309.73)	93.64 (69.89)	165.5 (118.66)
	Median (min, max)	227 (42.8,746.2)	721 (104,1701)	273 (33,858)	532.5 (76,1220)	84 (6.04,275)	136 (23,580)

(Source: FDA statistical reviewer's analysis)

Note: There were many subjects with baseline naïve/total CD cell counts but without the subsequent assessment results because the applicant had trouble collecting samples as subjects were referred back to their home hospital for follow-up care. The descriptive statistics were calculated based on available cell counts data.



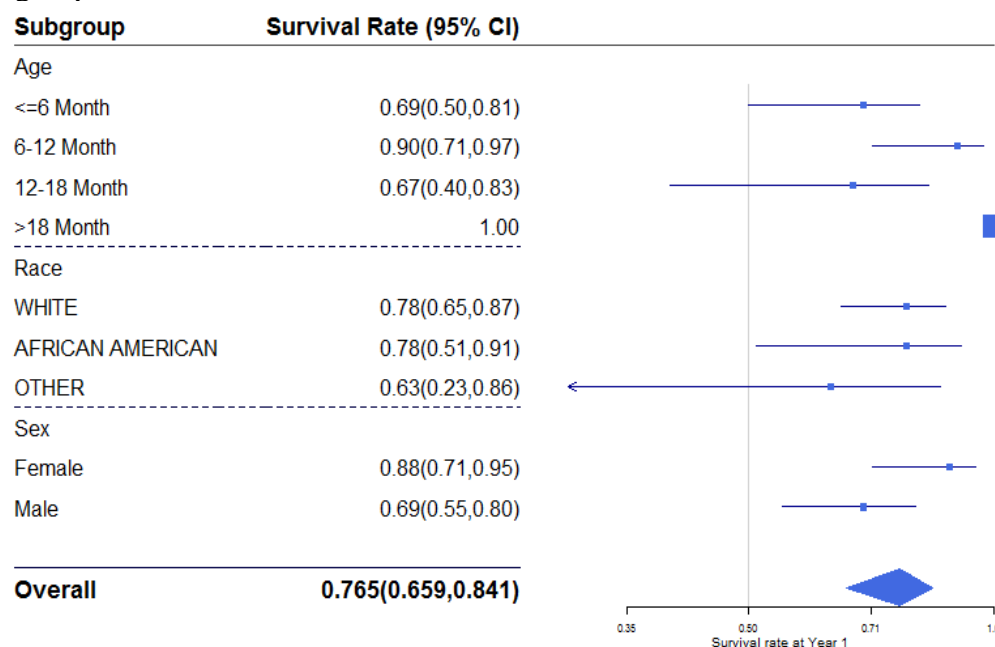
Similarly, the proliferative T cell response to PHA increased through Year 2 post-implantation. The median response to PHA at baseline is 3588 cpm (n=84), 92134 cpm (n=34) at Month 6, 143042 cpm (n=37) at Year 1 and 220647 cpm (n=20) at Year 2.

Among the EAS of 85 subjects, RVT-802 biopsies were performed for 50 subjects (53.8%). Of these 50 subjects, evidence of thymopoiesis was observed in 40 subjects (80%).

## 7.6 Subpopulations

Figure 3 shows the forest plot of survival rate at Year 1 estimated using the Kaplan-Meier method by age group, sex and racial groups in the EAS. Since African American and White subgroups combined counted for 90.6% of the efficacy analysis set, no additional subgroup analysis was carried out for other racial groups besides African American and White. Survival rate at Year 1 were generally consistent between African American and White subgroups. The number of treated subjects in the Other racial subgroup was too small to draw any conclusions.

Figure 3. Forest plot of survival rate at Year 1 estimated using the Kaplan-Meier method by subgroups

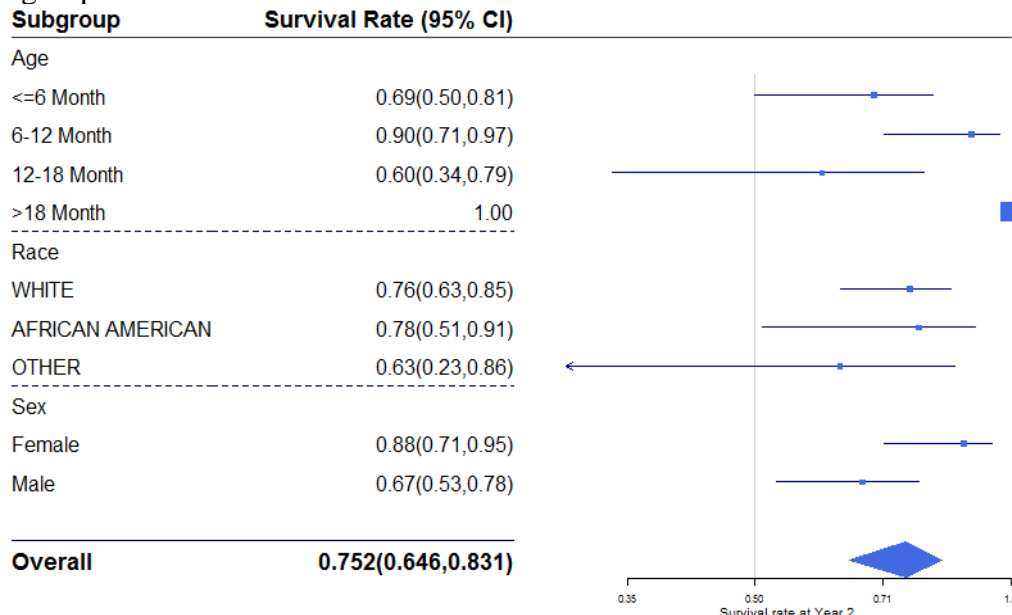


(Source: FDA statistical reviewer's analysis)

Note: Among 3 subjects in >18 months subgroup, all 3 were alive at Year 1, and 2 subjects were alive and 1 subject was censored at Year 2.

A similar pattern was observed in the forest plot of survival rate estimated based on the Kaplan-Meier method at Year 2 by subgroups (Figure 4).

Figure 4. Forest plot of survival rate at Year 2 estimated using the Kaplan-Meier method by subgroups



(Source: FDA statistical reviewer's analysis)

Table 8 shows subgroup analysis of survival rate at Year 1 and Year 2 estimated based on the Kaplan-Meier method by cDGA phenotype. Survival rate at Year 1 (and Year 2) was generally consistent between Typical cDGA and Atypical cDGA phenotype subgroups.

Table 8. Subgroup analysis of survival rate estimated using the Kaplan-Meier method by cDGA phenotype in the EAS

	Year 1		Year 2	
	Survival rate	95% CI	Survival rate	95% CI
Typical n=43 (50.6%)	81.4%	(66.2%,90.2%)	78.9%	(63.4%,88.4%)
Atypical n=39 (45.9%)	71.8%	(54.9%,83.3%)	71.8%	(54.9%,83.3%)
*Total n=85 (100%)	76.5%	(65.9%,84.1%)	75.2%	(64.6%,83.1%)

\*There are 3 subjects with three missing cDGA phenotype.

(Source: FDA statistical reviewer's analysis)

Table 9 shows subgroup analysis of survival rate at Year 1 and Year 2 estimated using the Kaplan-Meier method by immunosuppression in the EAS. Survival rate at Year 1 (and Year 2) was generally consistent between immunosuppression and non-immunosuppression subgroups.

Table 9. Subgroup analysis of survival rate estimated using the Kaplan-Meier method by immunosuppression in the EAS

	Year 1		Year 2	
	Survival rate	95% CI	Survival rate	95% CI
Yes n=54 (63.5%)	74.1%	(60.2%,83.7%)	72.0%	(57.9%,82.1%)
No n=31 (36.5%)	80.6%	(61.9%,90.8%)	80.6%	(61.9%,90.8%)
Total n=85 (100%)	76.5%	(65.9%,84.1%)	75.2%	(64.6%,83.1%)

(Source: FDA statistical reviewer's analysis)

## 7.7 Efficacy Conclusions

The primary source of evidence to support this application was based on the EAS that included subjects with athymia associated with cDGA or FOXP1 deficiency, who had no prior HCT and who were treated with RVT-802 once by implantation. Eighty-five (85) subjects were included in the EAS in the original BLA submission. Ninety (90) subjects were included in the EAS in the 120-day safety update report.

The primary efficacy endpoint, the survival rate at Year 1 was 76.5% (95% CI: 65.9%, 84.1%) in the EAS obtained from the Kaplan-Meier estimate. The supportive efficacy endpoint, the survival rate estimate at Year 2 was 75.2% (95% CI: 64.6%, 83.1%). Both lower limits of 95% CIs at Year 1 and Year 2 were greater than the pre-specified survival rate of 50% under the null hypothesis.

The median survival time for all subjects was yet to be reached as of the data cut-off date. No new death was observed for those subjects who survived to Year 9 post implantation and the first treated subject was censored at Year 24. Thus, the survival rate was 70.2% at Year 24 (95% CI: 58.7%, 79.1%) estimated based on the Kaplan-Meier method.

In addition, all the Naïve CD3, CD4, CD8 cell counts, Total CD3, CD4, CD8 cell counts showed generally increases in these T cell indicators of thymic function as the study follow-up period progressed. The proliferative T cell response to PHA also increased through Year 2 post-implantation.

Survival rate at Year 1 (and Year 2) were generally consistent among age, sex, race, cDGA phenotype or immunosuppression subgroups.

## 8. Integrated Overview of Safety

Descriptive statistics were used to summarize safety data for a total of 93 subjects who received RVT-802 implantation in the original BLA submission.

## 8.1 Deaths

The applicant reported the following deaths (Table 10). Among the 93 FAS subjects, 27 subjects (29%) died following treatment with RVT-802. Of these, 23 subjects died within 2 years of implantation. This included 22 subjects who died during the study follow-up period and 1 subject who died within 2 years of treatment but after having prematurely discontinued the study due to physician's decision. The time to death ranged from 0 to 480 days (1.3 years) in subjects who died within 2 years of implantation and from 0 to 3116 days (8.5 years) in all subjects who died. The majority of deaths (21 deaths) occurred within the first year after implantation, which was prior to the development of thymic function. The majority of these deaths were due to infections, complications associated with infection or respiratory failure/hypoxia.

Table 10. Deaths in each individual study

	668-1/668-2 N (%)	884 (including 884-1) N (%)	931 N (%)	932 N (%)	950 (including 950-1) N (%)	25966 N (%)	(b) (6) N (%)	51692 N (%)	735 N (%)	Pooled dataset N (%)
Within 2 years follow-up										
Death	8 (30.8%)	2 (16.7%)	1 (20%)	1 (28.6%)	4 (26.7%)	6 (25%)	1 (100%)	0	0	23 (24.7%)
At the time of analysis data cutoff										
Death	10 (38.5%)	3 (33.4%)	1 (20%)	2 (28.6%)	4 (26.7%)	6 (25%)	1 (100%)	0	0	27 (29%)
Total N	26	12	5	7	15	24	1	2	1	93

(Source: FDA statistical reviewer's analysis)

## 8.2 Nonfatal Serious Adverse Events

The applicant reported the following Serious Adverse Events (SAE) within 2 years of implantation and the Treatment-related Serious Adverse Events within 2 years of implantation. During the 2 years after implantation, 443 serious adverse effects (SAEs) were reported in 79 subjects. The most frequently reported SAEs were infections and infestations (213 SAEs), which occurred in 67 subjects.

Table 11. Serious Adverse Events reported in  $\geq 5\%$  FAS subjects within 2 years of implantation in study RVT-802

System Organ Class Preferred Term	EAS N = 85		FAS N = 93	
	n (%)	E	n (%)	E
<b>Number of subjects with SAEs</b>	<b>72 (84.7)</b>	<b>405</b>	<b>79 (84.9)</b>	<b>443</b>
<b>Infections and Infestations</b>	<b>63 (74.1)</b>	<b>200</b>	<b>67 (72.0)</b>	<b>213</b>
Device-related infection	39 (45.9)	93	41 (44.1)	96
Pneumonia	7 (8.2)	7	8 (8.6)	8
Lower respiratory tract infection bacterial	4 (4.7)	5	5 (5.4)	6
Viral upper respiratory tract infection	5 (5.9)	5	5 (5.4)	5
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>36 (42.4)</b>	<b>64</b>	<b>37 (39.8)</b>	<b>65</b>
Respiratory failure	16 (18.8)	19	16 (17.2)	19
Hypoxia	12 (14.1)	15	13 (14.0)	16
Respiratory distress	5 (5.9)	7	5 (5.4)	7
<b>General disorders and administration site conditions</b>	<b>18 (21.2)</b>	<b>21</b>	<b>19 (20.4)</b>	<b>23</b>
Pyrexia	16 (18.8)	18	17 (18.3)	20
<b>Gastrointestinal disorders</b>	<b>17 (20.0)</b>	<b>20</b>	<b>18 (19.4)</b>	<b>21</b>
Diarrhoea	6 (7.1)	7	6 (6.5)	7
<b>Blood and lymphatic system disorders</b>	<b>13 (15.3)</b>	<b>17</b>	<b>17 (18.3)</b>	<b>26</b>
Thrombocytopenia	5 (5.9)	7	6 (6.5)	8
Neutropenia	3 (3.5)	3	5 (5.4)	5
<b>Metabolism and nutrition disorders</b>	<b>13 (15.3)</b>	<b>14</b>	<b>15 (16.1)</b>	<b>16</b>
<b>Nervous system disorders</b>	<b>12 (14.1)</b>	<b>18</b>	<b>12 (12.9)</b>	<b>18</b>
<b>Immune system disorders</b>	<b>9 (10.6)</b>	<b>11</b>	<b>12 (12.9)</b>	<b>15</b>
<b>Renal and urinary disorders</b>	<b>7 (8.2)</b>	<b>9</b>	<b>7 (7.5)</b>	<b>9</b>
Renal failure	5 (5.9)	6	5 (5.4)	6
<b>Cardiac disorders</b>	<b>6 (7.1)</b>	<b>7</b>	<b>7 (7.5)</b>	<b>8</b>
<b>Vascular disorders</b>	<b>6 (7.1)</b>	<b>7</b>	<b>7 (7.5)</b>	<b>8</b>
Hypotension	5 (5.9)	5	6 (6.5)	6
<b>Investigations</b>	<b>5 (5.9)</b>	<b>6</b>	<b>6 (6.5)</b>	<b>7</b>

(Source: RVT-802 Clinical Safety Report Table 4-2, p.92)

During the 2 years after implantation, 58 treatment-related SAEs were reported in 30 subjects within 2-year implantation. The most frequently reported treatment-related SAEs were blood and lymphatic system disorders (22 events), which occurred in 13 subjects.

Table 12. Treatment-related Serious Adverse Events reported in  $\geq 2\%$  FAS subjects within 2 years of implantation in study RVT-802

System Organ Class Preferred Term	EAS N = 85			FAS N = 93		
	n	(%)	E	n	(%)	E
<b>Number of Related SAEs</b>	24	(28.2)	42	30	(32.3)	58
<b>Blood and lymphatic system disorders</b>	10	(11.8)	14	13	(14.0)	22
Thrombocytopenia	4	(4.7)	6	5	(5.4)	7
Neutropenia	3	(3.5)	3	5	(5.4)	5
Autoimmune haemolytic anaemia	1	(1.2)	1	2	(2.2)	3
Coombs positive haemolytic anaemia	1	(1.2)	1	2	(2.2)	2
Haemolysis	1	(1.2)	1	2	(2.2)	2
<b>Immune system disorders</b>	3	(3.5)	3	6	(6.5)	7
Cytokine release syndrome	3	(3.5)	3	3	(3.2)	3
Graft versus host disease	0	0	0	2	(2.2)	2
<b>Respiratory, thoracic and mediastinal disorders</b>	5	(5.9)	5	5	(5.4)	5
Hypoxia	2	(2.4)	2	2	(2.2)	2
Respiratory failure	2	(2.4)	2	2	(2.2)	2
<b>Renal and urinary disorders</b>	4	(4.7)	4	4	(4.3)	4
Renal failure	2	(2.4)	2	2	(2.2)	2
<b>Gastrointestinal disorders</b>	3	(3.5)	3	3	(3.2)	3
Pancreatitis	2	(2.4)	2	2	(2.2)	2
<b>Infections and infestations</b>	3	(3.5)	3	3	(3.2)	3
Cytomegalovirus infection	2	(2.4)	2	2	(2.2)	2
<b>Skin and subcutaneous tissue disorders</b>	1	(1.2)	2	2	(2.2)	3
<b>Endocrine disorders</b>	2	(2.4)	2	2	(2.2)	2
Hypothyroidism	2	(2.4)	2	2	(2.2)	2
<b>Investigations</b>	1	(1.2)	1	2	(2.2)	2
<b>Metabolism and nutrition disorders</b>	1	(1.2)	1	2	(2.2)	2
<b>Nervous system disorders</b>	2	(2.4)	2	2	(2.2)	2

(Source: RVT-802 Clinical Safety Report Table 4-3, p.93)

### 8.3 Adverse Events of Special Interest (AESI)

Adverse events considered to be AESIs included infection-related AEs, cancers, autoimmune diseases, Graft Versus Host Disease (GVHD), rashes, and granulomas. Table 13 summarizes the AESI in study RVT-802.

Table 13. Adverse Events of Special Interest reported in  $\geq 5\%$  FAS subjects within 2 years of implantation in study RVT-802

System Organ Class Preferred Term	EAS N = 85		FAS N = 93	
	n (%)	E	n (%)	E
<b>Number of subjects with an AESI</b>	<b>67 (78.8)</b>	<b>184</b>	<b>75 (80.6)</b>	<b>206</b>
<b>Skin and subcutaneous disorders</b>	<b>44 (51.8)</b>	<b>77</b>	<b>46 (49.5)</b>	<b>80</b>
Rash	30 (35.3)	45	31 (33.3)	46
Urticaria	7 (8.2)	9	8 (8.6)	10
Alopecia	5 (5.9)	5	5 (5.4)	5
<b>Blood and lymphatic system disorders</b>	<b>31 (36.5)</b>	<b>47</b>	<b>36 (38.7)</b>	<b>57</b>
Thrombocytopenia	21 (24.7)	26	22 (23.7)	27
Neutropenia	13 (15.3)	13	16 (17.2)	16
<b>Immune system disorders</b>	<b>26 (30.6)</b>	<b>34</b>	<b>31 (33.3)</b>	<b>40</b>
Cytokine release syndrome	18 (21.2)	20	18 (19.4)	20
Hypersensitivity	11 (12.9)	13	11 (11.8)	13
<b>Endocrine disorders</b>	<b>16 (18.8)</b>	<b>16</b>	<b>17 (18.3)</b>	<b>17</b>
Hypothyroidism	16 (18.8)	16	17 (18.3)	17

(Source: RVT-802 Clinical Safety Report Table 4-5, p.97)

## 10. Conclusions

### 10.1 Statistical Issues and Collective Evidence

RETHYMIC is a tissue therapy. It is allogeneic cultured postnatal thymus tissue manufactured from tissue obtained from unrelated donors under the age of 9 months. This Biologics License Application (BLA) seeks licensure of RETHYMIC for the immune reconstitution of pediatric patients with congenital athymia.

The primary source of evidence to support this application is data pooled from 7 core, single-site, open-label, non-randomized clinical studies in subjects with congenital athymia (Studies 668-1, 668-2, 884 [including 884-1], 931, 932, 950 [including 950-1] and 25966). Two additional IND 9836 protocols (Studies (b) (6) and 51692) and one non-IND protocol (Study 735) provided additional supporting data, though subjects treated in these studies were not included in the efficacy analysis set (EAS). Ninety-three (93) subjects were treated by a single surgical implantation procedure at the dose range of (b) (4) to 22,000 mm<sup>2</sup> of thymus tissue per recipient body surface area in m<sup>2</sup> and among those, 85 subjects were included in the EAS from the original BLA submission. One hundred (100) subjects received the treatment of RVT-802 and among those, 90 subjects were included in the EAS after 120-day safety update. Due to the limited follow-up period for the new treated patients, this review memo is mainly based on the original BLA application with 93 treated subjects and 85 subjects included in the efficacy analysis.

The primary efficacy endpoint, the survival rate at Year 1 was 76.5% (95% CI: 65.9%, 84.1%) in the EAS obtained from the Kaplan-Meier estimate. The supportive efficacy endpoint, the survival rate estimate at Year 2 was 75.2% (95% CI: 64.6%, 83.1%). Both lower limits of 95% CIs at Year 1 and Year 2 were greater than the pre-specified survival rate of 50% under the null hypothesis. The median survival time for all subjects was yet to be reached as of the data cut-off date. No new death was observed for those subjects who survived to Year 9 post implantation and the first treated subject was censored at Year 24. Thus, the survival rate was 70.2% at Year 24 (95% CI: 58.7%, 79.1%) estimated based on the Kaplan-Meier method. In addition, all the naïve CD3, CD4, CD8 cell counts, total CD3, CD4, CD8 cell counts showed generally durable increases in these T cell indicators of thymic function as the study follow-up period progressed. The proliferative T cell response to PHA also increased through Year 2 post-implantation.

Twenty-seven deaths occurred as of the data cutoff (July 16, 2018) after the administration of RVT-802 treatment. Of these, 23 subjects died within 2 years of implantation. This included 22 subjects who died during study follow-up period and 1 subject who died within 2 years of treatment but after having prematurely discontinued the study due to physician's decision. The time to death ranged from 0 to 480 days (1.3 years) in subjects who died within 2 years of implantation and from 0 to 3116 days (8.5 years) in all subjects who died. During the 2 years after implantation, 443 serious adverse effects (SAEs) were reported in 79 subjects. The most frequently reported SAEs were

infections and infestations (213 SAEs), which occurred in 67 subjects. In addition, 58 treatment-related SAEs were reported in 30 subjects within 2-year implantation. The most frequently reported treatment-related SAEs were blood and lymphatic system disorders (22 events), which occurred in 13 subjects.

## **10.2 Conclusions and Recommendations**

The efficacy results of Study RVT-802 met the study objective of demonstrating that the survival rate at Year 1 is greater than the pre-specified rate of 50%. The statistical analysis results provide evidence to support the safety and effectiveness of RETHYMIC in the proposed indication in this BLA.

## **References**

FOXN1 deficient nude severe combined immunodeficiency, Ioanna A. Rota and Fatima Dhalla. Orphanet J Rare Dis. 2017; 12: 6.