

BIOLOGICS LICENSE APPLICATION 125685

Application Type	Biologic License Application
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Division / Office	DCEPT /OTAT
Priority Review	Yes
Reviewer Name(s)	Winson Tang, MD FACP General Medicine I
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Supervisory Concurrence	Elizabeth Hart, MD Acting Team Leader, General Medicine I  Ilan Irony, MD Deputy Director, DCEPT
Applicant	Enzyvant Therapeutics GmbH/Roivant Science Inc
Established Name	RVT-802 (allogeneic cultured post-natal thymus tissue)
(Proposed) Trade Name	RETHYMIC
Pharmacologic Class	Somatic cell therapy
Formulation(s), including Adjuvants, etc	A single patient dose consists of up to (b) (4) slices of RVT-802 in sterile, polypropylene containers with media. Each polypropylene container contains (b) (4) _____, placed on top of a piece of filter paper.
Dosage Form(s) and Route(s) of Administration	Single surgical implantation of (b) (4) _____ mm <sup>2</sup> of thymus tissue/ m <sup>2</sup> recipient body surface area (BSA). The thymus tissue area is determined by image analysis with BSA determined according to the DuBois and DuBois formula using the patient's height (cm) and weight (kg). BSA=0.007184 × [height in cm] 0.725 × [weight in kg] 0.425.
Dosing Regimen	Surgical implantation into the quadriceps muscle
Dosing Schedule	Single administration
Indication(s) and Intended Population(s)	Immune reconstitution of patients with congenital athymia
Orphan Designated (Yes/No)	Yes



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**GLOSSARY**

AE	adverse event
AESI	adverse event of special interest
ALC	absolute lymphocyte count
BLA	biologics license application
BMTCTN	Blood and Marrow Transplant Clinical Trials Network
BSA	body surface area
BUN	blood urea nitrogen
BW	body weight
CBC	complete blood count
CBT	cord blood transplant
cDGA	Complete DiGeorge Anomaly
ConA	concanavalin A
CHARGE	Coloboma, heart defect, choanal atresia, growth and development retardation, genital hypoplasia, ear anomalies/deafness
CI	confidence interval
CMV	cytomegalovirus
cpm	counts per minute
CSA	cyclosporine A
CSE	clinical summary of efficacy
CSR	clinical study report
CSS	clinical summary of safety
CTCAE	Common Terminology Criteria for Adverse Events
DGA	DiGeorge Anomaly
DNA	deoxyribonucleic acid
DUMC	Duke University Medical Center
EAS	efficacy analysis set
EAScDGA	efficacy analysis set - complete DiGeorge anomaly
EBV	Epstein-Barr virus
eCRF	electronic case report form
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSPC	hematopoietic stem and progenitor cell
HSCT	hematopoietic stem cell transplant
ICH	International Council for Harmonization
IDM	infant of diabetic mother
Ig	Immunoglobulin
IGIV	Immunoglobulin intravenous
IND	investigational new drug
IS	immunosuppression
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety

IU	international units
IV	intravenous
Kg	kilogram
KM	Kaplan Meier
L	liter
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate
mL	milliliter
NK cell	natural killer cell
nm	nanometer
PCR	polymerase chain reaction
PH	proportional hazards
PHA	phytohemagglutinin A
PJP	pneumocystis jirovecii pneumonia
PT	preferred term
Q	quartile
RATGAM	Rabbit anti-thymocyte globulin
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class (MedDRA)
SoC	standard of care
TEAE	treatment emergent adverse event
TCR	T cell receptor
TREC	T cell receptor rearrangement excision circles
U	unit
uEAS	updated efficacy analysis set (120-day update)
uEAScDGA	updated efficacy analysis set - complete DiGeorge anomaly (120-day update)
uFAS	updated full analysis set (120-day update)
US	United States
vs	versus

## 1. EXECUTIVE SUMMARY

Enzyvant Therapeutics submitted an original Biologic License Application (BLA) for RVT-802 (Rethymic), an allogeneic cultured post-natal thymus tissue, for “immune reconstitution of patients with congenital athymia.” The proposed mechanism of action is migration of the recipient' bone marrow stem cells into the thymic allograft where they are “educated” to produce immunocompetent T cells that are tolerant of both donor and recipient tissues while maintaining the ability to respond to foreign antigens. RV-802 is manufactured from tissue obtained from unrelated donors under the age of 9 months undergoing cardiac surgery. Slices of RVT-802 are transplanted in a single surgical procedure into the quadriceps of patients with congenital athymia. The recommended dose of RVT-802 is (b) (4) to 22,000 mm<sup>2</sup> of total processed thymus tissue surface area/m<sup>2</sup> recipient body surface area.

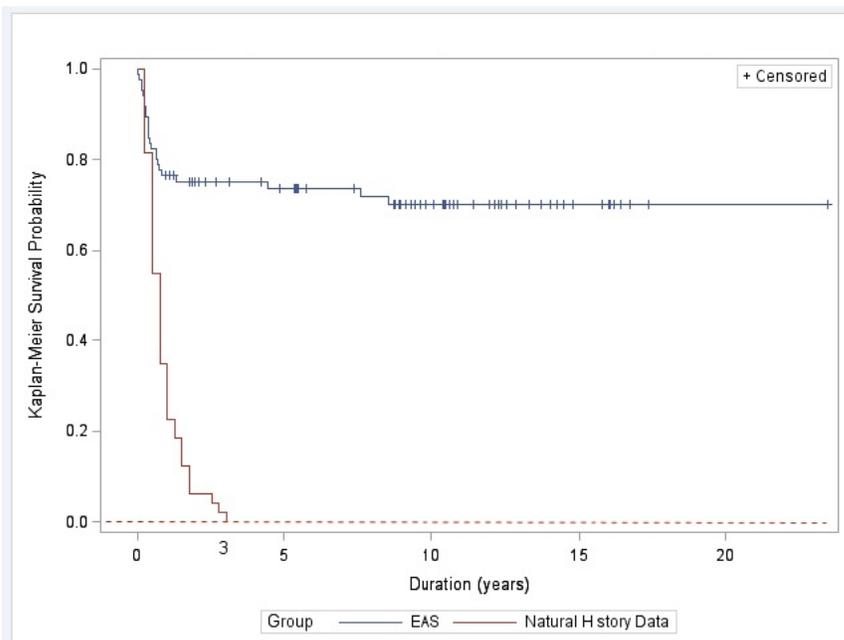
Congenital athymia results from inherited conditions in which the thymus does not develop, resulting in a low number of T cells with impaired function and recurrent serious infections, and is usually fatal by two years of age. Congenital athymia most commonly occurs as part of Complete DiGeorge Anomaly (cDGA), either typical or atypical, but can also occur in FOYN1 deficiency. Complete DGA is characterized by T-cell immuno-deficiency, congenital heart disease and hypocalcemia from hypoparathyroidism. FOYN1 deficiency is due to a homozygous autosomal recessive loss-of-function mutation in an essential transcription factor for thymic development. The applicant estimates that there are approximately 20 children born with congenital athymia annually in the United States. There are no definitive therapies for congenital athymia; infants are treated with IGIV and antibiotic prophylaxis.

To support the safety and effectiveness of RVT-802, the applicant conducted 10 open-label, prospective studies, in which 93 subjects were treated at a single-center. Seven of these studies treated multiple subjects while three studies were single-patient studies. The efficacy analysis set (EAS), was limited to subjects with congenital athymia who had not previously received hematopoietic stem cell transplant (HSCT) or fetal thymus transplants and had at least 1 year of follow-up data, as only those subjects who had congenital athymia and had not received other experimental therapies and were followed for sufficient duration could provide informative efficacy data. Specifically, the EAS population includes 85 subjects with congenital athymia, 83 with cDGA (including 43 with typical cDGA and 39 with atypical cDGA and 1 not documented, with documented mutations including hemizygous deletion of chromosome 22q11.2, CHD7 mutation and CHARGE) and two subjects with FOYN1. The demographics of the EAS population is consistent with the demographics of congenital athymia within the United States. The EAS included 52 (61%) males, 59 (69%) whites and 18 (21%) blacks/African-Americans. All subjects were under 2 years of age when RVT-802 was administered, the median age was 239 days and ranged from 33-664 days of life.

Primary evidence for efficacy is based on survival at 2 years amongst EAS subjects compared to the reported natural history of untreated subjects from the medical literature. Congenital athymia due to cDGA is generally fatal because of infections by 2 years of age, and approximately two-thirds of these infants die by 1 year of age. The clinical course of patients with FOYN1 mutations has not been well described as there have only been 10 cases of FOYN1 ever reported. Since athymia results in the same of symptoms irrespective of the etiology, the clinical review team believed that the natural history from cDGA could be

applied to all types of congenital athymia including FOYN1 deficiency. The Kaplan-Meier estimated survival rates were 76% (95% confidence interval (CI) [0.658, 0.838]) at 1 year and 75% (95% CI [0.646, 0.828]) at 2 years. The survival rate was essentially unchanged thereafter; 75% to 70% from Year 2 (n=56) to Year 9 (n=41) with no deaths after Year 9. The longest surviving subject was alive 25 years after receiving RVT-802. There were 42 subjects who had survived more than 9 years after receiving RVT-802, which according to the literature does not occur in the absence of therapy. Figure 1, demonstrates the survival of the EAS population compared to a case series of 49 subjects with cDGA receiving only standard of care.

**Figure 1. Survival in RVT-802 Treated Subjects in the EAS Population and Controls with cDGA receiving Supportive Care**



Source: Figure made by FDA statistical reviewer.

Natural history data is based on unpublished data from Dr. Markert included in the BLA (section 2.7.3). We assumed no censoring of control subjects and conservatively assumed that all subjects died at the end of the 3-month window in which their deaths were reported.

In the EAS population, there were 27 deaths following RVT-802 implantation including 23 deaths in the first two years after treatment. Most deaths (21 deaths, 77.8%) occurred within the first-year of implantation and most of these deaths (n=12) were due to infections or complications of the infection, prior to engraftment. The other causes of death were generally consistent with the underlying disease and included respiratory failure/hypoxia (n=5), hemorrhagic events (n=3) and cardiorespiratory arrest (n=1). Six subjects died more than one year after RVT-802 implantation; none of the deaths were considered related to RVT-802 treatment. Overall, only 3 deaths were considered possibly related to study treatment. Two of these deaths were attributed to the immunosuppressive agents, and one

death from CMV infection may have been due to RVT-802, although the origin of the infection remains unknown.

The survival benefit of RVT-802 transplantation was supported by several clinically meaningful secondary endpoints that were consistent with immune reconstitution including a decreased frequency of infections, evidence of thymopoiesis on biopsy 3 months after RVT-802 implantation, increasing numbers of naïve CD3, CD4 and CD8 T-cells, T-cell proliferation in response to antigen/mitogen, and emergence of a diverse TCRVβ repertoire.

Specifically, over time, the number of infections in subjects treated with RVT-802 decreased significantly, as shown in Table 1. The median difference in the number of reported infections was 2 infections between 0-6 months and 6-12 months after RVT-802 implantation, and the median difference was 3 infections between 0-12 months and 12-24 months after RVT-802 implantation (Wilcoxon signed-rank test  $p < 0.001$  for both).

**Table 1. Infections Over Time in EAS Subjects Treated with RVT-802**

	<6 months	6-12 months	12-24 months
# infection AEs	312	88	83
# Subjects with infection	78	37	31
% Subjects with infection (95% CI)	91.8% (83.8%, 96.6%)	43.5% (32.8%, 54.7%)	36.5% (26.3%, 47.6%)

Source: Table made by FDA Statistician.

Naïve CD4 and CD8 T-cells reconstituted over the first year, with a durable increase through year 2. At baseline, median naïve CD4 cell counts (cells/mm<sup>3</sup>) were 1.0 (n = 60) at baseline, 262 at Year 1 (n = 41), and 246 at Year 2 (n = 26). Median naïve CD8 cell counts (cells/mm<sup>3</sup>) were <1 (n = 54) at baseline, 59 at Year 1 (n = 38), and 81 at Year 2 (n = 26). Similar results were seen for naïve CD3 cells. This was accompanied by functional improvements based on T-cell proliferative response to the mitogen phytohemagglutinin (PHA) in a subset of subjects in whom these data were collected; at baseline the values were below normal (median 3,608 cpm, n=89) and increased to within normal limits (>75,000 cpm) (median:92,134 cpm, n=34) at 6 months after RVT-802 and sustained these values through year 2 (median:216,936 cpm, n=21).

All subjects had at least one adverse event (AE), and there were a total of 2003 AEs reported in subjects exposed to RVT-802. Most AEs (n=1684, 84%) occurred within the first 2 years after RVT-802 and they resolved. The most common AEs were pyrexia (65%), device-related (catheter) infections (53%), rash (36%), diarrhea (30%), hypertension (30%), increased alanine aminotransferase (29%), hypoxia (27%), thrombocytopenia (27%), anemia (27%), and increased aspartate aminotransferase (26%). Most of these AEs were related to the underlying disease and concomitant medications and were unrelated to RVT-802 or the implantation procedure. There were only 77 AEs occurring in 39 subjects that according to the Investigator and concurred by the FDA clinical reviewer were assessed as possibly related to RVT-802 or the implantation procedure. The AEs related to RVT-802 could be classified into 3 main categories: autoimmune diseases (cytopenia, hypothyroidism, hepatitis), complications associated with the implantation procedure, and T cell related events. The most common adverse reactions related to RVT-802 that occurred in more than 1 subject are shown in Table 2.

**Table 2. Most Common Adverse Reactions following RVT-802**

System Organ Class Preferred Term	RETHYMIC (N=93)
	n (%)
<b>Number of Patients with Related Adverse Events</b>	<b>39 (41.9)</b>
<b>Blood and lymphatic system disorders</b>	<b>19 (20.4)</b>
Thrombocytopenia	10 (10.8)
Neutropenia	7 (7.5)
Coombs positive haemolytic anaemia	2 (2.2)
Autoimmune haemolytic anaemia	2 (2.2)
Haemolysis	2 (2.2)
<b>Skin and subcutaneous tissue disorders</b>	<b>8 (8.6)</b>
Alopecia	4 (4.3)
Rash	2 (2.2)
<b>General disorders and administration site conditions</b>	<b>5 (5.4)</b>
Pyrexia	5 (5.4)
<b>Injury, poisoning and procedural complications</b>	<b>5 (5.4)</b>
Wound dehiscence (site of RETHYMIC implantation)	4 (4.3)
<b>Renal and urinary disorders</b>	<b>5 (5.4)</b>
Proteinuria	5 (5.4)
<b>Infections and infestations</b>	<b>4 (4.3)</b>
<b>Investigations</b>	<b>4 (4.3)</b>
Blood bicarbonate decreased	2 (2.2)
<b>Gastrointestinal disorders</b>	<b>3 (3.2)</b>
Diarrhoea	2 (2.2)
<b>Hepatobiliary disorders</b>	<b>2 (2.2)</b>
Autoimmune hepatitis	2 (2.2)
<b>Immune system disorders</b>	<b>2 (2.2)</b>

Source: Table by Statistical Reviewer and consistent with Applicant's table 3-10. This is based on the safety data at the time of the BLA submission.

The 120-day updated clinical efficacy and safety data included 7 new subjects who were treated after the original clinical submission in December 2018. There were no new safety concerns identified.

The BLA contains substantial evidence of effectiveness for RVT-802 for the reconstitution of the immune system in subjects with congenital athymia with a favorable benefit-risk profile. The primary clinical challenge in reviewing the data submitted in the BLA is that all studies were open-label, single-arm studies conducted at a single-center without a concurrent control group or subject-level data from a natural history study. However, the data provided were able to transcend these limitations. Specifically, the applicant provided data from a large number of subjects, especially given the rarity of the disease, had a long duration of follow-up (up to 24 years), the natural history is uniform and well characterized in the medical literature, and most importantly there was a large treatment effect as evidenced by survival and decreased infections with supportive biochemical immunologic data. Experience

regarding the use of RVT-802 could not be obtained in the geriatric, pregnant and lactating populations since this is a pediatric disease. Children treated with RVT-802 experienced many AEs and serious adverse events (SAEs), but these generally resolved, and many were consistent with the subject’s underlying disease and concomitant use of immunosuppression. The most common adverse reactions were autoimmune diseases, implantation procedure complication, and T cell related. In summary, the risk associated with the use of RVT-802 while not trivial can be viewed as favorable in the context of the ability of RVT-802 to prolong survival in a universally fatal disease.

**Recommended Action:** From a clinical perspective, this product appears to have a favorable benefit-risk profile which would support approval of RVT-802 for “immune reconstitution of patients with congenital athymia.” However, there are unresolved CMC issues that lead to a Complete Response (CR) action on this BLA.

**1.1 Demographics of Study Population**

The demographics of the subjects in the EAS and FAS who were enrolled in the 10 open-label, single-arm studies that treated at least 1 subject with congenital athymia with RVT-802 are summarized in Table 3.

**Table 3: Subject Demographics in Efficacy Studies**  
(Applicant’s Table)

	EAS N = 85	FAS N = 93
Age on day of implantation (days)		
N	85	93
Mean (SD)	249.9 (152.05)	449.1 (963.48)
Median	239.0	256.0
Minimum, Maximum	33, 664	33, 6163
Sex, n (%)		
Male	52 (61.2)	56 (60.2)
Female	33 (38.8)	37 (39.8)
Race, n (%)		
White	59 (69.4)	67 (72.0)
Black or African American	18 (21.2)	18 (19.4)
Asian	3 (3.5)	3 (3.2)
American Indian or Alaska Native	2 (2.4)	2 (2.2)
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.1)
More than one race	2 (2.4)	2 (2.2)
Unknown or not reported	0 (0.0)	0 (0.0)

**2. CLINICAL AND REGULATORY BACKGROUND**

The RVT-802 development program for the treatment of T cell immunodeficiency resulting from congenital athymia was conducted as an academic research program by Dr. M. Louise Markert at the Duke University Medical Center over the past 25 years. The program was licensed by Enzyvant Therapeutics GmbH from Duke University on 21 December 2016.

RVT-802 is an allogeneic, cultured, postnatal thymus tissue manufactured from the thymus obtained from allogeneic donors under the age of 9 months. The thymus is cut into thin (~ 0.5 to 1 mm) slices, which are placed on filters and cultured at the air-fluid interface in sterile tissue culture dishes in the processing laboratory. Thymic slices are cultured for 12 to 21 days, with daily replacement of culture media. After the spent medium is removed, fresh medium is dripped directly onto the thymic slices which washes the donor thymocytes out of the thymic tissue. Donor thymocytes die in situ while the functional architecture of the thymic stroma (thymic epithelial cells and fibroblasts) is preserved.

RVT-802 is transported to the operating room and implanted in the recipient's quadriceps muscles by an open surgical procedure. There was no set dose range during the early stages of the clinical development program. A minimum dose (0.20 g/kg) was established in 2002 and a dose range of 4 to 18 g of thymus tissue/recipient body surface area (BSA) was used from 2007 until 2015. In 2015, an Investigational New Drug (IND) Amendment SN 0209 established the current recommended dose range of 2,000 to 20,000 mm<sup>2</sup> of thymus tissue/m<sup>2</sup> BSA. While study protocols allowed for a dose as low as 2,000 mm<sup>2</sup>/m<sup>2</sup> BSA, the lowest dose that was actually administered in RVT-802 clinical studies was 4,522 mm<sup>2</sup>/m<sup>2</sup>. Furthermore, 4 subjects were successfully treated, with no apparent dose related adverse events (AEs), with a dose between 20,000 and 22,000 mm<sup>2</sup>/m<sup>2</sup> BSA. As such, the current clinical data support a dosing range of (b) (4) to 22,000 mm<sup>2</sup>/m<sup>2</sup> BSA.

There have been 10 clinical studies conducted with RVT-802. The first 7 studies in Table 3 are single-site, open-label, non-randomized clinical studies in subjects with congenital athymia that serves as the core of this BLA. The last 3 studies listed in Table 3 (IND 9836 protocols (b) (6) and 51692) and non-IND protocol 735) provide additional supporting data. The first RVT-802 implantation was performed in 1993 under Study 668-1. All of the studies have been completed with the exception of Studies 25966 and 51692 which are still open to enrollment.

**Table 4: RVT-802 Clinical Studies**  
(Applicant's Table)

Type of Study	Study Identifier	Study Title
Phase 1	668-1	Thymic transplantation in complete DiGeorge syndrome
Phase 2	668-2	Phase II study of thymus transplantation in complete DiGeorge syndrome
Phase 1	884 [884.1]	Thymus transplantation with immunosuppression
Phase 1	931	Parathyroid and thymus transplants in DiGeorge syndrome
Phase 2	932	Dose study of thymus transplantation in DiGeorge anomaly
Phase 1/2	950 [950.1]	Phase I/II trial of thymus transplantation with immunosuppression
Phase 1/2	25966	Safety and efficacy of thymus transplantation in complete DiGeorge anomaly
Expanded access	(b) (6)	Single-subject treatment plan: Thymus transplantation for EBV lymphoma
Expanded access	51692	Expanded access protocol. Thymus transplantation for immunodeficiency, hematologic malignancies, and autoimmune disease related to poor thymic function
Single subject protocol	735	Thymic transplantation in partial DiGeorge syndrome

On the basis of these clinical studies, Enzyvant was granted Breakthrough Therapy and Regenerative Medicine Advanced Therapy (RMAT) designation on April 14, 2017. A

number of meetings have been held with the Applicant subsequently and are summarized in Table 5.

**Table 5: Summary of Enzyvant-FDA Meetings  
(Post-BT and RMAT Designation)  
(Applicant’s Table)**

FDA Meeting	Meeting Date	Key Discussion Topics
Type B Meeting (End-of-Phase 3)	01 May 2017	Nonclinical, Clinical, and CMC programs
Type C Meeting	02 August 2017	CMC and manufacturing facilities
Type B Meeting	25 September 2017	CMC
Type B Pre-BLA Meeting (Agency Preliminary Comments only)	06 November 2017	Content and organization of the BLA
Type B Meeting	19 January 2018	Aseptic process validation
Type B Meeting	19 January 2018	Container Closure Integrity Testing
Type B Meeting	07 August 2018	Quantitative Histology Testing and Process Validation

**2.1 Congenital Athymia**

**2.1.1 DiGeorge Anomaly**

DiGeorge anomaly (DGA) is a congenital disease that is characterized by defects in organs derived from the third and fourth pharyngeal pouches and the intervening third pharyngeal arch. The signs and symptoms of DGA are highly variable and result from the defective development of the embryonic pharyngeal pouch leading to dysmorphogenesis of the thymus, thyroid, parathyroids, maxilla, mandible, aortic arch, cardiac outflow tract, and external/middle ear. The most common cardiac defects include interrupted aortic arches, truncus arteriosus, Tetralogy of Fallot, atrial or ventricular septal defects, and vascular rings. Hypocalcemia results from hypoplastic parathyroids and is potentially life-threatening. The thymus may be hypoplastic or completely absent resulting in a range of immune deficiencies. It is estimated that 1 in 4,000 to 6,000 live births may suffer from DGA although this disease is probably underdiagnosed because the phenotype may be very mild in some patients.

Historically, DGA was considered to be almost exclusively associated with 22q11.2 deletion syndrome. The latter is relatively common and may be the most prevalent microdeletion syndrome in the general population. Approximately 90% of those with DGA have a heterozygous chromosomal deletion at 22q11.2. The high incidence of chromosome 22q11.2 microdeletions may be attributed to homologous enrichment of low copy repeats in two areas of this region, which make it prone to homologous recombination deletion errors. The most common genetic deletion associated with DGA is a 1.5 to 3.0 Mb deletion in the 22q11.2 region (DGAI locus). This region of genomic DNA encodes ~30 genes (24 genes within the 1.5 Mb region). Another 2 to 5% of patients have heterozygous deletions in chromosome 10p13-14 (the DGAI locus). Phenotypic comparison of patients with DGAI and DGAI locus deletions demonstrate many similarities, although there is an increased incidence of

sensorineural hearing loss in patients with the DGAI locus deletion. There have also been isolated case reports of patients with phenotypic features of DGA and a microdeletion in chromosome 17 or an isochromosome 18q. Patients with the DGA phenotype and the chromosome 22q11.2 deletion are more precisely referred to as having "DGA with chromosome 22q11.2 deletion" and those with other mutations are referred to as having "DGA without chromosome 22q11.2 deletion".

In addition, there are other patients who have no genetic or syndromic abnormalities. DGA has also been found to be associated with the CHARGE syndrome (coloboma, heart defects, choanal atresia, retardation of growth or development, genital hypoplasia, and ear anomalies/deafness [most with mutations in *CHD7*]), variants in T-box transcription factor (*TBX*), and 10p deletion.

A spectrum of thymic abnormalities exists in DGA. The majority of patients have sufficient thymic tissue for the development of functional T cells (partial DGA). These patients have variable and non-life-threatening immunologic defects. T cell numbers and function may range from normal to immunodeficient. Thymic-derived CD25<sup>+</sup> T<sub>reg</sub> are diminished in numbers and may account for the increased incidence of autoimmune and atopic disease. B cells are usually normal or increased in number and mildly abnormal in function, consistent with defective T cell help. Although total B cell numbers are normal, the proportion of memory B cells is lower in patients with 22q11.2 deletions, especially in older patients. There is an increased prevalence of immunoglobulin A (IgA) deficiency and functional antibody defects (ie, polysaccharide antibody deficiency). Most patients with partial DGA do not suffer from opportunistic or life-threatening infections although many suffer recurrent sinopulmonary infections. By comparison, thymic tissue is completely absent in ~1-2% of patients with complete DGA. Both T cell numbers and function are highly abnormal with peripheral blood CD3 T cells that are >3 standard deviations below the normal age adjusted range (T cell count <50/mm<sup>3</sup>). Response to mitogens is absent or severely diminished. This form of DGA is fatal unless recognized promptly after birth and treated with thymic or bone marrow transplantation.

There are two phenotypes of complete DGA, typical and atypical. The latter is characterized by the presence of rash and lymphadenopathy with a peripheral blood T cell count <50/mm<sup>3</sup>. Some patients will switch to an atypical phenotype sometime after birth characterized by lymphadenopathy, rash due to infiltration of the skin by T cells, circulating oligoclonal T cells and peripheral blood T cell count <50/mm<sup>3</sup>. These T cells may proliferate in response to mitogens but are not protective against opportunistic infections. Immunosuppressive therapy with a calcineurin inhibitor is usually started when subjects transform to the atypical phenotype.

The pathogenesis of the thymic abnormalities in DGA patients remains poorly understood. One theory is that the T cell defects are secondary to an insufficient amount of thymic tissue but is otherwise functioning normally. A second and the more likely theory propose that the T cell defects in DGA are due to an abnormal anatomic location of the thymus.

### **2.1.2 FOXN1 Deficiency**

T cell immunodeficiency due to athymia can also arise from FOXN1 deficiency (also known as nude severe combined immunodeficiency, winged helix deficiency, and alymphoid cystic thymic dysgenesis). FOXN1 deficiency is an exceptionally rare inherited disease with an

estimated worldwide incidence <1 in 1,000,000 births. There have been only 10 cases reported in the literature as of November 2018. It is caused by homozygous autosomal recessive loss-of-function mutations in the *FOXP1* gene which encodes a transcription factor essential for development of the thymus. Clinical manifestations include athymia, lack of hair, and dysplastic nails. The lack of T cell development in these patients, as in patients with cDGA, render them susceptible to infection and these children die from infection in the first few years of life.

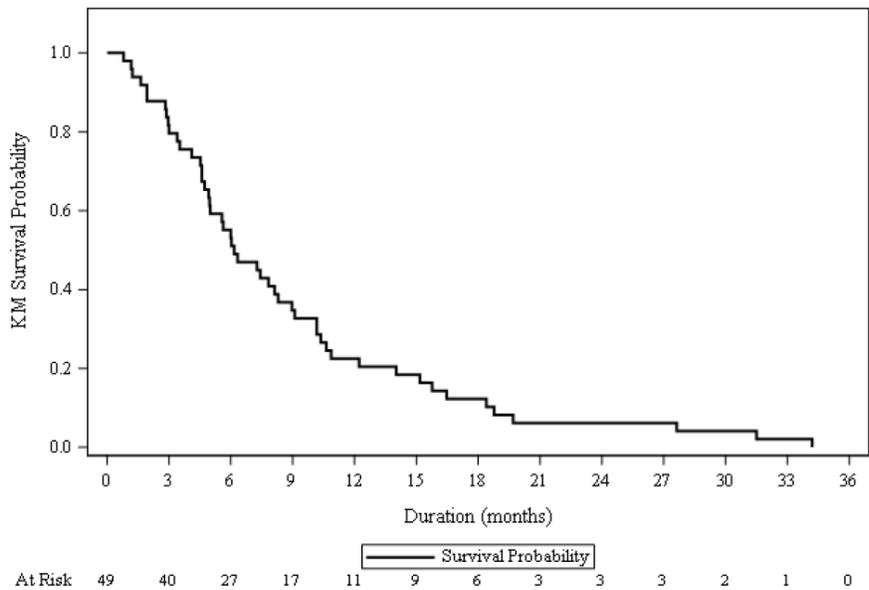
**2.2 Currently Available Treatments/Interventions**

**2.2.1 DiGeorge Anomaly**

The acute management of DGA includes aggressive treatment of hypocalcemia to improve cardiac function. Emergent surgery may be necessary for conotruncal cardiac defects. With regards to immune function, individuals with partial DGA may be at an increased risk of infection, autoimmune disease, and EBV associated lymphoproliferative disorders. Sino-pulmonary infections are common and should be treated aggressively with antibiotics. However, prophylactic therapy is usually not required. A minority of patients (~3%) may require intravenous immunoglobulin (IVIG) for hypogammaglobulinemia. In contrast, infants with complete DGA must be placed in protective isolation, maintained on IVIG and antibiotic prophylaxis for pneumocystis until immune reconstitution is achieved.

T cell immunodeficiency due to congenital athymia is fatal, with almost all infants dying within the first few years of life, most frequently from infections. 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, unpublished data from 49 cDGA patients receiving only supportive care demonstrated a 2-year survival rate of 6%, with all patients dying by 2 years of age (Figure 2).

**Figure 2: Survival of DGA Patients Receiving Supportive Care**  
(Applicant's Figure)



The only potential curative therapy for complete DGA is a hematopoietic stem cell transplant (HSCT) from bone marrow or cord blood. This requires the transfer of mature T cells from

the donor to the recipient as positive selection for CD34 cells (which removes the mature T cell population) is of limited benefit because the recipient does not have a thymus for T cell maturation from stem cells. In contrast, HSCT therapy without CD34 selection (a T cell replete transplantation) may provide benefit in patients with congenital athymia, particularly in limited instances where the patient has a significant viral infection and access to a sibling's HLA matched cells. However, the quality of long-term immune reconstitution achieved with HSCT is poor as the T cell receptor (TCR) repertoire that are transplanted is limited. Over time, with the death of CD4 T cells (because CD4 numbers depend on thymus production) and expansion of CD8 T cells due to viral infections, the T cell repertoire diminishes and the CD4 to CD8 ratio becomes markedly inverted. Consequently, immune reconstitution with HSCT is characterized by circulating T cells that exhibit a memory phenotype, a restricted repertoire, no evidence of naïve T cell development and a lack of T cell receptor rearrangement excision circles (TRECs). The latter re small circles of DNA created in T cells during their passage through the thymus as they rearrange their TCR genes. Overall, there is a low survival rate (~32%) with HSCT among the 31 cases cited in Table 5. Accordingly, T cell immunodeficiency associated with congenital athymia is a condition with a high unmet medical need and no effective therapeutic options.

**Table 6: HSCT for cDGA**  
(Applicant's Table)

Treatment <sup>a</sup>	Source	Number Treated	Number Survived	% Survived	GVHD N (%) > Stage 2/Grade 2
<b>Cord blood<sup>b</sup></b>	<b>Unrelated</b>	<b>4</b>	<b>1</b>	<b>25%</b>	<b>1 (25%)</b>
<b>Bone Marrow</b>	<b>All BM</b>	<b>15</b>	<b>4</b>	<b>27%</b>	<b>5 (33%)</b>
	Sibling	5	3	--	--
	Unrelated	9	1	--	5
	Parental	1	0	--	--
<b>PBMC</b>	<b>All</b>	<b>10</b>	<b>3</b>	<b>30%</b>	<b>4 (40%)</b>
	Sibling	7	3	--	1
	Unrelated	2	0	--	2
	Parental	1	0	--	1
<b>BM+PBMC</b>	<b>All Sibling</b>	<b>2</b>	<b>2</b>	<b>100%</b>	<b>2</b>
<b>Total</b>		<b>31</b>	<b>10</b>	<b>32%</b>	<b>12 (39%)</b>

Abbreviations: BM = bone marrow; cDGA = complete DiGeorge anomaly; GVHD = graft-versus-host disease; PBMC = peripheral blood mononuclear cells

A thymic tissue transplant is the only therapy that can reconstitute a fully functional T cell population. Allogeneic postnatal thymic tissue is cultured *ex vivo* for 2-3 weeks and then implanted in the quadriceps. The donor thymic tissue is obtained from infants under the age of 9 months since the thymus becomes more fibrotic with age. HLA and ABO matching is not required. Recipient bone marrow stem cells migrate to the allograft and develop into naïve T cells within 2 months of transplantation. Naïve T cells can be detected in the peripheral blood within 3 to 5 months. Immunosuppression is not required for patients with typical cDGA since they do not have T cells. However, those with atypical cDGA receive rabbit anti-thymocyte globulin on days -5, -4, and -3 prior to the transplant since the oligoclonal T cell can destroy the allograft. Calcineurin inhibitors are continued until naïve T cells constitute >10% of total T cells and then weaned over the ensuing 8-10 weeks. The most common adverse reactions following thymic transplantation are infections and autoimmune disease. The survival rate following transplant is ~72% and does not differ between typical and atypical cDGA with a median survival of 4.7 years (range 6 mos to 16

years). By comparison, the life expectancy of infants who do not undergo transplantation is less than two years.

**2.2.2 FOXN1 Deficiency**

There have been only 10 reported cases of athymia associated with FOXN1 deficiency in the literature. Eight patients died in early childhood while the only 2 surviving patients both received RVT-802. These two subjects remain alive at the time of this BLA, more than 10 years post-transplant.

**2.3 Previous Human Experience (Including Foreign Experience)**

There is no prior experience with this Investigational Product outside of the Clinical Studies that were conducted in support of this BLA. All of the studies were conducted at Duke University Medical Center in the United States.

**2.4 Summary of Pre-Submission Regulatory Activities**

The Applicant has conducted seven studies of RVT-802, an allogeneic, cultured, post-natal thymus tissue intended for transplantation. Of these studies (Table 6), one protocol was IND-enabling (668-1) and the remaining six studies were conducted under IND 009836. IND 9836 that was initiated on May 23, 2001. All seven studies were single site, non-randomized, uncontrolled, open-label interventional trials.

**Table 7: Summary of Clinical Studies**  
(Applicant’s Table)

Protocol	Primary Objective	Patients	Key efficacy outcome measures	Key safety outcome measures
668-1	To assess combination of thymus tissue plus either BM or cord blood derived stem cell transplant*	Typical cDGA (3 atypical cDGA received immunosuppression under treatment plans)	Descriptive study without specified endpoints; Assessments included evidence of cytokeratin and thymopoiesis from allograft biopsy and T cell count and phenotype	Deaths; AEs
668-2	To assess safety and efficacy as determined by survival; to assess thymopoiesis in the thymus graft and reconstitution of T cell function by flow cytometry and PCR	Typical cDGA; no immunosuppression; however, 2 atypical cDGA received immunosuppression under treatment plans	Survival; T cell function at 1 year as measured by T cell proliferative response to tetanus toxin; MLR to determine recipient tolerance of donor thymus; thymopoiesis	Deaths; AEs; infections; autoimmune disease
884	To assess safety, tolerability, and efficacy of thymus transplant with immunosuppression	Typical cDGA with but slightly elevated T cell function (PHA responses 20-fold over background) and atypical cDGA (7/12) with immunosuppression	Survival at 1 year; immune development assessments and analysis of allograft biopsy	Safety and toxicity of post-transplantation immunosuppression; AEs related to immunosuppression; AEs related to surgical procedures
931	To assess thymus tissue and parental parathyroid transplantation	Typical and atypical cDGA with hypoparathyroidism	Requirement for calcium supplementation at 1 year; survival at 1 year; T cell counts; proliferative responses to mitogens and antigens; TCRβV	Safety and tolerability of procedures; AEs; monitoring for autoimmune disease, infections, and endocrine function
932	To evaluate the correlations between dose of thymus tissue transplanted and immunological outcomes after transplant	Typical and atypical with immunosuppression	Survival at 1 year; relationship between tissue dose and immune response variables (T cell count and phenotype; biopsy; TCRβV; PHA response)	AEs and SAEs; infections and autoimmune disease; effect of dose on incidence of serious skin rashes
950	Thymus transplantation with immunosuppression tailored to patient immune status	3 groups of typical or atypical cDGA with varying PHA responses pre-transplantation	Survival at 1 year; T cell counts and phenotype; thymopoiesis (graft biopsy); proliferative T cell response to mitogens/antigens; TCRβV	AEs and SAEs; monitoring for autoimmune disease, malignancies, GVHD, cardiac status; incidence of infection; Grade 3 toxicities related to surgery and concomitant medications
25966	Thymus transplantation with immunosuppression regimens tailored to patient immune status as in 932 and 950	4 groups based on patient immune status and peri-transplantation immunosuppression regimen	Survival at 1 year	AEs and SAEs; clinical monitoring (chemistry, hematology, urinalysis, physical exam); endocrine studies (thyroid, calcium); CMV and EBV; monitoring for autoimmune disease, malignancies, GVHD, cardiac status; incidence of infection; description and location of rashes persisting more than 2 weeks

Source: Markert, 2010

Abbreviations: AEs, adverse events; cDGA, complete DiGeorge anomaly; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft versus host disease; MLR, mixed lymphocyte reaction; PCR, polymerase chain reaction; PHA, phytohemagglutinin; SAEs, serious adverse events; TCRβV, T-cell receptor beta chain variable region

This Investigational product was granted Orphan Designation on August 15, 2003 and Breakthrough Therapy and Regenerative Medicine Advanced Therapy Designation on April 14, 2017. A face-to face End of Phase 2 Meeting was held with the Applicant on May 1, 2017. Briefly, the FDA informed the Applicant that the cumulative results of the clinical studies conducted to date were adequate to support the filing of a BLA. The Applicant have subsequently conducted several teleconferences with the Division of Cell and Gene Therapy to discuss CMC issues (see Table 5).

**3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

**3.1 Submission Quality and Completeness**

The submission was well organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

**3.2 Compliance with Good Clinical Practice and Submission Integrity**

The trial was conducted in full conformance with the ethical principles that have their origin in the Declaration of Helsinki (Version of Fortaleza, October 2013). The trial was conducted in compliance with the protocol, Good Clinical Practice (GCP) regulations and the applicable regulatory requirements.

**3.3 Financial Disclosures**

<p><b>Covered clinical study (name and/or number):</b></p> <ul style="list-style-type: none"> <li>• Study 668-1: Thymic transplantation in complete DiGeorge syndrome.</li> <li>• Study 668-2: Phase II study of thymus transplantation in complete DiGeorge syndrome.</li> <li>• Study 884: Thymus transplantation with immunosuppression (includes data from a single subject enrolled in Study 884-1).</li> <li>• Study 931: Parathyroid and thymus transplants in DiGeorge syndrome.</li> <li>• Study 932: Dose study of thymus transplantation in DiGeorge anomaly.</li> <li>• Study 950: Phase I/II trial of thymus transplantation with immunosuppression (includes data from a single subject enrolled in 950-1).</li> <li>• Study 25966: Safety and efficacy of thymus transplantation in complete DiGeorge anomaly.</li> <li>• Study (b) (6) Single subject treatment plan: Thymus transplantation for Epstein-Barr virus (EBV) lymphoma.</li> <li>• Study 51692: Expanded access protocol. Thymus transplantation for immunodeficiency, hematologic malignancies, and autoimmune disease related to poor thymic function.</li> <li>• Study 735: Thymic transplantation in partial DiGeorge syndrome</li> </ul>		
<p>Was a list of clinical investigators provided:</p>	<p>Yes X <input type="checkbox"/></p>	<p>No <input type="checkbox"/> (Request list from applicant)</p>
<p>Total number of investigators identified: 1 principal investigator and 16 sub-investigatoirs</p>		

Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 (Louise Markert, MD PhD)		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Payments for the following</p> <p><u>Upfront licensing</u> (b) (4) :-</p> <p><u>BLA submission</u> (b) (4) :-</p> <p><u>BLA approval</u> (b) (4) :-</p> <p>Significant payments of other sorts:</p> <p><u>Sale of priority review voucher:</u> (b) (4) :-</p> <p><u>Support for Duke clinical thymus transplant program:</u> (b) (4) -/year until commercial launch and then (b) (4) year until Dec 31, 2019</p> <p><u>Support for Dr Markert's laboratory:</u> (b) (4) :-</p> <p>Proprietary interest in the product tested held by investigator: <u>No</u></p> <p>Significant equity interest held by investigator in sponsor of covered study: <u>No</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

**4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES**

**4.1 Chemistry, Manufacturing, and Controls**

A Complete Response will be generated for the following CMC and facility issues.

1. Samples used for final product release for potency, identity, impurity (residual donor thymocytes), and overall quality were tested up to <sup>(b) (4)</sup> days prior to drug product formulation, but the product continues to change over time in culture. There was no repeat testing in the case of a manufacturing deviation.
2. The non-quantitative histology release criteria lacked a minimum threshold, and the level of sensitivity of the assay was questionable. It was unclear if all lots were of the same

quality and some lots that were subjected to forced degradation still met some of the release criteria. Twenty subjects had low or delayed T cell counts and it is not clear whether a lower quality lot could have contributed to the clinical outcome.

3. Insufficient information was available to support the source material holding time of (b) (4) total at room temperature prior to processing or further hold (b) (4) at (b) (4).
4. Final product expiry of (b) (4) was not supported by available information
5. The original submission proposed to use a (b) (4) specimen container as the final container closure. The change to the (b) (4) container resulted in a change in formulation (b) (4) configuration of the culture slices (b) (4) instead of being suspended above the medium, longer shelf life, differences in product labels and handling procedures by surgical personnel. Proper risk management was not applied, and stability studies were considered insufficient. The Applicant was offered the option of reverting to the (b) (4) final product culture dish container, which Enzyvant chose. A new (b) (4) final container transport study was conducted, but the results were invalid, and thus the (b) (4) container closure has not been adequately validated.

#### **4.2 Assay Validation**

There were no assays required to validate RVT-802.

#### **4.3 Nonclinical Pharmacology/Toxicology**

There were no issues related to nonclinical pharmacology/toxicology.

#### **4.4 Clinical Pharmacology**

There were no Clinical Pharmacology data submitted with this application.

##### **4.4.1 Mechanism of Action**

The proposed mechanism for RVT-802 involves lymphoid progenitor cells from the recipient's bone marrow migrating into the implanted RVT-802 allograft, where they develop into immunocompetent naïve recipient T cells that are tolerant of both donor and recipient tissues. These T cells are also able to recognize foreign antigens in the context of recipient ("self") MHC proteins and, as a result, mount an adaptive immune response to foreign antigens.

Thymopoiesis is observed in biopsies of RVT-802 within 2 to 3 months of implantation. Naïve T cells, indicative of thymic function, are first detected in the peripheral blood at ~6 months. Normal T cell proliferative responses to mitogens and antigens develop within ~1 year. A diverse TCR variable beta (TCRV $\beta$ ) repertoire develops by 1-2 years post-implant. Naïve T cells increase over time with levels considered sufficient to protect against infection developing within 1 year after implantation. Molecular and/or cytogenetic testing has shown that the T cells that develop after treatment with RVT-802 are of recipient origin.

##### **4.4.2 Human Pharmacodynamics (PD)**

There were no human pharmacodynamic data submitted with this application.

##### **4.4.3 Human Pharmacokinetics (PK)**

There were no Human PK data submitted with this application.

#### **4.5 Statistical**

There were no statistical issues with this application.

#### 4.6 Pharmacovigilance

There were no pharmacovigilance data submitted with this application.

### 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

#### 5.1 Review Strategy

A literature search of the topic was conducted on PubMed and Up-toDate. The primary source references were then reviewed. After familiarizing myself with the disease and its challenges, the BLA and IND documents were then reviewed.

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

The documents that were reviewed for this Application includes submissions filed under BLA 125685 and IND 9836. These include meeting minutes, correspondence between the FDA and the Applicant, and documents submitted by the Applicant.

#### 5.3 Consultations

There were no consultations with individuals outside of the FDA for the review of this BLA.

#### 5.4 Literature Reviewed

A literature search was performed on PubMed with the search term “DiGeorge Anomaly” and “DiGeorge Syndrome” and the relevant articles were reviewed.

### 5 DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The RVT-802 clinical development program for the treatment of T cell immuno-deficiency resulting from congenital athymia has been conducted at Duke University Medical Center over the past 25 years. The clinical program consisted of 10 studies. The primary clinical efficacy data included in this BLA are derived from 7 core, single-site, open-label, non-randomized clinical studies in subjects with congenital athymia, 2 additional IND 9836 protocols and 1 non-IND protocol. Data from the latter 3 studies provided additional supporting data, although subjects treated in these studies are not included in the Efficacy Analysis Set.

#### Core IND 9836 BLA studies:

- Study 668-1: Thymic transplantation in complete DiGeorge syndrome.
- Study 668-2: Phase II study of thymus transplantation in complete DiGeorge syndrome.
- Study 884: Thymus transplantation with immunosuppression (includes data from a single subject enrolled in Study 884-1).
- Study 931: Parathyroid and thymus transplants in DiGeorge syndrome.
- Study 932: Dose study of thymus transplantation in DiGeorge anomaly.
- Study 950: Phase I/II trial of thymus transplantation with immunosuppression (includes data from a single subject enrolled in 950-1).
- Study 25966: Safety and efficacy of thymus transplantation in complete DiGeorge anomaly.

#### Additional IND 9836 studies:

- Study (b) (6): Single subject treatment plan: Thymus transplantation for Epstein-Barr virus (EBV) lymphoma.
- Study 51692: Expanded access protocol. Thymus transplantation for immunodeficiency, hematologic malignancies, and autoimmune disease related to poor thymic function.

Non-IND study:

- Study 735: Thymic transplantation in partial DiGeorge syndrome

**6.1 IND9836 Core BLA Studies.****6.1.1 Studies 668-1: Thymic transplantation in complete DiGeorge syndrome and 668-2: Phase II study of thymus transplantation in complete DiGeorge syndrome****6.1.1.1 Objectives**

The objectives of Study 668.1 were to assess:

- Immune reconstitution of T cell function (by proliferative responses to mitogens and antigens);
- Safety and long-term outcome;
- Thymopoiesis in the donor graft.

The objectives of Study 668.2 were to assess:

- Thymopoiesis in the donor graft
- immune reconstitution of T cell function (by flow cytometry and proliferative responses to mitogens and antigens)
- Minimally invasive methods of assessing thymopoiesis (by flow cytometry and polymerase chain reaction [PCR])
- Pre-transplant T cells which did not proliferate in response to mitogens (focusing on natural killer [NK]-T cells)
- Safety and efficacy.

**6.1.1.2 Design Overview**

The two studies were open-label, non-randomized, studies conducted at DUMC. The results of the two studies were combined into a single Clinical Study Report (CSR).

**6.1.1.3 Study Population**

Study 668-1 enrolled subjects with typical or atypical cDGA. Two treatment groups were defined:

- Group 1 included cDGA subjects with very low proliferative T cell function who were not expected to reject RVT-802.
- Group 2 included atypical cDGA subjects with some proliferative T cell function and potential need for immunosuppression. This group included subjects who had undergone previous unsuccessful attempts at T cell reconstitution.

Study 668-2 included subjects with typical cDGA, characterized by very low T cell numbers and very low proliferative T cell function. Subjects were not expected to reject RVT-802.

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

All subjects received a single implant of RVT-802. Both studies enrolled subjects where the likelihood of graft rejection was low, as determined based on studies conducted by the Investigator. Therefore, subjects were not immunosuppressed prior to receiving RVT-802.

**6.1.1.5 Sites and Centers**

The two study was conducted at Duke University in the United States between:

- Study 688.1: October 1991 (IRB approval date) to October 2001
- Study 668.2: October 2001 to 27 August 2009 (enrollment closure date)

Study data were collected through 31 December 2017.

#### **6.1.1.6 Surveillance/Monitoring**

Subjects were monitored for the first 2 to 3 months of the post-transplant period. A thymus allograft biopsy was planned for approximately 8 to 12 weeks post-transplant. The biopsied tissue was examined for graft rejection and evidence of thymopoiesis by immunohistochemical staining for the presence of cytokeratin, a marker of thymic epithelium, and for T cells populating the thymus. Following the biopsy, subjects who were medically stable were discharged to the care of the referring physician/pediatric immunologist. After transfer, subjects were monitored by requesting AE reports from the local physician and collection of blood samples as per the assessment schedule through 2 years post-transplantation. Subjects were also followed for vital status and non-infection-related AEs through 31 December 2017. In these studies, infection-related AEs were reported for 2 years post-transplantation.

#### **6.1.1.7 Statistical Considerations & Statistical Analysis Plan**

A single Statistical Analysis Plan (SAP) dated 28 September 2017 (updated on 19 September 2018) was created to support this and the 9 other clinical studies planned for inclusion in this BLA given the legacy data status and similarities across the 10 clinical studies in the RVT-802 program. The endpoints specified in the program-wide SAP were given precedence over the analyses originally planned for this study (See Sec 6.1.1.7.4 Endpoints and Criteria for Study Success).

##### **6.1.1.7.1 Study Population and Disposition**

A total of 26 subjects received RVT-802 in Study 668.1 (n=14) and Study 668.2 (n=12). Four subjects were enrolled under individual treatment plans, 1 subject was as an enrollment exception (Subject (b) (6) – FOXN1), and 1 subject was an enrollment exception through compassionate use (Subject (b) (6) – SCID).

All 26 subjects were included in the FAS. However, the EAS had 25 subjects and the EAS-cDGA had 24 subjects due to the following:

- Subject (b) (6) was an enrollment exception who was excluded from the EAS-cDGA because the subject had FOXN1 deficiency.
- Subject (b) (6) was a compassionate use subject and was excluded from the EAS and EAS-cDGA because this subject had SCID and previously had 2 (unsuccessful) HSCT.

Eight subjects (30.8%) in the FAS discontinued from the study prior to the second years of follow-up, including 7 subjects who died and 1 (Subject (b) (6)) who was withdrawn due to physician decision. Subject (b) (6) was withdrawn from the study and died after withdrawal on 375 days post-transplant.

##### **6.1.1.7.2 Protocol Deviations**

There were no protocol deviations that impacted subject safety or the integrity of study results. Missing data were not replaced in this study.

##### **6.1.1.7.3 Demographics & Disease Characteristics**

The demographic and baseline characteristics were similar across analysis populations. The median age on the day of RVT-802 transplantation was 123 days (range: 33 to 449 days) in the FAS. Fifteen subjects (58%) were male and 11 subjects (42%) were female. Sixteen subjects (62%) were white, 9 subjects (35%) were black, and 1 subject was Asian (4%). Five subjects (19%) were of Hispanic/Latino ethnicity. The median height and weight during screening were 58.3 cm (range: 49.0 to 72.0) and 4.5 kg (range: 2.6 to 8.9), respectively.

Median BSA was 0.271 m<sup>2</sup> (range: 0.225 to 0.428). Median head circumference was 39.3 cm (range: 33.5 to 46.8).

Twenty-four of the 26 subjects in the FAS (92%) had cDGA, 1 subject had SCID and another had FOXN1 deficiency. Notably, the distinction between atypical and typical cDGA had not been identified when the study was initiated. It was the treatment of Subjects (b) (6) in this study that led to the identification of the atypical phenotype of cDGA. Thereafter, subjects were retrospectively categorized by the Applicant/Investigator into the typical and atypical phenotypes. Nineteen subjects (73%) were classified as having the typical phenotype of cDGA and 5 subjects (19%) were considered to have atypical cDGA.

The median age at diagnosis was 27 days (range: 0 to 199 days). Diagnosis on Day 0 was based on the presence of clinical features consistent with DGA; however, the presence of athymia, required for the diagnosis of cDGA was not confirmed until later using flow cytometry. Among subjects who had cardiac surgery prior to treatment with RVT-802, confirmed visual evidence of the thymus during cardiac repair was not reported in any subject.

All subjects had a history of diminished age adjusted T cell count. Twenty-two subjects (85%) had congenital cardiac anomaly or cardiothoracic vascular anomaly. Growth or mental retardation and hypocalcemia were each observed for 19 subjects (73%). Dysmorphic facies and deafness or ear pinnae anomalies were each observed for 13 subjects (50%).

A hemizygous deletion of chromosome 22q11.2 was observed in 12 subjects (46%), CHARGE in 7 subjects (27%) one of whom also had a *CHD7* mutation (Subject (b) (6)). One subject (Subject (b) (6)) had no data for cDGA gene mutations as this subject had FOXN1 deficiency while an additional six subjects (23%) had no known cDGA gene mutation. Of the latter, 4 were infants of diabetic mothers including 3 subjects with mothers having type I diabetes (Subjects (b) (6) and 1 subject (Subject (b) (6)) with a mother who had type II diabetes. Five subjects (19%) had no family history of cDGA and the cDGA family history was unknown for 8 subjects (31%). No cDGA inheritance data was reported for 10 subjects due in part to the high-cost and limited availability of genetic sequencing at the time of their participation in this study.

Twenty one of 26 subjects (81%) in the FAS had a history of infection prior to study transplant procedures. The most frequent pre-transplantation infections were bacterial respiratory tract infection (5 subjects [19%]) and device-related infection (4 subjects [15%]). Oral candidiasis, staphylococcal bacteremia, and pneumonia were each reported for 3 subjects (12%). No other pre-transplantation infection was reported for more than 2 subjects.

The numbers of subjects who received immunosuppressive therapies were similar across analysis populations and are described for the FAS. Six subjects (23%) received at least one immunosuppressive agent during the study, including 4 subjects (Subjects (b) (6) enrolled under an individual treatment plan that included the use of immunosuppressive therapy as 3 of these subjects had atypical cDGA and would have likely rejected RVT-802 without immunosuppression. The fourth subject, Subject (b) (6) had typical DiGeorge, but had a high proliferative response to PHA that also required immunosuppression to prevent RVT-802 rejection. Methylprednisolone, which was received by 4 subjects (15%), was the most common immunosuppressive therapy. Three subjects (12%) received RATGAM; 2 subjects

(8%) received cyclosporine; and prednisolone and pentostatin were received by 1 subject (4%) each; the latter was used for Subject (b) (6) who was too sick/fragile to receive RATGAM.

**6.1.1.7.4 Endpoints and Criteria for Study Success**

There were no pre-specified study endpoints in Study 668.1 as this was a descriptive Phase 1 study first approved by an IRB in 1991, 10 years prior to the submission of the IND to the FDA. Study 668.2 was a Phase 2 study for which the endpoints were developed based on data obtained from Study 668.1. However, given the similarities of the 10 studies that constitute this BLA, the endpoints specified in the program-wide SAP were given precedence over the analyses planned in the original protocol. Thus, subject survival at Year 1 and Year 2 post-transplant using the binomial exact test was selected as the common primary endpoint for all studies as it meets the overall treatment goal. Furthermore, the Kaplan-Meier estimates of survival at 1- and 2-years post-transplant is provided.

**6.1.1.8 Efficacy Analyses**

**6.1.1.8.1 Primary Endpoint**

In the Efficacy Analysis Set (EAS), survival following transplant at one and two years was 72.0% (18 of 25 subjects) with 95% CI of [0.51, 0.88] and a p-value of 0.0216 from the binomial exact test on survival rate >50%.

- The median survival for the 9 subjects in the EAS who died during the study was 130 days (ranged 0 to 3116 days [8.5 years]) post RVT-802 transplantation. The median follow-up time for all subjects in EAS was 4436 days (~12.1 years; range 0 to 8569 days [23.5 years]) after RVT-802 transplantation.
- The estimated Kaplan-Meier survival rate at Year 1 post-transplantation in the EAS was 0.72 with a 95% CI of [0.501, 0.855]. The Kaplan-Meier estimates of survival were the same at Years 1, 2, 3, 4 and 5 post-transplantation because all subjects who survived at least 1-year post-transplant were still alive through at least 5 years post-transplant.

**6.1.1.8.2 Secondary Endpoints**

The data was limited as collection of blood samples was dependent upon parent(s), the referring/local physicians, and the subject’s medical condition. Nonetheless, there was evidence of thymic function as evidenced by increases from baseline in total and naïve T cell counts in subjects who had data available at Years 1 and 2 posttransplant.

**Naïve CD3, CD4 and CD8 T-cell Counts**

The median naïve CD3, CD4, and CD8 counts (cells/mm<sup>3</sup>) increased markedly from baseline to Year 1 post-transplant and were sustained at Year 2 post-transplant, although the available data were limited (Table 8).

**Table 8: Naïve CD3, CD4, and CD8 Counts (Applicant’s Table)**

Visit	Statistic	RVT-802 EAS = 25		
		Naïve CD3 (cells/mm <sup>3</sup> )	Naïve CD4 (cells/mm <sup>3</sup> )	Naïve CD8 (cells/mm <sup>3</sup> )
Baseline <sup>a</sup>	n	2	7	5
	Mean (SD)	51,390 (65,916)	2,786 (2,482)	6,902 (12,422)
	Median	51,390	3,000	2,380
	Q1, Q3	4,780, 98,000	0,000, 4,000	0,000, 3,150
	Min, max	4,78, 98,00	0,00, 7,14	0,00, 28,98
Year 1	n	1	13	11
	Mean (SD)	128,000 (NA)	279,468 (170,342)	77,037 (38,376)
	Median	128,000	269,730	65,000
	Q1, Q3	128,000, 128,000	212,000, 311,250	30,090, 118,080
	Min, max	128,00, 128,00	47,90, 669,00	2,68, 188,00
Year 2	n	--	7	7
	Mean (SD)	--	336,824 (144,026)	109,399 (73,020)
	Median	--	377,080	88,000
	Q1, Q3	--	271,000, 433,000	66,000, 174,800
	Min, max	--	100,44, 571,00	25,60, 240,10

**Total CD3, CD4 and CD8 T-cell Counts**

The median total CD3, CD4, and CD8 counts (cells/mm<sup>3</sup>) increased markedly from baseline to Year 1 post-transplantation and were sustained at Year 2 post-transplant, although there were limited data available (Table 9).

**Table 9: Total CD3, CD4, and CD8 Counts**  
(Applicant’s Table)

Visit	Statistic	<u>RVT-802</u> EAS = 25		
		Total CD3 (cells/mm <sup>3</sup> )	Total CD4 (cells/mm <sup>3</sup> )	Total CD8 (cells/mm <sup>3</sup> )
Baseline <sup>a</sup>	n	25	22	19
	Mean (SD)	226.390 (751.108)	65.438 (138.579)	37.421 (115.742)
	Median	16.000	7.000	0.000
	Q1, Q3	3.000, 47.000	0.000, 36.000	0.000, 4.000
	Min, max	0.000, 3768.000	0.00, 544.00	0.000, 502.000
Year 1	n	17	17	16
	Mean (SD)	834.153 (378.997)	619.506 (294.834)	147.156 (98.829)
	Median	770.000	570.000	122.000
	Q1, Q3	587.000, 1045.000	450.000, 734.000	71.500, 207.250
	Min, max	182.000, 1698.000	156.00, 1376.00	14.000, 382.000
Year 2	n	8	8	8
	Mean (SD)	928.125 (462.189)	659.000 (303.354)	174.375 (101.983)
	Median	779.500	543.000	165.500
	Q1, Q3	569.000, 1322.500	465.500, 898.000	105.000, 239.500
	Min, max	443.000, 1640.000	279.00, 1180.00	32.000, 343.000

**Other Lymphocyte Counts (Table 10)**

Absolute lymphocyte counts (ALC) fluctuated over time but remained above the 10th percentile for age at Year 1 and was slightly below the 10th percentile for age at Year 2.

Total B and NK cells generally remained normal throughout the course of the study for age and gender

A marked increase of the median for total αβ T cells from baseline to Year 1 was observed with results sustained at Year 2.

The median total γδ and DN T cells increased from baseline to Year 1 and continued to increase at Year 2.

The median total αβ, γδ and DN T cells at Year 2 were within the normal reference range

**Table 10: Lymphocyte Subsets (Median in cells/mm<sup>3</sup>)**  
(Reviewer’s Table)

	ALC	B-cell	NK-cell	αβ T cell	γδ T cell	DN T cell
<b>Baseline</b>	1850 (n=25)	956 (n=24)	356 (n=25)	29 (n=9)	0 (n=9)	8 (n=9)
<b>Year 1</b>	2365 (n=17)	807 (n=17)	288 (n=17)	769 (n=14)	22 (n=14)	35 (n=12)
<b>Year 2</b>	1720 (n=8)	659 (n=8)	402 (n=8)	695 (n=7)	50 (n=6)	53 (n=6)

**Proliferative T cell responses to Antigens**

There was a steady increase in the proliferative T cell response to PHA from baseline (N=24) to Year 1 (N=13) and Year 2 (N=6) post-transplant. The median PHA values were 985 cpm at baseline (normal >75,000 cpm), 133,000 cpm at Year 1, and 236,360 cpm at Year 2. Among 13 subjects with available data at Year 1, only 1 subject (Subject (b) (6)) had a PHA response less than 75,000 cpm (PHA response of 53,913 cpm on Day 379). This subject later went on to develop a normal T cell proliferative response to PHA of 215,797 cpm at the next assessment on 539 days post-transplantation.

Proliferative T-cell responses to ConA, immob CD3, sol CD3, and tetanus toxoid normalized within 2 years post-transplantation, indicating the development of a functional T cell population.

**Thymic Biopsy**

There was evidence of thymopoiesis defined as the presence of a lacy pattern of cytokeratin-positive thymic epithelial cells and the presence of CD3+CD1a+Ki-67+ cells in 17 of 19 subjects with RVT-802 biopsies.

Thymic rejection was noted in Subject (b) (6) (5.3%), a black male with atypical cDGA and severe rash who was enrolled under an individual treatment plan. His weight was below birthweight on admission to DUMC at 289 days of life. He received RVT-802 on Day 354 of life. The subject was treated with deoxycoformycin (1.12 mg IV) 16 days prior to receiving RVT-802 and again 10 days prior to transplantation. Deoxycoformycin was substituted for RATGAM because the subject was suffering from respiratory compromise. However, the deoxycoformycin may not have been sufficient to control the subject's oligoclonal T cell population. The subject died from sepsis 44 days after RVT-802 transplantation.

Subject (b) (6) had no evidence of thymopoiesis or rejection in his biopsy specimen. This may have been secondary to the use of pulse steroids (40 mg/kg/day x 3 days) when this subject first developed atypical cDGA shortly after transplantation. This subject never developed naïve T cells prior to death due to sepsis 130 days after transplantation.

**B cell Function**

B cell function was measured through the analysis of serum immunoglobulins. Subjects were maintained on monthly IGIV for up to 2 years post-transplant until they met protocol-specified criteria for discontinuation. Because subjects were receiving IGIV, values for IgG were influenced by the replacement therapy and not representative of the subjects' endogenous IgG production. The proportion of subjects reporting low levels of other measured immunoglobulins including IgA and IgM at baseline generally decreased with a higher proportion of subjects reporting normal values at Years 1 and 2 post-transplantation. Despite a shift to more normal levels over time, a relatively high proportion (21.4%) of subjects still reported low values for IgA and IgM at Year 1.

**Cytomegalovirus and Epstein-Barr Virus Infections**

There was only one reported case of CMV infection in this study. Subject (b) (6) was positive for CMV from a bowel biopsy on day -47 and in 4 urine samples during screening. However, there were also 5 negative urine samples for CMV during screening. Subject was treated with ganciclovir from Day -41 to Day -10 when foscarnet was started. CMV specific IgG was given beginning on Day -22. The subject had a positive CMV result in urine 1 day after

RVT-802 transplantation, but no other positive CMV result during the study (results reported through post-transplant Day 42). This subject died from respiratory failure 45 days after RVT-802 transplantation.

There was only one reported case of EBV infection in this study. Subject <sup>(b) (6)</sup> had positive EBV results in blood from post-transplantation Days 279 to 477 and in bone marrow on post-transplantation Day 313. EBV viremia was reported as a moderate AE that was unrelated to study treatment. The AE resolution date was post-transplantation Day 1069 suggesting that this subject's immune function was able to control this infection.

### **6.1.1.9 Safety Analyses**

#### **6.1.1.9.1 Methods**

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. AEs and serious AEs (SAEs) were summarized separately by presenting the number and percentage of subjects having any event, having a related event, having an event in each MedDRA system organ class (SOC) and preferred term (PT), having each individual event and the intensity, relationship and outcome of each event. The number of events was also presented. Any missing intensity, relationship, or outcome was classified as unknown.

A subject with more than 1 occurrence of the same AE in a particular SOC was counted only once in the total of those experiencing AEs in that particular SOC. If a subject had the same AE at more than one intensity or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug was given precedence.

Summaries classifying events according to intensity and relationship were presented. Related events were defined as events that were definitely, probably, or possibly related to study treatment or with an unknown relationship.

Non-infection-related AEs and SAEs were graded (Grades 1-5) according to Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). Infection-related AEs were evaluated using either CTCAE criteria or criteria defined in the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) definitions of infection intensity. Infection-related AEs with BMTCTN intensity  $\geq$  severe were included in the analysis of AEs of Grade  $\geq$  3.

Adverse events of special interest (AESI) were summarized by SOC and PT, and included infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas. Given the disease under study, infection related AEs were of interest as the ability to mount an immune response and control infections was indicative of the development of thymic function. Given the mechanism of action of RVT-802 and the ability to reconstitute the immune system, cancers, autoimmune diseases, GVHD, and granulomas were potential AEs that may have been related to study therapy. Granulomas may have been indicative of the development of sarcoidosis. Finally, rashes may have been indicative of the new development or flare of pre-existing features associated with the atypical phenotype of cDGA. Rashes persisting more than 2 weeks were biopsied to assess the etiology of the rash.

#### **6.1.1.9.2 Overview of Adverse Events**

The 26 subjects in this study received a median RVT-802 dose of 14,165 mm<sup>2</sup>/m<sup>2</sup> (range: 6828 to 20,764). The median number of RVT-802 slices received was 39 (range: 17 to 108). The dose was missing for the first 13 subjects treated as it was not recorded in the source

medical records at the time of transplantation. In a 2015 IND amendment, the recommended RVT-802 dose range was established as 2,000 to 20,000 mm<sup>2</sup>/m<sup>2</sup> BSA. Prior to the implementation of this dosing range, a single subject in this study (Subject <sup>(b) (6)</sup>) received a dose of 20,764 mm<sup>2</sup>/m<sup>2</sup>.

The AE profile matched expectations for this population of pediatric, immune compromised, and medically complex subjects. All 26 subjects in the study had at least 1 AE and 25 subjects (96%) had at least one AE of  $\geq$  Grade 3 in intensity. Twenty-three subjects (89%) had at least 1 SAE; 8 subjects (31%) had a life-threatening SAE and 7 subjects (27%) had a fatal SAE. Eighteen subjects (69%) had at least 1 AE that was considered related to study treatment. Seven subjects (27%) had at least 1 treatment-related AE that was considered severe in intensity and 3 subjects (12%) had a life-threatening, treatment-related AE. Twenty-five (96%) subjects had at least 1 infection-related AE, which included events of severe intensity for 13 subjects (50%) and life-threatening events for 4 subjects (15%). Four subjects (15%) had a fatal infection-related event.

### **Frequency of AEs**

The 26 subjects in this study had a total of 462 AEs. The most frequent AEs were in the SOCs of infections and infestations (25 subjects [96%]); respiratory, thoracic and mediastinal disorders (17 subjects [65%]), skin and subcutaneous tissue disorders (17 subjects [65%]); general disorders and administration site conditions (16 subjects [62%]); gastrointestinal disorders (16 subjects [62%]); and blood and lymphatic system disorders (13 subjects [50%]).

Pyrexia was the most frequent AE in this study (15 subjects [58%], 29 events) followed by device-related infection in 12 subjects (46%, 30 events) and rash in 9 subjects (35%, 17 events). Staphylococcal bacteremia was observed in 7 subjects (27%, 11 events) and hypoxia and hypothyroidism were each observed in 6 subjects (23%). AEs observed in 5 subjects (19%) included the following: thrombocytopenia, increased AST, hydronephrosis, oropharyngeal candidiasis, hepatomegaly, hypersensitivity, pleural effusion, and respiratory failure. No other AE was observed for more than 4 subjects (15%).

### **Relationship to Study Treatment**

A total of 41 AEs was considered study treatment related with 18 subjects (69%) having at least 1 TEAE. The most frequent TEAE was thrombocytopenia and was reported for 4 subjects (15%, 7 events). The following TEAEs were each observed for 2 subjects (8%): respiratory failure, rash, pyrexia, proteinuria, hypothyroidism, and wound dehiscence. No other TEAE was observed for more than 1 subject (4%).

The assessment of hypothyroidism was changed to “unlikely related” by the Investigator after 2 subjects had hypothyroidism that was considered treatment related. This was because a relatively high number of subjects presented with hypothyroidism prior to RVT-802 treatment. In addition, a relatively high proportion (20%) of adults with partial DGA who never received RVT-802 also developed hypothyroidism.

### **Severity of AEs**

There were 179 AEs of Grade  $\geq$  3 with 25 subjects (96%) experiencing at least 1 AE Grade  $\geq$  3. The most frequent AEs were in the SOCs infections and infestations (21 subjects [81%], 55 events); respiratory, thoracic and mediastinal disorders (11 subjects [42%], 31 events); and gastrointestinal disorders (10 subjects [39%], 14 events). The most frequent AEs of Grade  $\geq$

3 were device-related infection (10 subjects [39%], 22 events), and hypoxia (6 subjects [23%], 6 events). Respiratory failure (5 events) and pyrexia (8 events) were each observed for 5 subjects (19%). No other AEs of Grade  $\geq 3$  were observed for more than 3 subjects (12%).

Ten subjects (39%) had 18 events of Grade  $\geq 3$  that were related to study treatment. Thrombocytopenia, which was observed for 3 subjects (12%, 5 events), and respiratory failure, which was observed for 2 subjects (8%, 2 events) were the only AEs considered treatment-related and rated Grade  $\geq 3$  for more than 1 subject.

#### **6.1.1.9.3 Deaths**

There were 10 deaths reported after treatment with RVT-802 in the FAS; 7 subjects (27%) died within 2 years of RVT-802 transplantation and 2 subjects (8%) died more than 2 years after RVT-802 transplantation, and 1 subject died after study withdrawal. The causes of death for the 7 subjects who died within 2 years of RVT-802 transplant included: sepsis/presumed sepsis (4 subjects; 15%), respiratory failure (2 subjects; 8%), brain hemorrhage (1 subject), and hemorrhage associated with Nissen fundoplication surgery. The latter subject had a calcium accretion at the junction of the left hepatic vein and the inferior vena cava, which likely caused the hemorrhage. Respiratory failure was the cause of death for the 2 subjects who died more than 2 years after RVT-802 transplantation.

The single subject (Subject (b) (6)) who was withdrawn from the study died on 375 days post-transplant. As this death occurred 153 days after study withdrawal, this event was not reported as an SAE. No subject's death was considered related to study treatment.

#### **6.1.1.9.4 Nonfatal Serious Adverse Events**

There were 117 SAEs with 23 subjects (89%) having at least 1 SAE. SAEs were most frequent in the SOC of infections and infestations (20 subjects [77%], 53 SAEs). Device-related infection was the most frequent SAE (10 subjects [39%], 19 SAEs). Five subjects (19%, 5 SAEs) had a SAE of respiratory failure. The following SAEs were each observed for 3 subjects (12%): staphylococcal bacteremia, hypotension, and pyrexia. No other SAE was observed in more than 2 subjects.

Six subjects (23%) had a total of 12 SAEs that was possibly or probably related to study treatment:

- Subject (b) (6) respiratory failure; possibly related; resolved
- Subject (b) (6) thrombocytopenia; possibly related; resolved
- Subject (b) (6): hypothyroidism; probably related; ongoing
- Subject (b) (6): hypothyroidism; possibly related; ongoing
- Subject (b) (6) glomerulonephritis minimal lesion; possibly related; resolved
- Subject (b) (6): infantile spasms; possibly related; ongoing
- Subject (b) (6): respiratory failure; possibly related; resolved
- Subject (b) (6): thrombocytopenia; probably related; resolved
- Subject (b) (6): thrombocytopenia; possibly related; ongoing
- Subject (b) (6) Stevens-Johnson syndrome; possibly related; outcome unknown (Per the Investigator, findings associated with this event were also suggestive of acute GVHD. Chimerism performed on Day 211 (38 days after the onset of Stevens-Johnson syndrome)

showed 38% maternal T cells, suggesting a maternal etiology of skin GVHD).

GVHD in skin; probably related; ongoing.

#### **6.1.1.9.5 Adverse Events of Special Interest (AESI)**

Nineteen subjects (73%) had 53 AESI. The most frequent AESI were rash (9 subjects [35%], 17 events) and hypothyroidism (6 subjects [23%], 6 events). Hypersensitivity was observed in 5 subjects (19%, 5 events) and thrombocytopenia in 5 subjects (19%, 8 events). The following AESI were observed for 2 subjects (8%): alopecia, eczema, skin exfoliation, urticaria, and disseminated intravascular coagulation. One event of alopecia (Subject (b) (6)) was probably related to treatment, although this condition is known to be associated with hypothyroidism, which the subject also developed. The 2 events of skin exfoliation were Grade 1 and 2 and were unrelated to study treatment. No other AESI was observed for more than 1 subject. There were no cancer or granuloma observed during the study. One subject (Subject (b) (6)) developed GVHD in the skin that was likely related to maternal T cells developing in the thymus without education by host antigen presenting cells. While the event was considered likely related to pre-existing maternal T cells, the role of RVT-802 could not be excluded and the event was considered probably related to RVT-802.

Twenty-five subjects (96%) had at least one infection-related AE for a total of 141 infection-related AEs. The most frequent infection-related AEs were device-related infection (12 subjects [46%]), staphylococcal bacteremia (7 subjects [27%]), and oropharyngeal candidiasis (5 subjects [19%]). *Clostridium difficile* colitis and staphylococcal eye infection were each had by 4 subjects (15%). The following infection-related AEs were observed for 3 subjects (12%): enterococcal urinary tract infection, ear infection, enterococcal bacteremia, bacterial eye infection, gastroenteritis rotavirus, gastrointestinal viral infection, fungal urinary tract infection, and viral upper respiratory tract infection. No other infection-related AE was observed for more than 2 subjects.

#### **6.1.1.9.6 Vital Signs & Physical Examination**

The vital signs measured during this study included blood pressure, pulse rate, respiration rate, body temperature, head circumference, height, and weight but provided limited information regarding subject safety over the course of the study.

- Pyrexia was the most frequently abnormal vital sign reported as an AE within 2 years of transplantation (15 subjects, 58%), which was Grade  $\geq 3$  for 5 subjects (19%) and was treatment-related for 2 subjects (8%).
- Hypertension and hypotension were each observed for 3 subjects (12%) with the latter  $\geq$  Grade 3 for three subjects (12%).

There was no other abnormal vital sign result reported as  $\geq$  Grade 3 or treatment-related for more than 1 subject.

Physical examination data were not collected in this study.

#### **6.1.1.9.7 Clinical Laboratory Results**

The infants in this study had a history of abnormal laboratory results that continued throughout the study. The most frequent abnormal laboratory results were increased ALT (5 subjects [19%]) and increased AST (4 subjects [15%]). Three subjects (12%) had thrombocytopenia that was  $\geq$  Grade 3 and related to treatment. No other abnormal laboratory result  $\geq$  Grade 3 AE was considered treatment-related for more than 1 subject.

#### 6.1.1.10 Study Summary and Conclusions

The 668.1 and 668.2 studies enrolled 26 subjects, including 24 subjects with cDGA (19 with the typical phenotype and 5 with the atypical phenotype), 1 subject with FOYN1 deficiency, and 1 subject with SCID. Fifteen subjects (58%) were male and 11 subjects (42%) were female. Sixteen subjects (62%) were white, 9 subjects (35%) were black, and 1 subject was Asian (4%). The median age on the day of RVT-802 transplantation was 123 days (range: 33 to 449 days) in the FAS. Six subjects (23%) received at least 1 type of immunosuppressive therapy during the study.

The primary efficacy endpoint was survival at 1- and 2-year post-transplant. In the EAS, with no subject being censored, 18 of 25 subjects (72%) were alive one year after RVT-802 transplantation. The binomial exact test with the null hypothesis that no greater than 50% of subjects would survive at 1-year gave a 95% CI of [0.51, 0.88] with a p-value of 0.0216. The results of the binomial exact test at Year 2 were the same as at one year because all EAS subjects who survived at least 1 year were also alive at 2 years post-transplant. In the EAS, the estimated Kaplan-Meier survival rate at 1-year post-transplant was 0.72 with a 95% CI of [0.501, 0.855]. Because all subjects who survived at least 1 year were still alive through at least 5 years post-transplant, the Kaplan-Meier estimates of survival were the same at 1-, 2-, 3-, 4- and 5-years post-transplant. Finally, 64% of subjects were alive at the end of follow-up period for this report, which spanned up to 23.5 years.

Seven subjects had a fatal SAE within 2 years of RVT-802 transplantation; 3 died of infections in the first 6 months post-transplant and the other 4 subjects died due to respiratory failure (2 subjects), brain hemorrhage, and surgical complication (hemorrhage during Nissen fundoplication). Two subjects died due to respiratory failure (1 subject at 7.6 years and 1 subject at 8.5 years) after transplantation. A subject who had withdrawn from the study died due to infection 153 days after study withdrawal (375 days post-transplantation). No death was considered related to study treatment.

Immune reconstitution after treatment with RVT-802 was not expected to develop until approximately 6 to 12 months after RVT-802 transplantation. Subjects entered the study with athymia defined as <50 naïve T cells (or <5% naïve T cells) with the median naïve CD4 (N=13; 270 cells/mm<sup>3</sup>) and naïve CD8 (N=11; 65 cells/mm<sup>3</sup>) counts increasing at one year that were maintained at 2 years. A naïve CD4 count >100 cells/mm<sup>3</sup> is generally considered sufficient to fight infection. At one year, 11 of 13 subjects with available data had naïve CD4 counts above 100 cells/mm<sup>3</sup> while 2 subjects (Subjects (b) (6)) had naïve CD4 counts below 100 cells/mm<sup>3</sup>. However, both subjects did develop naïve CD4 counts >100 cells/mm<sup>3</sup> by Year 2 post-transplantation. The delay in the development of naïve T cells in these 2 subjects is not fully understood.

Increases in total CD3, CD4, and CD8 cell counts were also observed over time. While total T cell counts were generally below the 10<sup>th</sup> percentile for age at 1- and 2-years post-transplant, these levels were similar to subjects with partial DGA who were not transplanted indicating this was sufficient to enable survival. Importantly, the robust survival data demonstrates that the total T cell counts observed following RVT-802 treatment are generally adequate and effective to support a functional immune system.

The T cell population that developed post-transplant was normal as demonstrated by their proliferative responses to various mitogen/antigens. The median T cell proliferative response

to PHA increased from baseline (N=24, 985 cpm) to greater than 75,000 cpm at Year 1 (N=13, 133,000 cpm) and Year 2 (N=6, 236,359 cpm). Furthermore, 12 of 13 subjects and 6 of 6 subjects with data available at 1- and 2-years, respectively, developed normal responses (>75,000 cpm) to PHA. An increased median proliferative T cell response to other antigens including ConA, immob CD3, and sol CD3 was also observed. The only mitogen/antigen that did not lead to T cell proliferation over time was *Candida*, which may have been due to a lack of exposure to *Candida* in these subjects. This was expected as these subjects remained in reverse isolation until the development of thymic function approximately 6 months to 1-year post-transplant. Notably, one subject (Subject (b) (6)) developed normal responses to mitogens, but never developed antigen-specific T cell responses. This subject subsequently died from respiratory failure 7.6 years after transplantation. The pathogenesis of this subject's unique immune response is not fully understood. The subject presented with ectodermal dysplasia and coagulopathy, which may have contributed to this subject's immune response. This subject also had relatively low B cell counts at baseline (6 cells/mm<sup>3</sup>) and throughout participation in the study (range: 0 to 32 cells/mm<sup>3</sup>).

Data for TCRV $\beta$  repertoire by immunoscope/spectratyping and flow cytometry were limited, but generally demonstrated a shift from an oligoclonal T cell population at baseline to a more Gaussian repertoire at 1-year which, when combined with the development of naïve T cells, is consistent with the response to a wide variety of antigens and the ability to mount an immune response.

Thymopoiesis was demonstrated by biopsy at ~2 to 3 months post-transplant for 17 of 19 subjects in the EAS. One subject (Subject (b) (6)) had evidence of RVT-802 rejection at biopsy. This subject had severe atypical DiGeorge and had respiratory compromise too severe to allow for treatment with RATGAM to deplete the oligoclonal T cells prior to transplantation. The subject was treated with deoxycoformycin but it was likely insufficient to suppress the oligoclonal T cells associated with the atypical cDGA, ultimately resulting in the rejection of RVT-802. Subject (b) (6) had the other biopsy that did not provide evidence of thymopoiesis but there was also no evidence of rejection. The lack of thymopoiesis may have been secondary to the use of pulse steroids when this subject first developed what is now known as atypical cDGA shortly after transplantation. This subject did not develop naïve T cells and died from sepsis 130 days after transplantation.

B cell function was evaluated by analyzing serum immunoglobulins. Subjects were maintained on monthly IGIV for up to 2 years post-transplant. Thus, IgG levels were uninterpretable as they were affected by exogenous IGIV. The percentage of subjects reporting low levels of IgA and IgM at baseline generally decreased with a higher percentage of subjects reporting normal values at 1- and 2-years post-transplant. Despite the shift to more normal levels over time, a relatively high percentage (21.4%) of subjects still reported low values for IgA and IgM at one year. This was expected as IgA and IgM deficiencies have also been reported in subjects with partial DGA and suggest this may be related to DGA and not the athymia.

The safety profile of RVT-802 was consistent with pediatric, immunocompromised subjects who entered the study with extensive individual histories of serious medical conditions and surgical interventions. AEs that was considered related to study treatment included events related to immunosuppressive therapy, peri-transplant treatments/procedures, and autoimmunity. The latter were considered related to study treatment and reported by more

than 1 subject included thrombocytopenia (5 subjects) and hypothyroidism (total of 6 subjects but were related in only 2 subjects). A role of RVT-802 could not be excluded given the mechanism of action of RVT-802 and the development of thymic function. Laboratory and vital signs results did not raise any safety concerns for RVT-802 when administered with or without immunosuppression.

The results of studies 668.1 and 668.2 support the ability of RVT-802 to reconstitute the immune system and enable survival in subjects with congenital athymia, including subjects with cDGA and FOYN1 deficiency. The most frequent AEs included those known to be associated with cDGA such as infections, hypoxia, and clinical laboratory abnormalities. The safety profile of RVT-802 highlight the need for close observation and infection control/prevention measures until immune function is reconstituted.

### **6.1.2 Study 884/884.1: Thymus Transplantation with Immunosuppression.**

#### **6.1.2.1 Objectives**

The objectives of the study were:

- Evaluate the safety and toxicity of the procedure (3 doses of RATGAM [2 mg/kg/day]) followed by thymus transplantation. The safety of adding pre and post-transplantation cyclosporine was also assessed. This was evaluated descriptively by assessing survival at 1 year and the use of additional immunosuppressives after transplantation.
- Evaluate the allograft biopsy at 2-3 months after transplantation:
  - Thymopoiesis as defined by a) the presence of thymocytes expressing CD3, CD4, CD8, CD1a and Ki-67, and b) the presence of a reticular pattern of keratin reactivity.
  - Secondly, is there graft rejection? This was defined by the presence of mature CD8+ T cells carrying cytotoxic granules at the site of keratin-positive material and lack of thymopoiesis.
- Evaluate resulting immune function. T cell number and function were assessed by standard techniques.

#### **6.1.2.2 Design Overview**

This was a Phase 1, single-center, open-label, non-randomized study. The study enrolled subjects with T cell immunodeficiency associated with congenital athymia whose immune evaluations suggested that they would reject a thymus transplant if not treated with supporting immunosuppression.

#### **6.1.2.3 Population**

##### Inclusion Criteria

1. Diagnosis of DiGeorge syndrome (DGA) with one symptom from the following:
  - a. Congenital heart disease;
  - b. Hypocalcemia requiring replacement;
  - c. 22q11.2 hemizygoty;
  - d. 10p13 hemizygoty;
  - e. CHARGE (Coloboma; heart defect; choanal atresia; growth and development retardation; genital hypoplasia, ear anomalies/deafness) syndrome;
  - f. Abnormal ears plus mother with diabetes (type I, type II, or gestational);
2. To meet the criteria for atypical cDGA:

- a. Subjects had, or have had, a rash. If the rash was present, a biopsy of the rash had to show T cells in the skin. If the rash and adenopathy had resolved, the subject must still have had oligoclonal T cells (see below).
  - b. If the rash had just developed, the subject may not yet have had lymphadenopathy. It was also possible that the subject had lymphadenopathy in the past associated with rash. If this was the case, the subject still had to have oligoclonal T cells (see below).
  - c. PHA proliferative response of greater than 20-fold above background or over 5000 cpm, whichever was higher within 1 month of transplantation
  - d. Circulating CD3+ T cells greater than 50/mm<sup>3</sup>, but CD45RA+ CD62L+ CD3+ T cells less than 50/mm<sup>3</sup> or less than 5% of the total CD3 count, whichever was higher (this assay was performed twice).
  - e. Immunoscope with greater than 40% oligoclonal T cell receptor variable beta (TCRV  $\beta$ ) families: One assay was required. A second assay was done per Investigator/Applicant discretion if the T cell numbers increased or activation status changed. The reason for the second assay was to look for the predominance of a single clone that could require more immunosuppression than was included under this protocol.
  - f. T cell receptor rearrangement excision circle (TREC) assay <100 per 100,000 CD3+ cells. This assay was done if the subject's clinical condition allowed sufficient blood to be drawn;
3. To meet the criteria for typical cDGA:
    - a. Circulating CD3+ CD45RA+ CD62L+ T cells by flow cytometry <50/mm<sup>3</sup> or <5% of the total T cell count. PHA proliferative response >20-fold above background or >5000 cpm, whichever was higher. Two studies had to show similar immunological findings for a subject to qualify for this study.
    - b. Optional tests: TRECs, if done, had to be less than 100 per 100,000 CD3 cells.
  4. Each subject's legal guardian(s) signed the informed consent form;
  5. Medical screening was completed;
  6. Thyroid studies were completed and, if abnormal, the subject had to be on therapy.

A single subject with FOXP1 deficiency (Subject <sup>(b) (6)</sup>) was enrolled under a pre-planned enrollment exception. *FOXP1* affects thymic development, with homozygous mutations resulting in athymia. This subject met the criteria for athymia, defined as naïve T cell count <50/mm<sup>3</sup> or <5% of the total T cell count as assessed via flow cytometry.

A single subject (Subject <sup>(b) (6)</sup>) was enrolled under Protocol 884.1 as this subject required additional immunosuppression due to pre-existing GVHD from unirradiated blood received prior to enrollment for RVT-802 transplantation. This subject met the eligibility criteria for atypical cDGA.

#### Exclusion Criteria

1. Heart surgery conducted less than 4 weeks prior to projected transplantation date;
2. Heart surgery anticipated within 3 months of the proposed time of transplantation;
3. Rejection by the surgeon or anesthesiologist as surgical candidates;
4. Lack of sufficient muscle tissue to accept a transplant of 0.2 g/kg;
5. Evidence of the following infections had to be sought, but did not exclude potential subjects:
  - a. Evidence of Epstein-Barr virus by polymerase chain reaction (PCR);

- b. Evidence of cytomegalovirus by urine culture;
- c. Respiratory syncytial virus (RSV) or parainfluenza virus on nasopharyngeal screen;
- d. Enterovirus or adenovirus in stool;
- e. HHV6 by PCR.

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

The investigational product was allogeneic cultured postnatal thymus tissue product, RVT-802. RVT-802 was placed into the subject's quadriceps muscles in one or both legs by a pediatric surgeon. There was no control agent.

RATGAM (2 mg/kg/dose) was given for 3 days prior to thymus transplantation; usually on Days -5, -4, and -3, while Days -2 and -1 were usually rest days. However, other treatment schedules and rest days were permissible. The changes were dependent upon the medical condition of the subject.

Methylprednisolone was given at 0.5 mg/kg every 6 hours during the administration of RATGAM prior to thymus transplantation. Methylprednisolone could be given prior to the beginning of RATGAM at the discretion of the Investigator.

Cyclosporine was given to all subjects beginning with protocol amendment dated 29 December 2004. CSA was started the day prior to the administration of RATGAM and continued for at least 2 weeks post thymus transplantation, targeting a trough concentration of 180-300 ng/mL. CSA was then weaned over 8 weeks if the post-transplantation T cell count remained  $<4000/\text{mm}^3$ . If the T cell count rose to over  $4000/\text{mm}^3$ , CSA was held at 180-300 ng/mL and then weaned after the T cell count dropped below  $4000/\text{mm}^3$ .

Study 884.1 was implemented to address the specific needs of 1 subject. In this protocol, the planned immunosuppressive regimen was modified to include cyclophosphamide in addition to RATGAM and CSA.

#### **6.1.2.5 Sites and Centers**

This study was conducted at a single center (Duke University) in the United States between Feb 15, 2002 and Feb 5, 2007.

#### **6.1.2.6 Surveillance/Monitoring**

Subjects were hospitalized for ~2 months after RVT-802 transplantation for monitoring. A biopsy of the RVT-802 allograft was obtained at 2 to 3 months after transplantation under general anesthesia in the operating room, if the subject's medical condition permitted. The site of the allograft was exposed and several samples of tissue, approximately 4 x 4 mm each, were removed. The biopsied tissue was stained with antibodies to keratin, CD3, CD1a (cortical thymocytes), and Ki-67 (proliferation marker of cortical thymocytes) to evaluate thymopoiesis.

Interval history and physical examination were performed weekly during the post-transplant hospitalization. Careful attention was directed to the height of the subjects since autoimmune thyroid disease can first be detected when the height stops increasing. Laboratory evaluation included a CBC with differential which was assessed twice a week for the first 2 weeks after thymus transplantation, then weekly until Week 12. A sudden increase in the ALC could indicate GVHD, growth of pre-existing host clones, or B cell lymphoproliferative disease. Flow cytometry, along with a CBC with manual differential, was evaluated once or twice a week to assess T, B, and natural killer (NK) cell numbers. The frequency of the tests then

decreased to every other week. This monitoring also provides information as to whether abnormal B cell proliferations were occurring. Evaluation of naïve T cells was included since increases in T cells ( $>3000/\text{mm}^3$ ) post-transplant could signal GVHD.

Subjects were then discharged to their referring physician and follow-up care and study assessment were conducted at the subject's home facility. Study evaluations were conducted at Months 4, 5, 6, 8, 10, 12, 15, 18, 21 and 24. These evaluations included CBC with differential, flow cytometry to assess lymphocyte subsets, immunoglobulin, TCR $\beta$ V repertoire diversity, T cell proliferative responses to mitogen/antigen, However, compliance with the testing schedule depended upon the primary physician.

#### **6.1.2.7 Statistical Considerations & Statistical Analysis Plan**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this and the 9 other clinical studies that are included in this BLA given the legacy data status and similarities across the 10 clinical studies in the RVT-802 program. The endpoints specified in the program-wide SAP were given precedence over the analyses originally planned for this study (See Sec 6.1.2.7.4 Endpoints and Criteria for Study Success). The primary endpoints as defined in the SAP were survival at 1- and 2-year post-transplantation.

Summary statistics (n, mean, standard deviation [SD], median, quartiles, and ranges) were presented for continuous variables and frequencies and percentages were presented for categorical variables. As applicable, continuous variables were dichotomized to reflect whether they achieved preset threshold values and then summarized using methods for categorical variables. Descriptive summaries were provided for the overall sample.

##### **6.1.2.7.1 Study Population and Disposition**

There were 11 subjects enrolled in Study 884 and a single subject enrolled in Study 884.1 for a total population of 12 subjects. Subject (b) (6) enrolled in Study 884.1 had cDGA and received a modified immunosuppression including cyclophosphamide as this subject had pre-existing GVHD caused by unirradiated blood transfusions received prior to study enrollment. This subject's cDGA phenotype could not be determined because of the pre-existing GVHD.

The Full Analysis Set (FAS) included all 12 subjects who received RVT-802.

The Efficacy Analysis Set (EAS) included 11 subjects as Subject (b) (6) was excluded because the subject had received 2 fetal thymus tissue transplants prior to this study.

The Efficacy Analysis Set – complete DGA (EAS-cDGA) included ten subjects as the following two subjects were excluded.

- Subject (b) (6) was excluded from the EAS-cDGA analysis set as this subject had received 2 prior fetal thymus transplants.
- Subject (b) (6) was excluded from the EAS-cDGA analysis set as this subject had FOXN1 deficiency.

##### **6.1.2.7.2 Protocol Deviations**

There was one major protocol deviation in this study. Subject (b) (6) was administered a single dose of RATGAM prior to the availability of immunoscope results required for determining enrollment eligibility. The pre-transplant treatment was cancelled. Subsequently, it was confirmed that the subject required RATGAM and treatment with RATGAM was reinitiated.

The subject received an additional 3 doses of RATGAM (per protocol) prior to receiving RVT-802.

There were no protocol deviations that impacted subject safety or the integrity of this study.

#### **6.1.2.7.3 Demographics & Disease Characteristics**

The EAS comprised 11 subjects, one fewer than the FAS. The subject excluded from the EAS (Subject (b) (6)) was the oldest subject in the study, but the median values for body measurements in the EAS and FAS were comparable. The median age on the day of RVT-802 transplantation in the EAS was 197 days (range 55 to 424 days) as compared to 220.5 days in the FAS. The median age of the 12 subjects in the FAS on the day of RVT-802 transplantation was 220.5 days (range 55-4741 days). Subject (b) (6) was the oldest subject at 4741 days (13 years old) of age on the day of transplantation.

The majority of subjects (8 subjects, 67%) were male while the remaining four subjects (33%) were female. Eleven subjects (92%) were white and 1 subject (8%) was Asian. Three of the white subjects (25%) were of Hispanic/Latino ethnicity. The median BSA was 0.308 m<sup>2</sup> (range: 0.245 to 1.141).

The median age of diagnosis of the 12 subjects in the FAS was 38 days (range: 0 to 338). Subjects diagnosed on Day 0 were diagnosed based on the presence of clinical features consistent with DGA; the diagnosis of cDGA was later confirmed by flow cytometry. In this study, eleven subjects (92%) had cDGA and one subject (Subject (b) (6)) had FOXN1 deficiency. Seven of the 11 subjects with cDGA have the atypical phenotype while the remaining 3 subjects have typical cDGA. An additional subject (Subject (b) (6)) was treated under an individual treatment plan (study 884.1) because of GVHD from prior blood transfusions, and thus the phenotype of cDGA could not be determined.

CHARGE syndrome was reported for 4 subjects and hemizygous deletion of chromosome 22q11.2 was reported for 3 subjects. Four subjects had no known cDGA gene mutation or syndrome association. One subject had FOXN1 deficiency. The mothers of 2 subjects had type II diabetes.

All subjects had a history of diminished T cell count for age, 10 subjects had a congenital cardiac anomaly or cardiothoracic vascular anomaly, and 10 subjects had hypocalcemia. Growth or mental retardation was reported for 7 subjects. There were 6 subjects who underwent cardiac surgery prior to RVT-802 therapy; the absence of thymus was confirmed in 1 subject and the presence of thymic tissue was either not reported or unknown for the other 5 subjects.

The medical history of this pediatric FAS study population reflected the intensive medical challenges and surgical interventions due to the subjects' background conditions. Individual medical history PTs most frequently reported were consistent with the disease under study. The most common disease manifestations included hypocalcemia (n=10), gastroesophageal reflux disease (n=8), gastrointestinal tube insertion (n=8), and hypoparathyroidism (n=8).

All subjects had a history of infection prior to study transplant procedures. The most frequent pre-transplantation infection was staphylococcal bacteremia in 4 subjects (33%). Enterococcal bacteremia, pneumonia, and rotavirus gastroenteritis were each reported for 3 subjects (25%).

All subjects received RATGAM and methylprednisolone. The protocol was amended after enrollment of Subject (b) (6) to include cyclosporine treatment pre- and post-transplantation. Cyclosporine was administered to 6 subjects (50%) and prednisolone to 5 subjects (42%). One subject (Subject (b) (6) with pre-existing GVHD from a prior unirradiated blood transfusion) received cyclophosphamide in addition to RATGAM, CSA, methylprednisolone, and prednisolone, per an individualized treatment Protocol 884.1.

Six of the 12 subjects in the FAS had a skin biopsy, and T cells were detected in each of these subjects consistent with the atypical cDGA subject population of this study.

**6.1.2.7.4 Endpoints and Criteria for Study Success**

In the original protocol, there were no predefined criteria for study success as this was a single arm study. However, a single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this study as well as the 9 other clinical studies planned for inclusion in this BLA. The endpoints specified in the program-wide SAP were given precedence over the analyses planned in the protocol. Thus, all 10 CSRs have the same common primary endpoint: survival at 1-year and 2-year post-transplant >50% using a binomial exact test. Furthermore, a Kaplan-Meier survival analysis was also performed with median follow-up time post-transplant for all subjects and median survival time post-transplant for the subjects who died during the study being reported.

The secondary efficacy endpoints included CD3, CD4, CD8, naïve CD4, and naïve CD8 cell counts; proliferative T cell responses to mitogens/antigens (PHA, ConA, Sol CD3, Immob CD3, tetanus toxoid, and *Candida*); TREC; TREG, TCR repertoire variability; and biopsy of RVT-802. Sol CD3, Immob CD3, TREG, and TRECs were not measured (or not consistently measured) in this study. Descriptive summaries were calculated at baseline, Year 1 and Year 2 post-transplantation as data permitted.

**6.1.2.8 Efficacy Analyses**

**6.1.2.8.1 Primary Endpoint**

In the EAS, with no subject being censored, 9 of 11 subjects (81.8%) were alive at 1 year after RVT-802 transplantation. The exact binomial test with null hypothesis that no greater than 50% of subjects would survive at Year 1 gave a 95% confidence interval (CI) of [0.48, 0.98] with a p-value of 0.0327 (Table 11). The results of the binomial exact test at Year 2 were the same as Year 1 since all EAS subjects who survived at least 1-year post-transplant were also alive at 2 years.

**Table 11: Survival at Year 1 Post-Transplantation (Binomial Exact Test)**  
(Applicant’s Table)

	<b>EAS-cDGA (N = 10)</b>	<b>EAS (N = 11)</b>	<b>FAS (N = 12)</b>
Alive at Year 1, n (%)	8 (80.0)	9 (81.8)	10 (83.3)
Dead at Year 1, n (%)	2 (20.0)	2 (18.2)	2 (16.7)
Censored at Year 1, n (%)	0	0	0
95% CI <sup>a</sup>	0.44, 0.97	0.48, 0.98	0.52, 0.98
One-Sided P-value <sup>a</sup>	0.0547	0.0327	0.0193

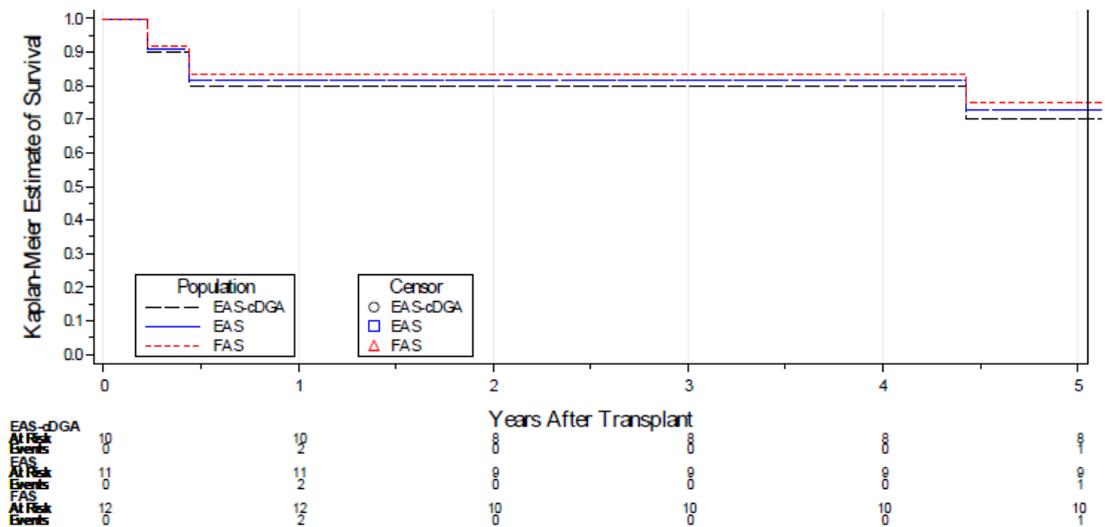
In the EAS-cDGA, 8 of 10 subjects (80.0%) were alive 1 year after RVT-802 transplantation with no subject being censored. The exact binomial test with null hypothesis that no greater

than 50% of subjects would survive at year 1 gave a 95% CI of [0.44, 0.97] with a p-value of 0.0547. Because all EAS-cDGA subjects who survived at least 1-year posttransplant were also alive at 2 years, the results of the binomial exact test at Year 2 were the same as Year 1.

The median follow-up for all subjects in the EAS was 12.3 years and ranged from 82 to 5391 days (14.7 years) after RVT-802 transplantation. A Kaplan-Meier survival estimate by year is presented in Figure 2. Three subjects died over the course of the study including 2 subjects within 6 months of transplantation. The third subject died 1617 days (approximately 4.4 years) post-transplantation. The median survival time for subjects who died was 160 days and ranged from 82 to 1617 days after RVT-802 transplantation. The estimated Kaplan-Meier survival rate at Year 1 post-transplant was 0.82 with a 95% CI of [0.447, 0.951]. Because all subjects who survived at least 1-year post-transplant were still alive through at least 4 years post-transplantation, the Kaplan-Meier estimates of survival were the same at Years 2, 3, and 4. The estimated Kaplan-Meier survival rate at Year 5 post-transplantation was 0.73 with a 95% CI of [0.371, 0.903].

In the EAS-cDGA, the estimated Kaplan-Meier survival rate at Year 1 post-transplant was 0.80 with a 95% CI of [0.409, 0.946]. Because all subjects who survived at least 1-year post-transplant were still alive through at least 4 years post-transplantation, the Kaplan-Meier survival estimates were the same at Years 2, 3, and 4 post-transplant. In the EAS-cDGA, the estimated Kaplan-Meier survival rate at Year 5 post-transplantation was 0.70 with a 95% CI of [0.329, 0.892].

**Figure 3: Kaplan-Meier Survival**  
(Applicant's Figure)



**6.1.2.8.2 Secondary Endpoints**

There were several non-survival related efficacy endpoints assessed in this study. However, the data collected for some of the planned secondary endpoints were limited because subjects were transferred back to the care of their referring pediatric physician (~2 to 3 months post-transplantation).

**Naïve CD3, CD4, and CD8 Cell Counts**

The development of naïve and total T cells in the peripheral blood was monitored by flow cytometry. Few subjects had data regarding naïve T cells at baseline since the subjects were athymic. Naïve CD3 cell count results were available for 1 EAS subject at baseline and Year 1 and no subjects at Year 2. The naïve CD3 cell counts for that subject at baseline and Year 1 were 0 cells/mm<sup>3</sup> and 350 cells/mm<sup>3</sup>, respectively.

For naïve CD4 and CD8 cells, results were available at Year 1 and Year 2. At baseline the median naïve CD4, and CD8 cell counts were 5 cells/mm<sup>3</sup> (N=11; range: 1 to 35), and 22 cells/mm<sup>3</sup> (N=8; range: 2 to 46), respectively. The median counts increased to 289 cells/mm<sup>3</sup> (N=7; range: 90 to 677) for naïve CD4 cells and 79 cells/mm<sup>3</sup> (N=7; range: 20 to 237) for naïve CD8 cells at Year 1, reflecting a median increases from baseline of 258 cells/mm<sup>3</sup> (N=7; range: 81 to 675), and 38 cells/mm<sup>3</sup> (N=4; range: 18 to 51) for naïve CD4 and CD8 cells, respectively. At Year 2, the median naïve CD4 and CD8 cell counts were 361 cells/mm<sup>3</sup> (N=3; range: 202 to 858) and 131 cells/mm<sup>3</sup> (N=3; range: 129 to 275), respectively, showing increases again compared to Year 1 with 359 cells/mm<sup>3</sup> (N=3; range: 194 to 856) for naïve CD4 cells. No results for changes from baseline were available for naïve CD8 cells.

#### **Total CD3, CD4, and CD8 Cell Counts**

Subjects enrolled in this study had elevated total T cell counts at baseline indicating the need for immunosuppression. These elevated T cell counts were usually due to an oligoclonal T cell population that was not thymically derived. Given the elevated total T cell counts present at baseline, change from baseline values for total T cell counts were not considered clinically meaningful in this study.

At baseline, the median CD3, CD4, and CD8 cell counts were 1011 cells/mm<sup>3</sup> (N=11; range: 29 to 7384), 473 cells/mm<sup>3</sup> (N=11; range: 11 to 2382), and 50 cells/mm<sup>3</sup> (N=11; range: 0 to 4594), respectively. Among the 7 subjects who had cell count results at Year 1, the median CD3, CD4 and CD8 counts were 941 (range 551 to 1188 cells/mm<sup>3</sup>), 603 (range 307 to 898 cells/mm<sup>3</sup>) and 174 (range 113 to 312 cells/mm<sup>3</sup>) cells/mm<sup>3</sup>, respectively. At Year 2 (N=3), the median CD3, CD4, and CD8 were comparable to the results for the respective parameters observed at Year 1.

#### **Other Lymphocyte Counts**

Total cell counts and changes from baseline in ALC, B cells, NK cells,  $\alpha\beta$  T cells,  $\gamma\delta$  T cells and double negative (DN) T cells in the EAS are summarized in Table 12. The median reported ALC was 3193 cells/mm<sup>3</sup> (N=11; range: 774 to 6448) at baseline, 2226 cells/mm<sup>3</sup> (N=7; range: 1225 to 2920) at Year 1 and 2734 cells/mm<sup>3</sup> (N=4; range: 1280 to 3714) at Year 2 post-transplant. Although no increase of the median of ALC from baseline to Year 1 and Year 2 post-transplant was observed, the reported median values of ALC at Year 1 and 2 were still within the normal reference range for age (i.e., 2000 to 6000 cells/mm<sup>3</sup>).

**Table 12: Lymphocyte Subsets (Median in cells/mm<sup>3</sup>)**  
(Reviewer’s Table)

	ALC	B-cell	NK-cell	αβ T cell	γδ T cell	DN T cell
<b>Baseline</b>	3193 (n=11)	552 (n=11)	379 (n=11)	861 (n=11)	25 (n=11)	168 (n=11)
<b>Year 1</b>	2226 (n=7)	714 (n=7)	333 (n=7)	862 (n=7)	44 (n=7)	73 (n=7)
<b>Year 2</b>	2734 (n=4)	737 (n=3)	212 (n=4)	750 (n=3)	60 (n=3)	75 (n=3)

The median number of B cells increased from 552 cells/mm<sup>3</sup> (N=11; range: 84 to 2734) at baseline to 714 cells/mm<sup>3</sup> (N=7; range: 514 to 1486) at Year 1 and 737 cells/mm<sup>3</sup> (N=3; range: 531 to 1734) at Year 2 which was within the normal range for age.

The median values for NK cells in the EAS decreased from a median of 379 cells/mm<sup>3</sup> at baseline (N=11, range: 276 to 2029) to 333 cells/mm<sup>3</sup> at Year 1 (N=7, range: 181 to 1274) and to 212 cells/mm<sup>3</sup> at Year 2 (N=4, range: 89 to 309) at Year 2, but remained within the normal range for age.

The results for other T cell markers including γδ, αβ cells, and DN T cell counts generally did not change over time.

**T Cell Proliferative Response to Phytohemagglutinin**

The median proliferative response to PHA was 32,404 cpm (range: 137 to 110,580) at baseline. In general, subjects showed a normal PHA response (i.e., greater than 75,000 cpm) within 2 years after transplantation. Of subjects with data available at only 1 year, 1 subject (Subject <sup>(b)</sup>(6)) had a lower than anticipated T cell proliferative response to PHA. This subject reported a PHA response of 8,595 cpm 348 days after transplantation. A normal response to PHA was not noted for this subject until 726 days after transplantation when a response of 263,656 cpm was reported.

**6.1.2.8.3 Subpopulation, Exploratory, and Post Hoc Analyses**

There was no subpopulation, exploratory or post hoc analyses conducted for this study.

**6.1.2.8.4 Dropouts and/or Discontinuations**

A total of 2 subjects in the FAS discontinued from the study within 2 years of RVT-802 transplantation due to death.

**6.1.2.9 Safety Analyses**

**6.1.2.9.1 Methods**

The safety population consisted of 12 subjects in the FAS. All safety analyses included available data reported within 2 years of transplantation through 31 December 2017. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. AEs and SAEs were summarized separately by presenting the number and percentage of subjects having any event, having a related event, having an event in each MedDRA system organ class (SOC) and preferred term (PT), having each individual event and the intensity, relationship and outcome of each event.

The number of events was also presented. A subject with more than one occurrence of the same AE in a particular SOC was counted only once in the total of those experiencing AEs in that particular SOC. If a subject had the same AE at more than one severity, or with more

than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug was given precedence. Any missing severity, causality, or outcome was not imputed and classed as unknown. Summaries classifying events according to severity and relationship were presented. Related events were defined as events that were definitely, probably, or possibly related to study treatment or with an unknown relationship.

Non-infection-related AEs and SAEs were graded (Grades 1-5) according to the CTCAE (version 3.0). Infection-related AEs were evaluated using either CTCAE criteria or criteria defined in the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) definitions of infection severity. Infection-related AEs with BMTCTN severity  $\geq$  severe were included in the analysis of AEs of Grade  $\geq$  3. Life-threatening infection-related AEs with an outcome of fatal were reported as Grade 5 events in the summary tables. For the purposes of summarization, all AEs including infection-related AEs, reported in the first 2 years post-transplant, were included in AE summary tables unless otherwise specified.

Adverse events of special interest (AESI) were summarized by SOC and PT, and included infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas.

#### **6.1.2.9.2 Overview of Adverse Events**

All 12 subjects in the study had at least 1 AE and at least 1 AE of  $\geq$  Grade 3 in intensity. In addition, all subjects had at least 1 study treatment-related AE (TEAE). The TEAE was rated as severe in intensity in eight subjects (67%) and life-threatening in 2 subjects (17%). There were 206 AEs within 2 years of transplant. The most frequent AEs were in the SOCs of infections and infestations (12 subjects [100%]), investigations (10 subjects [83%]), administration site conditions (10 subjects [83%]), and skin and subcutaneous tissue disorders (10 subjects [83%]).

#### **Frequency of Adverse Events**

A summary of the most frequent AEs ( $>25\%$  of subjects) within 2 years of transplantation is given in Table 13. Pyrexia was the most frequent AE in the study (10 subjects [83%], 24 events). Other frequent AEs included the following which were observed in 5 subjects (42%) each: device-related infection, thrombocytopenia, *Clostridium difficile* colitis, ALT increased, anemia, and rash. Most of the other more frequent AEs were infection-related or abnormal laboratory values.

**Table 13: AEs Reported >25% of Subjects within 2 Years of Transplantation**  
(Applicant's Table)

Preferred Term	FAS	
	(N = 12)	N (%) E
Number of AEs	12 (100.0)	206
Pyrexia	10 (83.3)	24
Device-related infection	5 (41.7)	8
Thrombocytopenia	5 (41.7)	7
Clostridium difficile colitis	5 (41.7)	6
Alanine aminotransferase increased	5 (41.7)	5
Anaemia	5 (41.7)	5
Rash	5 (41.7)	5
Hypoxia	4 (33.3)	8
Urinary tract infection enterococcal	4 (33.3)	8
Blood creatinine increased	4 (33.3)	5
Viral upper respiratory tract infection	4 (33.3)	5
Blood alkaline phosphatase increased	4 (33.3)	4
Staphylococcal bacteraemia	4 (33.3)	4

**Relationship to Study Treatment**

Study treatment-related adverse events were defined as AEs the Investigator considered definitely, probably, or possibly related to study treatment and events that had an unknown relationship to study treatment. All AEs related to the use of RATGAM, steroids or CSA and all AEs related to anesthesia or fluid management for transplantation, as judged by the Investigator, were considered study-related AEs. The Investigator generally considered autoimmune diseases diagnosed after RVT-802 transplantation to be possibly related to RVT-802 transplantation given the mechanism of RVT-802 and the development of thymic function.

All 12 subjects had at least 1 AE considered related to study treatment, and a total of 27 AEs were considered related to study treatment. No study treatment-related AE was observed in more than 3 subjects (25%) and there were no notable trends in study treatment-related AEs in any SOC. The most frequent study treatment-related AEs, which were each reported for 3 subjects (25%, 3 events), were hypomagnesemia (related to calcineurin inhibitor therapy), cytokine release syndrome (related to RATGAM), and hypertension (related to calcineurin inhibitor therapy). Treatment-related rash and thrombocytopenia were reported for 2 subjects (17%; 2 events).

Of the 2 treatment-related rashes, one (Subject (b) (6)) occurred with the initiation of RATGAM prior to RVT-802 and was considered related to RATGAM. The other (Subject (b) (6)) was considered possibly related to RVT-802 treatment. Of the 2 treatment-related thrombocytopenia, one event reported in Subject (b) (6) occurred 3 days prior to RVT-802 transplant and was considered related to the use of cyclophosphamide. The second event of thrombocytopenia (Subject (b) (6)) was considered potentially autoimmune in nature.

**Severity of Adverse Events**

There were 86 AEs of Grade ≥ 3 with all subjects in the study having at least 1 AE Grade ≥ 3. The most frequent AEs of Grade ≥ 3 by SOC were infections and infestations (10 subjects [83%], 35 events) and blood and lymphatic system disorders (7 subjects [58%], 10 events). The most frequent AEs of Grade ≥ 3 were anemia (5 subjects [42%], 5 events), hypoxia (4 subjects [33%], 8 events), and device-related infection (4 subjects [33%], 7 events). Pyrexia and neutropenia were observed for 3 subjects (25%; 3 events). No other Grade ≥ 3 AE was observed for more than 2 subjects.

**Infection-related Adverse Events**

A summary of infection-related AEs reported within 2 years after transplantation is provided in Table 14. All 12 subjects had at least 1 infection-related AE, including 9 subjects (75%) who had a severe infection-related AE, for a total of 63 infection-related AEs reported within the first 2 years post-transplantation. The most frequent infection-related AEs were device-related infection (5 subjects [42%]), *Clostridium difficile* colitis (5 subjects [42%]), enterococcal urinary tract infection (4 subjects [33%]), viral upper respiratory tract infection (4 subjects [33%]), and staphylococcal bacteremia (4 subjects [33%]). No other infection-related AE was observed for more than 2 subjects. One subject (Subject (b) (6); RSV infection) had a fatal infection-related AE prior to the development of thymic function (onset 151 days post-transplant).

**Table 14: Infection-Related AEs within 2 Years Transplant (≥ 25% Subjects)**  
(Applicant’s Table)

Preferred Term	FAS (N = 12)	
	N	(%) E
Number of infection-related AEs	12 (100.0)	63
Device-related infection	5 (41.7)	8
Clostridium difficile colitis	5 (41.7)	6
Urinary tract infection enterococcal	4 (33.3)	8
Viral upper respiratory tract infection	4 (33.3)	5
Staphylococcal bacteraemia	4 (33.3)	4

**6.1.2.9.3 Deaths**

Three subjects (25.0%) died during the study that were unrelated to study treatment.

- Subject (b) (6) cardio-respiratory arrest; 1617 days after RVT-802 transplantation.
- Subject (b) (6) hypoxia; 82 days after RVT-802 transplantation.
- Subject (b) (6) respiratory failure due to RSV infection; 160 days after RVT-802 transplantation.

**6.1.2.9.4 Nonfatal Serious Adverse Events**

Eleven subjects had at least 1 SAE with a total of 3 SAEs; Four subjects with a life-threatening SAE and 3 subjects with a fatal SAE including 2 subjects in the first 2 years post-transplant (Subjects (b) (6)). The most frequent SAEs were in the SOC of infections

and infestations (7 subjects [58%], 16 events). Hypoxia was the most frequent SAE (4 subjects [33%], 7 events). No other SAE was reported for more than 3 subjects.

#### **6.1.2.9.5 Adverse Events of Special Interest (AESI)**

Adverse Events of Special Interest for this study were defined as cancers, GVHD, rashes, autoimmune diseases, and granulomas. Ten subjects (83%) had 22 AESIs. The most frequent AESI were rash (5 subjects [42%], 5 events) and thrombocytopenia (5 subjects [42%], 7 events). Rash and thrombocytopenia were considered treatment-related for 2 of 5 subjects and for the 3 subjects who had cytokine release syndrome. All other AESI occurred in single subjects. No subject developed a cancer or granuloma during the study.

There was an AE of Omenn syndrome (verbatim term: autologous GVHD) in Subject <sup>(b) (6)</sup> who had *FOXN1* deficiency. It occurred 62 days post-transplantation and was considered resolved after 44 days. This subject's endoscopy/colonoscopy on Day 99 post-transplant showed a lack of disaccharidases in the small bowel and scattered apoptotic cells in the gut consistent with mild GVHD. The event was unrelated to the study treatment. It was deemed possible that this event was pre-existing. The subject's T cell chimerism was all recipient (ie: self) prior to transplantation as well as a high proliferative response to PHA (>100,000 cpm). It was likely these T cells were contributing to the gut disease but could not be confirmed as the subject also had bacillus Calmette-Guerin (BCG) infection and rotavirus in the gut.

#### **6.1.2.9.6 Vital Signs & Physical Examination**

Vital sign measurements provided limited information regarding subject safety over the course of this study. The most frequent vital sign AE was pyrexia, which was observed for 10 subjects (83%) and was the only AE which assessed as Grade  $\geq 3$  for more than 1 subject (3 subjects, 25%). The only other vital sign AE that was treatment-related for more than 1 subject was hypertension (3 subjects, 25%).

Vital sign related SAEs included supraventricular arrhythmia and hypotension, each in 1 subject (8%, 1 event) and pyrexia (2 subjects [17%], 2 events).

#### **6.1.2.9.7 Clinical Laboratory Results**

These infants with congenital athymia were enrolled with a history of abnormal laboratory results that continued during the study. Analyses of individual safety laboratory parameters assessed in the study showed no clinically meaningful overall changes from baseline in this population. The most frequent abnormal laboratory result AEs were increased ALT, thrombocytopenia, and anemia, with each reported in 5 subjects (42%).

There were only two laboratory AEs that were related to study treatment for more than 1 subject: hypomagnesemia (3 subjects, 25%), and thrombocytopenia (2 subjects, 17%). Abnormal laboratory result AEs that had a maximum intensity of Grade 3 included anemia (5 subjects, 42%), increased ALT (2 subjects, 17%), and neutropenia (2 subjects, 17%). The following AEs  $\geq$  Grade 3 were reported for single subjects (8%): increased blood creatinine, increased AST, decreased blood albumin, increased blood sodium, hypomagnesemia, hypercalcemia, hypernatremia, cytokine release syndrome, hyperbilirubinemia, and thrombocytopenia.

Abnormal laboratory result AEs of Grade  $\geq 3$  related to study treatment were increased ALT, thrombocytopenia, hypomagnesemia increased WBC, neutropenia, and cytokine release

syndrome. Thrombocytopenia was the only abnormal laboratory AE of Grade  $\geq 3$  that was reported for more than a single subject.

There were 4 abnormal laboratory results that were considered Grade 4 (life-threatening) SAEs. Each was reported for single subjects (8%): thrombocytopenia, decreased WBC, hypoglycemia, and neutropenia. In addition, there were two abnormal laboratory results of any grade that were considered SAEs: increased AST and thrombocytopenia.

#### **6.1.2.10 Study Summary and Conclusions**

Study 884 was the first RVT-802 study to include immunosuppression as part of the study treatment. The study treated 12 subjects with congenital athymia including 1 subject with FOYN1 deficiency and 11 subjects with cDGA (7 atypical phenotype, 3 typical phenotype and one additional subject of unknown cDGA phenotype). Subjects were administered cyclosporine and/or steroids prior to and after RVT-802 transplantation as clinically indicated, to suppress the expansion of oligoclonal T cells and the associated morbidity from rash, lymphadenopathy, and hepatomegaly. An additional subject was treated with additional immunosuppression including cyclophosphamide under an individual treatment plan (Study 884.1) because of pre-existing GVHD from prior blood transfusions.

The primary efficacy analysis (in the EAS) showed 9 of 11 subjects (82%) alive at 1- and 2-year post-transplant with 8 of 11 subjects (73%) remaining alive at the end of the follow-up period encompassed by this report, with a median post-transplant follow-up of 4507 days (approximately 12 years). There was supporting evidence of thymic function as evidenced by thymopoiesis on RVT-802 biopsy, the development of naïve T cells, improved proliferative response to mitogen/antigen, and increased T cell receptor diversity.

RVT-802 was safe and tolerable as the safety profile was consistent with this population of pediatric, immunocompromised subjects who entered the study with extensive individual histories of serious medical and surgical conditions. The AEs that were considered related to study treatment included those related to peri-transplant treatments/procedures, immunosuppressive therapy, and autoimmune related conditions. The development of the latter may be related to RVT-802 given the mechanism of action of RVT-802 and the development of thymic function.

In conclusion, the safety and efficacy data support the use of RVT-802 with immunosuppression in subjects with congenital athymia, including those with cDGA and FOYN1 deficiency.

#### **6.1.3. Study 931: Thymus and Parathyroid Transplantation for Complete DiGeorge Syndrome**

##### **6.1.3.1 Objectives**

The objectives of the study were to assess:

- parathyroid function after parathyroid allotransplantation into infants with complete DiGeorge anomaly (cDGA)
- development of immune function in the recipient
- safety and tolerability of the procedures.

### 6.1.3.2 *Design Overview*

This was a Phase 1, single-center, open-label, non-randomized study. The study initially included only subjects diagnosed with typical cDGA but subjects with atypical cDGA were added with an 20 July 2005 protocol amendment.

### 6.1.3.3 *Study Population*

#### Inclusion Criteria

1. Male or female subjects <24 months of age
2. The subject's parents signed the informed consent form (ICF).
3. The subject's parents agreed to central line placement if recommended by Investigator.
4. At least one of the subject's parents agreed to be a parathyroid donor.
5. The subject's parents agreed to have the infant stay in close proximity to DUMC until the RVT-802 biopsy was performed at 2 to 3 months after transplantation and agreed to return for the follow-up RVT-802/parathyroid biopsy if either tissue stopped functioning between 3 and 1 months after transplantation.
6. The subject had to have circulating CD3+ T cells by flow cytometry <50/mm<sup>3</sup> OR circulating CD3+ T cells that were also positive for CD45RA and CD62L <50/mm<sup>3</sup> or < 5% of total T cells, as evidenced by 2 studies showing similar findings.
7. The subject had hypoparathyroidism requiring calcium supplementation to maintain ionized calcium >1.0 mmol/L OR the intact PTH was below the lower limit of normal when the ionized calcium was <1.2 mmol/L. The intact PTH was measured twice before transplantation. Any of the following defects were noted:
  - Heart defect
  - 22q11.2 hemizygosity
  - 10p13 hemizygosity
  - CHARGE (Coloboma, heart defect, choanal atresia, genital hypoplasia, growth or development retardation, ear anomalies/ deafness) syndrome
  - Abnormal ears plus mother with diabetes (type I, type II, or gestational)
8. To meet the criteria of typical cDGA, the subject's PHA response had to be tested twice. If the proliferation was >50,000 cpm AND the subject did not have a rash with T cells on biopsy or lymphadenopathy, then the subject was treated as in Group 2 with both RATGAM and CSA. If the proliferation was <50,000 cpm, AND the subject did not have a rash with T cells on biopsy or lymphadenopathy, then the subject was treated as in Group 1 with only RATGAM.
9. To meet the criteria of atypical cDGA, the subject's PHA response was <75,000 cpm on 2 occasions. The subject must have also had a rash with T cells on biopsy and may have had lymphadenopathy. The PHA response test could have been done while the subject was on immunosuppression. These subjects were treated in Group 2 with both RATGAM and CSA. Beginning in 08/29/2005, an immunoscope and/or a full panel of T cell receptor (TCR) antibodies on flow cytometry was required prior to transplantation. There were no requirements as to the result of either test. A second assay could have been done if the T cell numbers increased or activation status changed. The reason for the second assay was to look for the predominance of a single clone that would have required more immunosuppression than was planned in the protocol. Beginning in 08/29/2005, a TCR rearrangement excision circle (TREC)

- assay was done on blood obtained prior to transplantation if the subject's clinical condition allowed sufficient blood to be drawn for this assay.
10. Thyroid testing had to be done within 1 month prior to transplantation, and if abnormal, the subject had to be on therapy, if recommended by endocrinologist.
  11. Prothrombin time and partial thromboplastin time within 1 month prior to transplantation had to be <2 x upper limit of normal (ULN)
  12. Absolute neutrophil count (ANC) within 1 month prior to transplantation had to be >500/mm<sup>3</sup>.
  13. Platelet count within 1 month prior to transplantation had to be >50,000/mm<sup>3</sup>.
  14. Aspartate transaminase (AST) and alanine transaminase (ALT) within 1 month prior to transplantation had to be <5 x ULN.
  15. Creatinine within 1 month prior to transplantation had to be <1.5 mg/dL.

#### Exclusion Criteria

1. Heart surgery conducted <4 weeks prior to projected transplantation date.
2. Heart surgery anticipated within 3 months of the proposed transplantation.
3. Rejection by the surgeon or anesthesiologist as surgical candidate.
4. Lack of sufficient muscle tissue to accept a transplant of 0.2 g/kg.
5. Prior attempts at immune reconstitution, such as bone marrow transplant or previous thymus transplantation.
6. Not committed to remaining at DUMC until the RVT-802 allograft biopsy at 2 to 3 months post-transplantation.

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

The investigational product was allogeneic cultured postnatal thymus tissue product (RVT-802) obtained from unrelated donors under the age of 9 months. The minimum dose planned for transplantation was 0.2 grams/kg recipient body weight. There was no maximum dose. In 2015, after enrollment in this study closed, the Investigational New Drug (IND) application was updated to define a dose range of (b) (4) mm<sup>2</sup> of thymus tissue per recipient BSA in m<sup>2</sup> (IND 9836 Amendment Serial Number 0209).

Subjects were treated with 1 of 2 different immunosuppression regimens depending on their T cell phenotype and function.

- Group 1: Typical cDGA subjects with a proliferative response to PHA <50,000 counts per minute (cpm) at baseline received RATGAM before transplantation and no post-transplant immunosuppression.
- Group 2: Typical cDGA subjects with a proliferative response to PHA >50,000 cpm at baseline and atypical cDGA subjects with a proliferative response to PHA <75,000 cpm at baseline received RATGAM pretransplant and CSA pre- and post-transplant.

Parathyroid tissue was not considered an investigational product in this study. The parathyroid gland was obtained from the donor parent immediately prior to implantation. One gland was transplanted per subject and there was no minimum dose. The parathyroid tissue slices were placed in the subject's quadriceps of one extremity at a site distant from the RVT-802 slices during the same surgical procedure with the exception of Subject (b) (6) who was transplanted with the parathyroid tissue at a separate time after RVT-802 implantation.

#### **6.1.3.5 Sites and Centers**

This study was conducted at a single center (Duke University) in the United States between May 31, 2004 (IRB approval date) and May 24, 2007 (enrollment closure date).

#### **6.1.3.6 Surveillance/Monitoring**

Prospective subjects were screened as an inpatient at DUMC over a period of ~4 weeks. The prospective subject was kept in reverse isolation and received PJP prophylaxis and IGIV. Pre-transplantation medical testing including a renal ultrasound, cardiac evaluation, and immunologic studies (ie: TREC, TCRV $\beta$ , flow cytometry, etc) was performed to characterize the subject's cDGA phenotype. Eligible subjects were transplanted with RVT-802 and parathyroid tissues in the quadriceps muscle under general anesthesia.

Subjects were followed as inpatients at DUMC through the time of graft biopsy at 8 to 12 weeks post-transplantation. A biopsy of the RVT-802 allograft was taken from the leg that did not receive any parathyroid tissue to ensure that no parathyroid tissue was accidentally removed. The biopsied tissue was stained with antibodies to keratin, CD3, CD1a (cortical thymocytes), and Ki-67 (proliferation marker of cortical thymocytes) to assess thymopoiesis. Subjects who were medically stable were discharged to the care of their referring physician. After discharge, blood samples were obtained for immune testing every 2 weeks until the PHA response normalized, then every 1 to 3 months through 2 years post-transplantation. Ionized calcium and PTH values were measured every 2 to 4 weeks for 1 year, then every 1 to 3 months through 2 years post-transplantation.

#### **6.1.3.7 Statistical Considerations & Statistical Analysis Plan**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this and the 9 other clinical studies planned for inclusion in this BLA given the legacy data status and similarities across the 10 clinical studies in the RVT-802 program. The endpoints specified in the program-wide SAP were given precedence over the original analyses plan.

Summary statistics (n, mean, SD, median, quartiles, and ranges) were presented for continuous variables and frequencies and percentages were presented for categorical variables. As applicable, continuous variables were dichotomized to reflect whether or not they achieved preset threshold values and then summarized using methods for categorical variables as discussed above. Descriptive summaries were provided for the overall sample. There was no imputation of missing data.

##### **6.1.3.7.1 Study Population and Disposition**

All subjects who received RVT-802 were included in the full analysis set (FAS). The efficacy analysis set (EAS) included all subjects with athymia associated with cDGA or FOXP1 deficiency, who had no prior HSCT and were treated with RVT-802. A modified efficacy analysis population (EAS-cDGA) analysis set was defined for all EAS subjects except those with FOXP1 deficiency.

Five subjects with cDGA (4 typical, 1 atypical) who did not undergo HSCT prior to receiving RVT-802 are included in this report. Four of the subjects also received a parathyroid transplant; only Subject <sup>(b) (6)</sup> did not receive the latter. All subjects met the criteria for inclusion in the FAS, EAS, and EAS-cDGA analysis populations. Data are presented for the FAS only given that the analysis populations were identical. Four subjects were alive at the most recent study follow-up, which ranged from 3683 days (10.1 years) to 4434 days (12.1 years) after transplantation. One subject was discontinued from the study due to death 289 days after RVT-802 transplantation (Subject <sup>(b) (6)</sup>; respiratory failure).

**6.1.3.7.2 Protocol Deviations**

There were no protocol deviations that impacted subject safety or the integrity of study results in this study. However, there was one major protocol deviation, related to Subject (b) (6) informed consent. The signed ICF for the parathyroid transplant surgery was not found during a review of the subject's research record approximately 1-year post-transplant. It is not known if the original ICF was not obtained or if it was obtained and subsequently lost.

**6.1.3.7.3 Demographics & Disease Characteristics**

There were 2 males and 3 females with a median age of diagnosis of 35.0 days (range: 20 days to 81 days). All were Caucasian with a median height and weight during screening of 58.5 cm (range: 55.0 cm to 65.2 cm) and 4.9 kg (range: 3.7 kg to 6.1 kg), respectively. The median BSA was 0.29 m<sup>2</sup> (range: 0.24 m<sup>2</sup> to 0.34 m<sup>2</sup>) while the median head circumference was 39.8 cm (range: 37.0 cm to 41.4 cm).

The five subjects had cDGA; 4 with the typical phenotype and 1 subject had the atypical phenotype. There was no visual evidence of a thymus for the 4 subjects who underwent heart surgery. One subject did not have the heart surgery performed prior to receiving RVT-802. All subjects had congenital cardiac anomaly or cardiothoracic vascular anomaly, hypocalcemia, and diminished T cell counts for age. Hemizygous deletion of chromosome 22q11.2 was detected in 3 subjects. No known cDGA gene mutation was identified for 1 subject and no genetic testing was performed for another subject. The mothers of 2 subjects had diabetes (one with type II and the other with gestational diabetes).

All subjects in the study had a history of hypocalcemia and 3 subjects had a history of hypocalcemic seizure. Four subjects were also anemic, and the following were each reported for 3 subjects: atrial septal defect, ventricular septal defect, gastroesophageal reflux disease, and hypoparathyroidism. All subjects in the study had a history of infection prior to study transplantation, including 2 subjects who had a history of systemic infection. Device-related infection (i.e., catheter-related infection), infection (not otherwise specified), and staphylococcal bacteremia were each reported for 2 subjects.

T cells were detected in the skin of 2 subjects (Subjects (b) (6) who had a skin biopsy performed. The presence of T cells in Subject (b) (6) was consistent with the subject's atypical cDGA phenotype. This subject's rash was not considered related to atypical cDGA. Subject (b) (6) had typical cDGA at the time of transplantation with only a few lymphocytes detected in the screening skin biopsy.

**6.1.3.7.4 Endpoints and Criteria for Study Success**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this study as well as the 9 other clinical studies planned for inclusion in this BLA. The endpoints specified in the program-wide SAP were given precedence over the analyses planned in the study protocol. Thus, all 10 CSRs have the same common primary endpoint: survival at 1-year and 2-year post-transplant >50% using a binomial exact test. Furthermore, a Kaplan-Meier survival analysis was also performed with median follow-up time post-transplant for all subjects and median survival time post-transplant for the subjects who died during the study being reported.

The Secondary efficacy endpoints (at Year 1 and Year 2 [as data permitted]) were:

- Total CD3, CD4 and CD8 cell counts
- Total naïve CD3, naïve CD4 and naïve CD8 cell counts

- Proliferative T cell responses to antigens (PHA, ConA, Sol CD3, Immob CD3, tetanus toxoid, and *Candida* skin test antigen)
- TCR repertoire variability
- TREC/regulatory T cells (TREG) (if available)
- Biopsy of transplanted thymus
- Calcium or calcitriol supplement needed at one year

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

Safety parameters including laboratory evaluations, vital signs measurements, and physical examinations were measured for 2 years post-transplant.

**6.1.3.8 Efficacy Analyses**

**6.1.3.8.1 Primary Endpoint**

Four of 5 subjects (80%) were alive 2 years after RVT-802 transplantation with one subject dying 289 days after transplantation. The primary efficacy endpoint, patient survival, was identical at Year 1 and Year 2 across analysis populations. The exact binomial test with null hypothesis that no greater than 50% of subjects would survive at Year 1 / Year 2 gave a 95% CI of [0.28, 0.99] with a p-value of 0.1875.

The median follow-up time for all subjects was 3876 days (10.6 years) and ranged from 289 to 4434 days (12.1 years) after RVT-802 transplantation. The estimated Kaplan-Meier survival rate at Year 1 post-transplant was 0.80 with a 95% CI of [0.204, 0.969]. Because all subjects who survived at least 1-year post-transplant were still alive through at least 5 years post-transplant, the Kaplan-Meier estimates of survival were the same at Years 1, 2, 3, 4 and 5 post-transplantation.

**6.1.3.8.2 Secondary Endpoints**

**Naïve CD4 and CD8 Cell Counts**

Naïve CD4 and naïve CD8 cells were detected at baseline for 1 subject and data for these parameters were available for 3 subjects at Year 1 and Year 2. Although the data were limited, naïve CD4 and naïve CD8 cells showed increases in cell counts over the course of the study with the exception of Subject <sup>(b) (6)</sup> (Table 15).

**Table 15: Naïve CD4 and CD8 Cell Counts**  
(Reviewer’s Table)

	Naïve CD4 (cells/mm <sup>3</sup> )		Naïve CD8 (cells/mm <sup>3</sup> )	
	Median	Change from Baseline	Median	Change from Baseline
<b>Baseline</b> (n=1)	8	---	1	---
<b>Year 1</b> (n=3)	333	228	138	48
<b>Year 2</b> (n=3)	360	441	148	93

**Total CD3, CD4, and CD8 cell counts**

The median total CD3 cell count (cells/mm<sup>3</sup>) was 32.0 at baseline (N=5), 775.0 at Year 1 (N=3), and 887.0 at Year 2 (N=3). For total CD4 and CD8 cell counts, cells were detected for 2 subjects at baseline and cell count data were available for 3 subjects at Year 1

and Year 2. The total CD3, CD4, and CD8 cells showed increases in cell counts over the course of the study although the data were limited (Table 16).

**Table 16: Naïve CD4 and CD8 Cell Counts**  
(Reviewer’s Table)

	CD3 (cells/mm <sup>3</sup> )		CD4 (cells/mm <sup>3</sup> )		CD8 (cells/mm <sup>3</sup> )	
	Median	Range	Median	Range	Median	Range
<b>Baseline</b>	32 (n=5)	4-1314	197 (n=2)	15-378	71 (n=2)	10-132
<b>Year 1</b>	775 (n=3)	771-790	517 (n=3)	509-535	171 (n=3)	160-175
<b>Year 2</b>	887 (n=3)	706-1115	629 (n=3)	424-768	215 (n=3)	188-219

The data collected for many of the secondary efficacy parameters including T cell proliferative response to PHA and other antigens, immunoglobulins, B-cell function, TRECS TREGS, TCR diversity, and TCR flow were too limited to draw any meaningful conclusions.

**Thymic biopsy**

Three subjects underwent a biopsy of the thymic implant, but no thymic tissue was found in the biopsy of Subject (b) (6). However, there was evidence of thymopoiesis in the biopsies from Subject (b) (6). CD1a, CD3, Ck14, and Ki-67 expressing cells were observed in both subjects and cortical medullary distinction was observed for 1 subject. There was no evidence of graft rejection for either subject.

**Parathyroid transplantation**

The parathyroid gland was not considered an Investigational Product in this study. Nonetheless, 4 subjects received both RVT-802 and a parathyroid transplant in this study with 3 subjects alive at 1-year post-transplant. Subject (b) (6) suffered a fatal respiratory failure 289 days after RVT-802 and parathyroid transplantation. Two of the 3 remaining subjects (Subjects (b) (6)) were off calcium supplementation at Year 1. Calcium supplements were restarted in Subject (b) (6) at 398 days and for Subject (b) (6) at 3533 days (9.7 years) post-transplant. Based on binomial exact test of calcium usage rate <30%, with 50.0% of subjects requiring calcium supplementation at Year 1 post-transplant, the 95% CI was [0.07, 0.93]; p = 0.6517.

Subjects (b) (6) had typical cDGA. Both subjects developed PTH values in the normal range with peak values >40 pg/mL. However, this was not sustained as both subjects eventually required calcium supplementation. Both subjects had mismatches in HLA-DRB1 as the parathyroid donor expressed an allele that was not present in either the recipient or the thymus donor. This was important because tolerance is induced by the HLA antigens expressed on recipient dendritic cells that migrate to the thymus and by the HLA antigens expressed on the thymus donor epithelium. As a result, the recipient’s T cells developing in the donor thymus were not tolerant to the mismatched parental parathyroid donor HLA Class II allele which lead to the eventual rejection of the parathyroid transplant.

Subject (b) (6) had atypical cDGA with circulating T cells that were attacking the recipient. The function of the parathyroid transplant was minimal as PTH levels only reached the normal range once, at 205 days post-transplant (19 pg/ml, the lower limit of normal was 15 pg/ml). It was likely that recipient’s pre-existing atypical T cells rejected the parathyroid gland as the

immunosuppressive regimen was probably insufficient to protect the allogeneic parathyroid prior to the formation of tolerant T cells in the donor thymus.

For Subject (b) (6), all of the HLA Class II molecules in the parental donor parathyroid were expressed either in the recipient or in the thymus donor. Thus, tolerance to HLA Class II of the parathyroid donor was expected. Subject (b) (6) was able to remain off calcium supplements for 9.7 years until he was vaccinated with the measles, mumps and rubella (MMR) vaccine. Two weeks later, parathyroid function was lost. The Investigator speculated that the measles virus led to an expansion of recipient CD8 T cells. As one third of CD8 T cells are allo-reactive, these alloreactive T cells would have attacked the Class I HLA-B\*35:03 and the HLA-C\*04:01 alleles of the parathyroid gland and destroyed the latter.

#### **6.1.3.8.3 Subpopulation, Exploratory, and Post Hoc Analyses**

There was no subgroup, exploratory, or post hoc analyses performed for this study.

#### **6.1.3.8.4 Dropouts and/or Discontinuations**

There was no subject who dropped out of this study. One subject (Subject (b) (6)) was discontinued from the study due to death from respiratory failure 289 days after RVT-802 transplantation.

### **6.1.3.9 Safety Analyses**

#### **6.1.3.9.1 Methods**

Safety data were reported through 31 December 2017 for all subjects from the beginning of the study to 2 years post-transplantation. Safety endpoints were assessed while the subject was in the hospital following transplantation and additional assessments were scheduled at Months 3, 6, 9, 12, 18, and 24.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. AEs and SAEs were summarized separately by presenting the number and percentage of subjects having any event, having a related event, having an event in each MedDRA system organ class (SOC) and preferred term (PT), having each individual event and the intensity, relationship and outcome of each event. The number of events was also presented. Any missing intensity, relationship, or outcome was classified as unknown.

A subject with more than 1 occurrence of the same AE in a particular SOC was counted only once in the total of those experiencing AEs in that particular SOC. If a subject had the same AE at more than one intensity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug was given precedence.

Summaries classifying events according to intensity and relationship were presented. Related events were defined as events that were definitely, probably, or possibly related to study treatment or with an unknown relationship.

Non-infection-related AEs and SAEs were graded (Grades 1-5) according to CTCAE (version 3.0). Infection-related AEs were evaluated using either CTCAE criteria or criteria defined in the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) definitions of infection intensity. Infection-related AEs with BMTCTN intensity  $\geq$  severe were included in the analysis of AEs of Grade  $\geq$  3.

Adverse events of special interest (AESI) were summarized by SOC and preferred term, and included infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas.

#### **6.1.3.9.2 Overview of Adverse Events**

All 5 subjects in the study had at least one AE with 4 subjects having at least one AE  $\geq$  Grade 3 in intensity within 2 years of transplantation. All subjects in the study had at least 1 infection-related AE; of these, the maximum intensity of the AE was moderate for 2 subjects and severe for 2 subjects. Three subjects had at least 1 AE that was related to study treatment; the maximum intensity of these AEs was moderate for 1 subject and severe for 2 subjects.

#### **Frequency of AEs**

The most frequent AEs were device-related infection, diarrhea, hypoxia, pyrexia, and rash, each of which affected 3 subjects. No other AE (abdominal distension, anemia, hypersensitivity, hypertension, hypothyroidism and bacterial urinary tract infection) was reported by more than 2 subjects.

#### **Relationship to Study Treatment**

Three subjects had 11 AEs that were related to study treatment (RVT-802 or parathyroid tissue or immunosuppression). All study treatment-related AEs were single occurrences and there was no concentration of study treatment-related AEs in any SOC. These were single occurrences of anemia (secondary to excessive phlebotomy), coombs autoimmune anemia, cytokine release syndrome, hypersensitivity, sinus tachycardia, autoimmune hepatitis, decreased blood cortisol, seizure, hypoxia, rash and hypertension.

AEs related to the use of RATGAM, steroids or CSA as well as those related to anesthesia or fluid management for transplantation were considered study-related AEs. These included single occurrences of decreased blood cortisol, cytokine release syndrome, hypertension, hypoxia, rash, seizure, and sinus tachycardia.

#### **Severity of AEs**

There were 22 AEs that were  $\geq$  Grade 3 in intensity reported for 4 subjects. The SOC in which Grade  $\geq$  3 AEs were most frequent (on the basis of subject count) was metabolism and nutrition disorders (3 subjects; 4 AEs). In this SOC, 1 subject had Grade  $\geq$  3 hypocalcemia (total of 2 AEs), and there were single observations of Grade  $\geq$  3 hypercalcemia and hyponatremia. Grade  $\geq$  3 device-related infection (2 AEs) and hypoxia (2 AEs) were observed for 2 subjects. No other Grade  $\geq$  3 AE was observed for more than 1 subject.

#### **6.1.3.9.3 Deaths**

One subject died during the study. Subject <sup>(b) (6)</sup> was a male with typical cDGA presenting with congenital cardiothoracic vascular anomaly, diminished T cell counts for age, dysmorphic facies, growth or mental retardation, hypocalcemia, and rib or vertebral anomalies. The subject's mother had type 2 diabetes. He was administered methylprednisolone (from 5 days to 1 day prior to transplant), and RATGAM (from 5 days to 3 days prior to transplant) before receiving RVT 802 (total dose 17870 mm<sup>2</sup>/m<sup>2</sup>) and a parathyroid transplant on Day 103 of life.

The subject was ventilator-dependent at the time of enrollment because of chest wall deformities and heart failure. Previous history included heart surgery (details not provided)

prior to RVT-802. Subject was eventually discharged back to the care of his referring physician and remained ventilator dependent throughout life. He suffered a fatal respiratory failure at 392 days of life, 289 days after RVT-802 and parathyroid transplantation.

#### **6.1.3.9.4 Nonfatal Serious Adverse Events**

Two subjects had at least 1 SAE within 2 years of transplantation. A total of 9 SAEs were reported during this period with 2 considered related to study treatment (Coombs positive hemolytic anemia and autoimmune hepatitis). Eight of the SAEs occurred in Subject (b) (6); 2 SAEs of device-related infection (central venous catheter) and 2 SAEs of hypocalcemia. The remaining 4 SAEs were single observations and there was no concentration of SAEs in any SOC. Subject (b) (6) had a single SAE of fatal respiratory failure.

#### **6.1.3.9.5 Adverse Events of Special Interest (AESI)**

A total of 4 subjects had 11 AESIs. The most frequent AESI were rash (3 subjects, 4 events), hypersensitivity (2 subjects, 2 events), and hypothyroidism (2 subjects, 2 events). No other AESI was observed for more than 1 subject. The single occurrences of rash (at the time of RATGAM therapy), cytokine release syndrome, autoimmune hepatitis, and Coombs positive hemolytic anemia were related to study treatment. No subject developed a cancer or granuloma during the study.

All subjects in the study had at least 1 infection-related AE within 2 years of transplantation. Device-related infection (4 AEs) and bacterial urinary tract infection (2 AEs) were each reported for 2 subjects. Other infection-related AEs were reported as single observations. No subjects had an infection-related AE considered related to study treatment.

#### **6.1.3.9.6 Vital Signs & Physical Examination**

The vital signs (blood pressure, pulse rate, respiration rate, body temperature) measured in this study had limited utility in characterizing subject safety over the course of the study. There were two treatment-related AEs, sinus tachycardia and hypertension, each reported for one subject, but none were considered SAEs.

#### **6.1.3.9.7 Clinical Laboratory Results**

Analyses of individual safety laboratory parameters from this study showed no clinically meaningful changes from baseline in this population. Several abnormal laboratory results were considered SAEs and included hypocalcemia (1 subject; 2 events) and a single observation of Coombs-positive hemolytic anemia. The abnormal laboratory result that were considered AEs/SAEs related to study treatment were observed in single subjects included decreased blood cortisol, Coombs-positive hemolytic anemia (SAE), and anemia.

#### **6.1.3.10 Study Summary and Conclusions**

Study 931 assessed the reconstitution of immune function following RVT-802 transplantation in five athymic recipients with cDGA; four subjects also received parathyroid transplants due to hypocalcemia. The subjects ranged in age from 3 to 9 months of age. Four of the subjects (3 who received both RVT-802 and a parathyroid transplant and 1 who received only RVT-802) were alive at the end of follow-up, ranging from 10 to 12 years after transplantation. Survival at 1- and 2-year post-transplant was 80.0% with a 95% CI of [0.28, 0.99] and a p-value of 0.1875 from the binomial exact test on a survival rate >50%. The subject who died had been ventilator-dependent since birth and died from respiratory failure secondary to bronchopulmonary dysplasia at 289 days post-transplant. The estimated Kaplan-Meier survival rate at 1-year post-transplant was 0.80 (95% CI 0.204, 0.969). The

Kaplan-Meier estimates of survival were the same at Years 1, 2, 3, 4 and 5 since all subjects who survived at least 1 year were still alive through at least 5 years post-transplantation.

The improvements in survival was accompanied by immune reconstitution as evidenced by the development of naïve T cells. The data was limited as cell counts were available for only 3 subjects within the analysis window (baseline through Year 2). Nonetheless, naïve T cell numbers increased as expected within the first 2 years post-transplant except for one subject; the reason for this is not fully understood. However, the Applicant speculated it was possibly related to the occurrence of cardiopulmonary arrest 73 days post-transplant. The associated hypoxia may have damaged the RVT-802 graft, resulting in a decreased ability to produce naïve T cells. In addition, this subject received prolonged immunosuppressive therapy for autoimmune hepatitis which may have inhibited the development of naïve T cells. This subject went on to develop low levels of naïve T cells after the 2-year assessment period, which likely enabled this subject to remain alive more than 10 years after transplantation.

These data demonstrate the ability of RVT-802 to enable immune reconstitution and patient survival but the benefits of parathyroid transplantation were less apparent. With the long-term follow-up of over 10 years, the Investigator developed an opinion regarding the suboptimal outcomes of parathyroid transplantation. The Investigator believed that full HLA Class I and Class II matching is needed for tolerance induction of a solid organ. The relevant HLAs expressed on the parathyroids must also be expressed on the recipient's bone marrow derived dendritic cells or on the donor thymus. Given the current manufacturing process, RVT-802 expressing the desired specificities cannot be obtained quickly enough to support parathyroid transplantation in patients with cDGA who are at risk of dying from infection.

The AE profile of RVT-802 was within expectations for the population under study. All AEs related to the use of RATGAM, steroids or CSA, anesthesia, or fluid management for transplantation were considered study-related AEs. In this study, these included single observations of the following: decreased blood cortisol, cytokine release syndrome, hypertension, hypoxia, rash, seizure, and sinus tachycardia.

Most of the post-transplant autoimmune conditions were related to study treatment and included single observations of autoimmune hepatitis and Coombs positive hemolytic anemia. Because RVT-802 does not result in an immediate correction of the T cell repertoire, autoimmune conditions are expected to occur until thymic function has developed at approximately 1 year. Furthermore, autoimmune conditions have been reported in subjects with partial DGA who did not receive RVT-802.

Safety laboratory and vital signs data in this population of immunocompromised pediatric subjects provided limited information regarding subject safety over the course of the study. The available results did not raise any safety concerns for subjects who were transplanted with RVT-802 and parathyroid gland in combination with immunosuppression.

In conclusion, the safety and efficacy data from this study support the use of RVT-802 in subjects with congenital athymia, including subjects with cDGA.

#### **6.1.4. Study 932: Dose Study of Thymus Transplantation in DiGeorge Anomaly**

##### **6.1.4.1 Objectives**

The objectives of the study were to:

- correlate the RVT-802 dose to immunologic parameters after thymic transplant

- assess the efficacy of RVT-802 transplantation
- assess the efficacy of parental parathyroid transplantation
- assess the safety at 1 Year after transplantation.

#### **6.1.4.2 Design Overview**

This was a Phase 2, single-site, open-label, non-randomized study.

#### **6.1.4.3 Study Population**

This study enrolled male or female subjects of any age who met the following criteria:

1. A parent or guardian of the cDGA subject signed the consent form.
2. Medical screening was completed.
3. For a diagnosis of DiGeorge Syndrome (DGA), the subject had to have one of the following:
  - Congenital heart disease;
  - Hypocalcemia requiring replacement;
  - 22q11.2 hemizyosity or 10p13 hemizyosity;
  - CHARGE (coloboma, heart defect, choanal atresia, growth and development retardation, genitourinary defects, ear defects including deafness) association or chromodomain helicase deoxyribonucleic acid (DNA) binding protein 7 (CHD7) mutation;
  - A subject with abnormal ears whose mother had diabetes (type I, type II or gestational).
4. To meet the criteria of typical cDGA the subject had to have either:
  - Circulating CD3+ T cell count by flow cytometry  $<50/\text{mm}^3$  OR;
  - Circulating CD3+ T cells that were also positive for CD45RA, CD62L and were  $<50/\text{mm}^3$  or  $<5\%$  of total T cells.

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

RVT-802 Transplantation: Subjects received an allogeneic cultured thymus tissue product (RVT-802) surgically implanted into the subject's quadriceps muscles by a pediatric surgeon in an open procedure under general anesthesia.

Parathyroid Transplantation: Subjects were eligible to receive a parathyroid transplantation in addition to RVT-802 beginning with Protocol Amendment 5. One parental donor parathyroid gland was to be transplanted into quadriceps muscle by a parathyroid surgeon or a general pediatric surgeon at the same time as RVT-802. If not possible, a follow-up surgery for the parathyroid transplant could be done between 3 and 8 weeks post-RVT-802 transplantation. However, no subject received a parathyroid transplant in this study.

#### **6.1.4.5 Sites and Centers**

The study was conducted by a single Investigator at a single site (DUMC) in the US.

#### **6.1.4.6 Surveillance/Monitoring**

Prospective subjects were screened as an inpatient at DUMC over a period of ~4 weeks. Pre-transplantation medical testing including a renal ultrasound, cardiac evaluation, and immunologic studies (ie: TREC, TCRV $\beta$ , flow cytometry, etc) was performed to characterize the subject's cDGA phenotype. Eligible subjects were transplanted with RVT-802 in the quadriceps muscle under general anesthesia.

Subjects were followed as inpatients at DUMC through the time of graft biopsy at 8 to 12 weeks post-transplantation. The RVT-802 allograft was biopsied and stained with antibodies to keratin, CD3, CD1a (cortical thymocytes), and Ki-67 (proliferation marker of cortical thymocytes) to assess thymopoiesis. Subjects who were medically stable were then discharged to the care of their referring physician. After discharge, blood samples were scheduled to be obtained for immune testing every at 3, 6, 9, 12, 18 and 24 months.

#### **6.1.4.7 Statistical Considerations & Statistical Analysis Plan**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this and the 9 other clinical studies planned for inclusion in this BLA given the legacy data status and similarities across the 10 clinical studies in the RVT-802 program. The endpoints specified in the program-wide SAP were given precedence over the analyses originally planned for this study (See Sec 6.1.4.7.4 Endpoints and Criteria for Study Success).

Summary statistics (n, mean, standard deviation [SD], median, quartiles, and ranges) were presented for continuous variables and frequencies and percentages were presented for categorical variables. Continuous variables were dichotomized to reflect whether they achieved preset threshold values and then summarized using methods for categorical variables when applicable. Descriptive summaries were provided for the overall sample. Study data through 31 December 2017 were included in the analyses for this report.

##### **6.1.4.7.1 Study Population and Disposition**

The study was terminated prior to meeting enrollment goals. The parathyroid arm was not used for two reasons. First, data from Protocol 931 indicated that for tolerance to develop to the parental parathyroid transplant, the thymus donor had to express all HLA Class II antigens in the parental donor that were not inherited by the recipient. It was not feasible to find such matched thymuses without a cryopreserved, HLA-typed thymus tissue bank and such a bank was not available. Secondly, parental CMV seropositivity was an exclusion criterion for the parathyroid donor and most parents were CMV seropositive.

A total of 7 subjects were treated in this study between 02 September 2004 (IRB approval date) to 31 December 2010 (enrollment closure date). All subjects received RVT-802. Five subjects (Subjects (b) (6)) were enrolled with no intention of parathyroid co-transplantation. Two subjects (Subjects (b) (6)) were consented to receive both RVT-802 and parathyroid transplantation. However, the potential parental parathyroid donors did not meet donor criteria, so the subjects received only RVT-802. Therefore, all 7 subjects were treated with RVT-802 but no subject was transplanted with a parathyroid gland.

The full analysis set (FAS) included all 7 subjects who received RVT-802. However, there were only 6 subjects in the efficacy analysis set (EAS) because one subject (Subject (b) (6)) was withdrawn from the study on Day 1051 of life, 379 days after transplantation. He was found to have been erroneously diagnosed with cDGA. Genetic testing performed after study discontinuation identified a homozygous deletion of DNA cross-link repair 1C (*DCLRE1C*). Defects in this gene cause a deficiency of the protein Artemis and as such the subject was diagnosed with Artemis SCID. This subject was only included in the FAS. The EAS-cDGA analysis set included all 6 EAS subjects and thus the two populations were identical.

There were two deaths on this study, Subject <sup>(b) (6)</sup> died on Day 128 after transplant and Subject <sup>(b) (6)</sup> (Artemis SCID) died on Day 1622 of life, 950 days after transplantation.

#### **6.1.4.7.2 Protocol Deviations**

There were no major or minor protocol deviations during this study that would have impacted subject safety or the integrity of the study results.

#### **6.1.4.7.3 Demographics & Disease Characteristics**

The demographic and baseline characteristics in the FAS (n=7) were similar to those in the EAS (n=6). In the former, most of the subjects were male (4 of 7) and white (5 of 7). Six subjects had cDGA with the typical phenotype and 1 subject had SCID. The median age of diagnosis was 42.0 days (range: 0-109 days) with a median age of 289 days at the time of transplantation (range: 117-672 days). The majority of subjects were diagnosed in the first few weeks of life by flow cytometry. The subject diagnosed on Day 0 (Subject <sup>(b) (6)</sup>) was diagnosed based on the presence of clinical features consistent with DGA and because the mother had 22q11.2 DS. The diagnosis was later confirmed using flow cytometry. The mothers of 4 subjects had diabetes (3 with type II and 1 with gestational diabetes). All subjects had diminished T cell counts for their age. Six subjects in the FAS had a congenital cardiothoracic anomaly and hypocalcemia. Hemizygous deletion of chromosome 22q11.2 was observed for 4 subjects (Subjects <sup>(b) (6)</sup>). One subject (Subject <sup>(b) (6)</sup>) also reported a mosaic partial trisomy at 14q; however, this genetic defect is not known to be associated with the development of cDGA. There was no visual evidence of thymic tissue for the 6 subjects who underwent cardiac surgery.

Six subjects in the FAS had a history of hypocalcemia (Subjects <sup>(b) (6)</sup>). Hypocalcemia was only temporary in Subject <sup>(b) (6)</sup>; it was suspected the subject's parathyroid gland grew so that calcium supplementation was no longer needed. Subject <sup>(b) (6)</sup> had hypocalcemia due to illness, not to hypoparathyroidism. Four subjects (Subjects <sup>(b) (6)</sup>) had hypoparathyroidism documented prior to transplantation.

Hypothyroidism developed in Subject <sup>(b) (6)</sup> prior to transplantation, and in Subject <sup>(b) (6)</sup> thirty days after transplantation.

All 7 subjects in the study had a history of infection prior to transplantation. However, only staphylococcal bacteremia (4 subjects), respiratory tract infection bacterial (2 subjects), and device-related infection (2 subjects) were reported in more than 1 subject in the FAS. With respect to the site of infection, 3 subjects had systemic infections and 3 subjects developed pneumonia.

Subjects were not prescribed immunosuppressive therapy prior to transplantation but a single subject received immunosuppressive therapy after transplant. Subject <sup>(b) (6)</sup>, a subject with SCID, had maternal T cells prior to transplantation which required immunosuppression. Following transplantation, this subject received calcineurin inhibitors, including cyclosporine and tacrolimus from Day -4 to Day 155 and methylprednisolone or prednisolone intermittently from Day 62 to Day 377.

#### **6.1.4.7.4 Endpoints and Criteria for Study Success**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this study as well as the 9 other clinical studies planned for inclusion in this BLA. The endpoints specified in the program-wide SAP were given precedence over the analyses

planned in the protocol. Thus, all 10 CSRs have the same common primary endpoint: survival at 1-year and 2-year post-transplant >50% using a binomial exact test. Furthermore, a Kaplan-Meier survival analysis was also performed with median follow-up time post-transplant for all subjects and median survival time post-transplant for the subjects who died during the study being reported.

The secondary efficacy endpoints included CD3, CD4, CD8, naïve CD4, and naïve CD8 cell counts; proliferative T cell responses to mitogens/antigens (PHA, ConA, Sol CD3, Immob CD3, tetanus toxoid, and *Candida*); TREC; TREG, TCR repertoire variability; and biopsy of RVT-802. Sol CD3, Immob CD3, TREG, and TRECs were not measured (or not consistently measured) in this study. Descriptive summaries were calculated at baseline, Year 1 and Year 2 post-transplantation as data permitted.

A planned descriptive analysis to assess calcium and calcitriol supplementation at 1 year in subjects transplanted with RVT-802 and parathyroid tissue was canceled since no subjects were transplanted with parathyroid glands in this study.

#### **6.1.4.8 Efficacy Analyses**

There were no analyses in the RVT-802 plus parathyroid group since no subject received a parathyroid transplant during this study.

##### **6.1.4.8.1 Primary Endpoint**

The primary efficacy results were survival at one and two years and the results were identical at Year 1 and Year 2 in the EAS (n=6) and FAS (n=7), respectively. No subject was censored and 5 (83.3%) and 6 (85.7%) subjects were alive in the EAS and FAS, respectively, at 2 years after RVT-802 transplantation. Subject <sup>(b) (6)</sup> died at 128 days after transplantation due to a large right parietal intracranial hemorrhage. The exact binomial test with null hypothesis that no greater than 50% of subjects would survive at Year 1/Year 2 gave a 95% CI of [0.36, 1.00] with a p-value of 0.1094.

The median follow-up time for all subjects in EAS was 3542.5 days (9.7 years) and ranged from 128 to 4165 days (11.4 years) after RVT-802 transplantation. The estimated Kaplan-Meier survival rate at Year 1 post-transplantation in EAS was 0.83 with a 95% CI of [0.273, 0.975]. Because all subjects who survived at least 1-year were still alive through 5 years, the Kaplan-Meier estimates of survival were the same at Years 1, 2, 3, 4 and 5 post-transplant.

The subject who was diagnosed with SCID and included in the FAS discontinued from the study 379 days after RVT-802 transplant due to physician decision and died 950 days (2.6 years) after transplantation. Therefore, the estimated Kaplan-Meier survival rate in the FAS at Year 1 and Year 2 post-transplantation was 0.86 (95% CI 0.334, 0.979); the estimated Kaplan-Meier survival rate at Year 3, Year 4 and Year 5 post-transplantation was 0.71 (95% CI 0.258, 0.920).

##### **6.1.4.8.2 Secondary Endpoints**

###### **Naïve CD3, CD4 and CD8 cells**

Naïve T cells were defined as those cells expressing CD45RA+ and CD62L+. There were no naïve CD4 or naïve CD8 cells detected at baseline consistent with athymia. Naïve CD3 counts at baseline were only available for two subjects with one subject having no naïve CD3 and the other subject having only 2 cells/mm<sup>3</sup>. Naïve T cell counts increased over time beginning at ~6 months after transplantation. The median naïve CD4 and naïve CD8 counts

had increased to over 200 cells/mm<sup>3</sup> at Year 1. By Year 2, the values had decreased but remained above baseline values. No data were available for naïve CD3 at Year 1. At Year 2, data were available for only one subject for whom a naïve CD3 cell count of 746 cells/mm<sup>3</sup> was reported.

**Total CD4, CD8 and CD3 Cell Counts**

In the EAS, the median total CD4, CD8 and CD3 cell counts were low (38, 2 and 28 cells/mm<sup>3</sup>, respectively) at baseline. One year after transplantation, the median CD4 cell count had increased by more than 10-fold (median: 499; range: 93 to 874), and the CD8 cell count had increased by more than 50-fold (median: 116; range: 23 to 625) relative to baseline. The CD3 cell count had increased by more than 22-fold (median: 635, range: 119 to 1947). The cell counts decreased thereafter but remained more than 5-fold higher than baseline for CD4 (median: 228; range: 76 to 798), more than 40-fold higher for CD8 (median: 97; range: 23 to 258) and more than 13-fold higher for CD3 cells (median: 373; range: 104 to 1234) at Year 2.

**Other Lymphocyte Subsets**

The following were noted for the lymphocyte subsets in the EAS (Table 16):

- ALC: median counts remained within the reference range for age at baseline and Year 1 but dropped below the 10th percentile for age at Year 2 consistent with the reported decrease in total CD3+ T cells, B cells, and NK cells.
- B cell: median counts decreased from baseline to Year 1 and to Year 2 post-transplant. However, these values were still within the normal range for age
- NK cell: median counts fluctuated over time but remained within the reference range for age
- αβ, γδ, and DN T cells: median values for these cells increased post-transplantation as compared to Baseline

**T Cell Proliferative Response to Phytohemagglutinins**

At baseline, data were available from all 6 subjects in the EAS. In the EAS, the median T cell proliferative responses to PHA at baseline was 1436 cpm. The median response at Year 1 had increased 94-fold (to 135,016 cpm). At Year 2, the median response had increased 154-fold to 220,820 cpm. These data indicate an improvement in proliferative response to PHA to the normal range (i.e. >75,000 cpm) within 2 years after transplantation.

**Table 17: Lymphocyte Subsets (Median in cells/mm<sup>3</sup>)**  
(Reviewer’s Table)

	ALC	B-cell	NK-cell	αβ T cell	γδ T cell	DN T cell
<b>Baseline</b>	2160 (n=6)	1567 (n=6)	442 (n=6)	40 (n=4)	5 (n=4)	4 (n=11)
<b>Year 1</b>	2247 (n=4)	999 (n=4)	649 (n=4)	611 (n=4)	25 (n=4)	4 (n=7)
<b>Year 2</b>	822 (n=3)	436 (n=3)	180 (n=3)	308 (n=3)	57 (n=3)	2 (n=3)

**T Cell Proliferative Response to Other Antigens**

The T cell proliferative response to other antigens including: Con A, Immo CD3, soluble CD3, tetanus toxoid and *Candida* skin test antigen were assessed. The data on response to ConA was available from 4 subjects at Year 1 post-transplant with the value from 2 subjects

being below the normal range and the other 2 subjects within the normal range (i.e., >75,000 cpm). At Year 2, two subjects reported a response to ConA that was within the normal range. For Immo CD3, the stimulation index (ratio of the median of patient response value/median of patient background value) was 39 at Year 1 (N=3) and 9.2 at Year 2 (N=2) respectively; both were below the normal range (normal >50). For Sol CD3, the stimulation index was 33 at Year 1 (N=3) and 6.3 (N=2) at Year 2. The stimulation index at Year 1 was within the normal range (>15), whereas the stimulation index at Year 2 was below the normal range.

For tetanus toxoid, the stimulation index was 1.49 at Year 1 and 90 at Year 2 respectively. The stimulation index at Year 1 was below the normal range (>2), whereas the stimulation index at Year 2 was within the normal range.

A low response value relative to the control was reported at Year 2 from one subject in response to *Candida* skin test antigen, due to the lack of exposure to this antigen.

### **T Cell Receptor Diversity – Immunoscope Spectratyping**

The presence of TCRV $\beta$  repertoire diversity depends on a functioning thymus and was assessed by spectratyping and quantified using the DKL statistic where divergence from a normal repertoire is characterized by a higher DKL. In the EAS, the CD4 DKL was only available from one subject at baseline with a value of 1.91. At 1-year post-transplant, two subjects had values of 0.082 and 0.225 while one subject had a CD4 DKL value at Year 2 of 0.067. Although the data were limited, the shift in DKL score posttransplant was indicative of the development of a more diverse TCRV $\beta$  repertoire.

There was also a shift from a more oligoclonal CD4 population at baseline (median % oligoclonal at baseline of 100% [N=1] versus 0% gaussian [N=1]) to a more gaussian distribution at Year 1 (median % oligoclonal at Year 1 of 3.5% [N=2] versus 66.5% gaussian [N=2]). The median % skewed values at baseline and Year 1 were 0 and 30.5%, respectively. These data support the emergence of a normal T cell repertoire

### **T Cell Receptor Excision Circles**

Subjects did not have evidence of thymic function at baseline as documented by a naïve T cell count of <50 cells/mm<sup>3</sup>. CD3 TRECs were only reported for a single subject (Subject (b) (6); 240 TRECs/100,000 cells) at baseline. The presence of 240 TRECs/100,000 cells was higher than expected given the absence of naïve T cells in this subject; the clinical significance of this finding is unknown. Only Subject (b) (6) had a CD3 TREC value available after transplantation (4540 TRECs/100,000 cells 464 days after treatment). This finding supports the development of mature T cells post-transplant in this single subject.

### **Regulatory T Cells**

Data regarding TREGs were only available for a single subject 252 days after transplantation. Subject (b) (6) had CD3 and CD4 cells that expressed FoxP3 252 days after transplantation. However, given the limited data available, the significance of these findings is unknown and no conclusions regarding TREGs can be made.

### **B Cell function**

All subjects received immunoglobulin replacement therapy through ~2 years after transplant. Because subjects were receiving immunoglobulin replacement through 2 years after transplantation, Thus, the values for IgG were not representative of the subject's endogenous IgG production. However, IGIV does not impact the development of IgA, IgE, and IgM so

these values were representative of the subject's endogenous immunoglobulin levels. In general, a greater proportion of subjects had serum immunoglobulin values in the normal range at 2 years post-transplant as compared to baseline.

### **RVT-802 Biopsy**

RVT-802 was biopsied in 2 subjects in the EAS (Subjects (b) (6) and 3 subjects in the FAS (Subjects (b) (6)). The allografts were biopsied on Days 75, 61, and 112 after transplantation, respectively. There was no evidence of rejection in any subject and definitive evidence of thymopoiesis was observed in 1 subject (Subject (b) (6)) where cortical thymocytes CD1a, CD3, CK14 and Ki-67 were observed. The biopsy specimen from Subject (b) (6) was insufficient for analysis and thus, there was no conclusive evidence of thymopoiesis although the presence of Hassall bodies and CK14 was reported. In Subject (b) (6), the Investigator commented that evidence of thymopoiesis was not definite but CD3, CK14 and Ki-67 were observed in this subject.

### **CMV and EBV Infection**

No subjects tested positive for CMV or EBV infection within 2 years of transplantation.

### **Skin Biopsy**

T cells were detected in the skin biopsy of 1 of 2 subjects for whom a post-transplant skin biopsy was performed. T cells were detected in biopsies conducted at screening (Day -12) and following RVT-802 transplantation (Day 61) in Subject (b) (6) who entered the study with a pre-existing rash.

#### **6.1.4.8.3 Subpopulation, Exploratory, and Post Hoc Analyses**

There was no subgroup, exploratory, or post hoc analyses.

#### **6.1.4.8.4 Dropouts and/or Discontinuations**

There were two subjects who were discontinued from this study.

- Subject (b) (6) died 128 days after transplantation.
- Subject (b) (6) was withdrawn from the study on Day 1051 of life (379 days after RVT-802 transplantation) when it was determined that the subject had Artemis SCID and not cDGA. RVT-802 would not be effective since the subject lacked the hematopoietic precursors required to develop T cells. The subject died on Day 1622 of life, 950 days after transplantation.

### **6.1.4.9 Safety Analyses**

#### **6.1.4.9.1 Methods**

All 7 subjects included in the FAS received RVT-802. The median total dose of RVT-802 received was 13,721 mm<sup>2</sup>/m<sup>2</sup>, with a range of 4902 to 17,900 mm<sup>2</sup>/m<sup>2</sup>. The median number of RVT-802 slices received was 30, with a range of 11 to 33 slices. This was similar to the EAS. No subject received an RVT-802 dose greater than the maximum recommended dose (20,000 mm<sup>2</sup>/m<sup>2</sup> BSA).

#### **6.1.4.9.2 Overview of Adverse Events**

The AEs in the FAS were similar to those in the EAS. All 7 subjects in the FAS had at least 1 AE during the study with 6 subjects in the FAS having at least 1 SAE, including 4 subjects with life-threatening SAEs. One subject (Subject (b) (6)) died during the study. An additional subject (Subject (b) (6)) died after the Year 2 assessment. Six subjects had at least 1 AE of Grade ≥ 3. Six subjects had at least 1 infection-related AE within 2 years of transplantation.

Of these, the maximum intensity of the AE was severe for 4 subjects, and life threatening for 2 subjects. Three subjects had at least 1 AE related to study treatment, including 2 subjects with life threatening events.

### **Frequency of Adverse Events**

There was a total of 163 AEs reported. Pyrexia was the most frequent AE in the study and was reported by 5 (71%) subjects with 15 events. Other frequent AEs ( $\geq 3$  subjects) included: device-related infection (4 subjects), hypoxia (4 subjects), ALT elevation (3 subjects), AST elevation (3 subjects) and anemia (3 subjects).

### **Relationship to Study Treatment**

AEs related to study treatment were those related to the RVT-802 implantation procedure or biopsy, RVT-802, protocol required immunosuppression, or supportive care associated with these procedures. Autoimmune diseases diagnosed after RVT-802 transplantation was considered possibly related to RVT-802 transplantation. Three subjects in the FAS had 15 AEs that was related to study treatment. Most of the treatment-related AEs (13/15) were reported by Subject <sup>(b) (6)</sup> (see narrative under Section 6.1.4.9.3 Deaths). As this subject was not included in the EAS, there were fewer treatment related AEs reported in the EAS (2 subjects, 2 AEs). No study treatment-related AE was reported by more than 1 subject. The only SOC in which study treatment-related AEs were reported in more than 1 subject were the blood and lymphatic systems disorder SOC (3 subjects).

### **Severity of Adverse Events**

Seventy of the 163 AEs reported in the FAS within 2 years of transplantation were assessed as  $\geq$  Grade 3 in intensity. The most frequent SOC was infections and infestations. Six subjects reported at least one Grade  $\geq 3$  AE in this SOC but only 3 PTs (device-related infection, pneumonia and viral upper respiratory infection) were reported by  $\geq 2$  subjects. None of the  $\geq$  Grade 3 AEs in this SOC were assessed as related to treatment. Grade  $\geq 3$  AEs were also frequent in the blood and lymphatic system disorders and respiratory, thoracic and mediastinal disorders SOCs. A total of 5 subjects in the FAS reported at least one Grade  $\geq 3$  AE in the blood and lymphatic system disorders SOC, but only anemia was reported by  $\geq 2$  subjects. No events of Grade  $\geq 3$  anemia were assessed as related to treatment. The Grade  $\geq 3$  events assessed as related to treatment in this SOC included autoimmune hemolytic anemia, hemolysis, neutropenia and thrombocytopenia, and were reported in 1 subject each. A total of 4 subjects in the FAS reported at least one Grade  $\geq 3$  AE in the respiratory, thoracic and mediastinal disorders SOC, but only 2 PTs (hypoxia and respiratory failure) were reported by  $\geq 2$  subjects. No events of Grade  $\geq 3$  in this SOC were assessed as related to treatment.

The only other PTs with Grade  $\geq 3$  reported by  $\geq 2$  subjects were feeding intolerance in the metabolism and nutritional disorders SOC, aspartate aminotransferase increased in the investigations SOC, and gastroesophageal reflux disease in the gastrointestinal disorders SOC. None of these AEs were assessed as related to treatment.

There were 6 AEs reported for 3 subjects that were assessed as Grade  $\geq 3$  and related to study treatment.

- Subject <sup>(b) (6)</sup> had autoimmune hemolytic anemia from Day 344 to Day 353, characterized by low hemoglobin and a positive Coombs test. This was assessed as serious but resolved on treatment with immunoglobulin replacement and a blood transfusion.

- Subject (b) (6) developed thrombocytopenia from Day 160 to Day 1587. The event was assessed as serious but resolved on treatment with immunoglobulin replacement and rituximab.
- Subject (b) (6) reported 4 AEs which were assessed as Grade  $\geq$  3 and related to study treatment. They were seizure, pure red blood cell aplasia, neutropenia and GVHD.

### **Infection-related Adverse Events**

Six subjects in the FAS had at least 1 infection-related AE but none was assessed as related to treatment. However, the only events reported by  $\geq$  2 subjects were device-related infection (12 events), lower respiratory tract infection bacterial (5 events), pneumonia pseudomonas (4 events), urinary tract infection enterococcal (2 events) and viral upper respiratory infection (2 events). The severity of 26 infection-related AEs in 6 subjects was Grade  $\geq$  3. Two events in one subject were life threatening.

- Subject (b) (6) had two concurrent events of life-threatening respiratory tract infection bacterial (*Pseudomonas aeruginosa* and *Stenotrophomonas*). The pseudomonas infection was present prior to RVT-802 treatment but increased in severity during the study. The subject was treated for both events in the pediatric intensive care unit and recovered.

#### **6.1.4.9.3 Deaths**

There were two deaths reported in this study.

Subject (b) (6) developed a large right parietal intracranial hemorrhage on Day 127 following transplantation and died on Day 128 (Day 510 [1.4 years] of life) following withdrawal of life support. This fatal CNS hemorrhage was unrelated to study treatment.

Subject (b) (6) was a female initially diagnosed with typical cDGA who died 950 days after RVT-802 transplantation. The subject had a hemizygous deletion of chromosome 22q11.2. Phenotypic features included congenital cardiac anomaly or cardiothoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, growth and mental retardation, hypocalcemia, limb anomalies, and renal anomalies. She received RVT-802 (total dose of 13721 mm<sup>2</sup>/m<sup>2</sup>) on Day 672 of life. The subject received treatment with cyclosporine or tacrolimus (from 4 days prior to RVT-802 transplantation until 155 days after RVT-802 transplantation). However, it was subsequently determined that the subject had Artemis-deficient SCID (not cDGA) at which time the subject was discontinued from the study (Day 379 post-transplant, Day 1051 of life). The AEs included device-related infection (2 events), hemolysis, hypotension, pyrexia (2 events), neutropenia, abnormal lymphocyte count, GVHD, transfusion reaction, abdominal distension, GVHD in the gastrointestinal tract, lower respiratory tract infection, liver abscess, hypoxia, and brain abscess. The subject died on Day 1662 of life and the cause of death was not reported.

#### **6.1.4.9.4 Nonfatal Serious Adverse Events**

Six subjects in the FAS had at least 1 SAE within 2 years of transplantation. Device-related infection, pyrexia, and hypoxia were the most frequent SAEs. Device-related infection was reported in 4 subjects (12 events). All were infections of catheters or central lines.

- Subject (b) (6) had infections due to *Achromobacter xylosoxidans*, *Citrobacter freundii* (2 events), coagulase-negative *Staphylococcus*, *Enterobacter* and *Pseudomonas* (2 events).
- Subject (b) (6) had infections due to *Enterobacter sakazakii* and *Enterococcus faecium*.

- Subject (b) (6) had one infection due to *Candida albicans*
- Subject (b) (6) had infections due to *Enterobacter aerogenes* and *Enterobacter cloacae*.

All SAEs were Grade  $\geq 3$  except for the infection due to coagulase negative *Staphylococcus* in Subject (b) (6), which was Grade 2. No SAEs were related to treatment and they all resolved with the subjects recovering.

Pyrexia was reported by 3 subjects in the FAS (5 events).

- Subjects (b) (6) (2 events; Grade  $\geq 3$ ),
- Subject (b) (6) (1 event; Grade 1)
- Subject (b) (6) (2 events; Grade 1).

All SAEs were unrelated to study treatment and resolved with subjects recovering.

Hypoxia was reported for 3 subjects in the FAS (3 events).

- Subject (b) (6) (1 event; Grade  $\geq 3$ )
- Subject (b) (6) (1 event; Grade  $\geq 3$ )
- Subject (b) (6) (1 event; Grade 1)

None of these SAEs were assessed as related to study treatment. Events in Subjects (b) (6) resolved and the subjects recovered. The event in Subject (b) (6) was ongoing at the end of the study.

The only other SAEs reported for more than 1 subject were pneumonia and respiratory failure, each of which was reported for 2 subjects. All other SAEs were reported by only 1 subject each.

There were 7 SAEs reported in 3 subjects that were assessed as related to study treatment.

- Subject (b) (6) had Grade 3 autoimmune hemolytic anemia 344 days after RVT-802 transplantation (serious because “other medically important event”).
- Subject (b) (6) had Grade 4 thrombocytopenia 160 days after RVT-802 transplantation (serious due to hospitalization).
- Subject (b) (6) had Grade 3 hemolysis 126 days after RVT-802 transplantation (serious because “other medically important event”), Grade 4 neutropenia 147 days after RVT-802 transplantation (serious due to hospitalization), Grade 3 GVHD of the bone marrow 150 days after RVT-802 transplantation (serious because “other medically important event”) and Grade 2 GVHD in the gastrointestinal tract 358 days after RVT-802 transplantation (serious because “other medically important event”).

None of these treatment related SAEs had a fatal outcome.

#### **6.1.4.9.5 Adverse Events of Special Interest (AESI)**

Four subjects in the FAS had 10 AESIs which included autoimmune hemolytic anemia, hemolysis, neutropenia, thrombocytopenia, hypersensitivity, GVHD, GVHD of the gastrointestinal tract, drug eruption and eczema. However, no AESI was reported by more than 1 subject.

#### **6.1.4.9.6 Vital Signs & Physical Examination**

Pyrexia was the most common vital sign AEs and was reported by 5 subjects in the FAS (15 events). Of these, only 1 event (Subject (b) (6)) was assessed as related to treatment. Pyrexia was assessed as serious in 3 subjects in the FAS.

Hypertension was reported as an AE in 2 subjects.

- Subject (b) (6) had Grade 2 hypertension on Days 142 to 152 after transplantation. The event was assessed as not serious and was related to the subject's Fanconi syndrome, not study treatment.
- Subject (b) (6), who was included in the FAS but not in the EAS, had Grade 2 hypertension on Day 179 that continued to the end of the study. It was assessed as not serious and related to study treatment; cyclosporine and steroids administered for GVHD. The event was treated with lisinopril.

Hypotension was reported as an AE in 2 subjects.

- Subject (b) (6) had Grade 1 hypotension on Day 13 after transplantation. The event was assessed as not serious and not related to treatment. The Investigator noted that the subject's blood pressure had been taken after a dose of enalapril.
- Subject (b) (6), who was included in the FAS, but not in the EAS, had Grade 2 hypotension with onset on Days 136 to 138. The event was assessed as serious, and not related to study treatment. The subject presented to clinic with low grade temperature, elevated BUN, hypotension (73/44 mmHg), and ongoing anemia. Her hypotension resolved after treatment with blood transfusion, fluids, and intravenous antibiotics.

There were 4 AEs of cardiac rhythm disturbance.

- Sinus tachycardia was reported as an AE in 2 subjects. Both events were assessed as not serious or related to study treatment
  - Subject (b) (6) had Grade 1, asymptomatic sinus tachycardia on Day 25 after transplantation
  - Subject (b) (6) had Grade 2 sinus tachycardia on Days 21 to 32 after transplantation and again on Day 47.
- Ventricular extrasystole was reported for Subject (b) (6); assessed as not serious or related to study treatment
- Ventricular tachycardia was reported for Subject (b) (6); assessed as not serious or related to study treatment

#### **6.1.4.9.7 Clinical Laboratory Results**

The nature of the laboratory abnormalities reported as AEs was consistent with the nature of the clinical population under study. The abnormal laboratory results most frequently reported as AEs included anemia (3 subjects), ALT increase (3 subjects) and AST increase (3 subjects). Increases in bilirubin and international normalized ratio were each reported by 2 subjects. All other laboratory abnormalities reported as AEs were reported in only 1 subject each.

The abnormal laboratory results reported as AEs related to study treatment included thrombocytopenia (serious), abnormal lymphocyte count (serious), blood bicarbonate decreased, hypomagnesemia, lactase deficiency, hemolysis (serious) and neutropenia (serious). Each was reported in only 1 subject. The abnormal lymphocyte count, neutropenia, hemolysis and thrombocytopenia were assessed as serious and treatment related. Anemia, thrombocytopenia, hemolysis and neutropenia were thought to be possibly related to autoimmunity post RVT-802 transplantation.

#### **6.1.4.10 Study Summary and Conclusions**

These data demonstrate the development of thymic function following treatment with RVT-802 is associated with prolonged survival. In this study, 6 subjects with cDGA and 1 subject

with SCID received RVT-802. Five subjects (5 subjects with cDGA and 1 subject with SCID) were alive at least 2 years post-transplant with a follow-up of up to 11.4 years. The estimated Kaplan-Meier survival rate at Year 1 post-transplant was 0.83 with a 95% CI of [0.273, 0.975]. Because all subjects who survived at least 1-year post-transplant were still alive through at least 5 years, the Kaplan-Meier estimates of survival were the same at 1, 2, 3, 4 and 5-years post-transplant. By comparison, most infants with congenital athymia are dead by the age of 2 years.

The immune system reconstituted with the development of naïve CD4, CD8, and CD3 cells over time. Naïve T cells co-expressing CD45RA<sup>+</sup> and CD62L<sup>+</sup> emerged from the thymus and responded to pathogens that the immune system had not previously encountered. The subject's immune profiles changed from having <50 cells/mm<sup>3</sup> naïve T cells at baseline to median naïve CD4 and CD8 T cell counts >200 cells/mm<sup>3</sup> at 1-year post-transplant. Thereafter, the median naïve CD4 and CD8 counts decreased but remained above baseline values. Although the naïve T cell counts were lower than in normal age-controlled individuals, they were consistent with naïve T cell numbers in subjects with partial DGA and were sufficient to prevent life threatening infections. Median values for NK and B cells fluctuated over time but remained within the expected range for age.

One subject (Subject <sup>(b) (6)</sup>) did not respond as well with a naïve CD4 T cell count <100 cells/mm<sup>3</sup> 1-year post-transplant. The reason for this subject's low values is not entirely understood although it may be related to the presence of a mosaic partial trisomy at 14q. While this genetic mutation has not been linked to the development of cDGA, it is notable that this subject consistently reported the lowest total and naïve T cell counts throughout the post-transplantation period.

The development of thymic function post-RVT-802 implantation was further corroborated by the T cell proliferative responses to mitogen/antigens including PHA, ConA, and tetanus toxoid. In particular, cDGA subjects developed normal proliferative responses to these mitogen/antigens within 2 years of transplantation. Data from flow cytometry and spectratyping were also indicative of improved thymic function as evidenced by the emergence of a normal TCRVB repertoire over time. These results are significant as a diverse TCRV $\beta$  repertoire is necessary to recognize and respond to a broad range of antigens.

The AE profile of RVT-802 were consistent with the disease under study and was expected. The most common s included infections, hypoxia, and clinical laboratory abnormalities. There were no indications of a safety concern regarding RVT-802 transplantation in this study.

This study was terminated prior to meeting enrollment goals. In addition, no subjects received a parathyroid transplant as originally proposed in the protocol. Data from Protocol 931 indicated that for tolerance to develop to the parental parathyroid transplant, the thymus donor had to express all HLA Class II antigens in the parental donor that were not inherited by the recipient. It was not feasible to find such matched thymuses without a cryopreserved, HLA-typed thymus tissue bank, and such a bank does not exist. Secondly, CMV seropositivity was an exclusion criterion for the parental parathyroid donor and most parents were CMV seropositive. Since no subjects received a parathyroid transplant, it was not possible to evaluate the effect of parathyroid co-transplantation on the efficacy of RVT-802.

Nonetheless, the efficacy and safety support the use of RVT-802 to reconstitute the immune system in subjects with congenital athymia, including cDGA.

### **6.1.5 Study 950/950.1: Phase 1/2 Trial of Thymus Transplantation with Immunosuppression**

#### **6.1.5.1 Objectives**

The objectives for Study 950 were to evaluate:

- the safety and toxicity of RVT-802 administered with immunosuppression, both with and without parathyroid transplantation.
- the allograft biopsy at 2 to 3 months post-transplantation for immunohistochemical evidence of thymopoiesis or graft rejection.

Study 950.1 did not have pre-defined objectives, but the protocol was developed to provide a higher dose of immunosuppression therapy for a single athymic subject following stem cell transplantation.

#### **6.1.5.2 Design Overview**

Study 950 was a Phase 1/2, single-site, open-label, non-randomized study. The study planned to include subjects diagnosed as having the typical or atypical cDGA.

Study 950.1 was an expanded access protocol to treat a single subject.

#### **6.1.5.3 Study Population**

Inclusion

1. Male and female subjects of any age
2. One of the following for a diagnosis of DiGeorge syndrome:
  - Congenital heart disease;
  - Hypocalcemia requiring replacement;
  - 22q11.2 hemizyosity or 10p13 hemizyosity;
  - CHARGE (coloboma, heart defect, choanal atresia, growth and development retardation, genital hypoplasia, ear anomalies/deafness) syndrome or chromodomain-helicase-deoxyribonucleic acid (DNA)-binding protein 7 (*CHD7*) mutation;
  - Abnormal ears plus mother with diabetes (type I, type II, or gestational).
3. To meet the criteria for typical cDGA, the subject had:
  - Circulating CD3+ CD45RA+ CD62L+ T cell count  $<50/\text{mm}^3$  or  $<5\%$  of the total T cell count by flow cytometry;
  - PHA proliferative response  $>20$ -fold above background or  $>5000$  cpm. In addition:
    - Group 1: PHA  $<50,000$  cpm;
    - Group 2: PHA  $>50,000$  cpm.
4. To meet the criteria for atypical cDGA, the subject had:
  - Rash at screening or had previously had a rash. If a rash was present, a biopsy of the rash showed T cells in the skin. If the rash and adenopathy had resolved, the subject had  $>50/\text{mm}^3$  T cells and the naïve T cell count was  $<50/\text{mm}^3$  or  $<5\%$  of the T cells.
  - PHA proliferation response:
    - Group 2:  $<40,000$  cpm on IS or  $<75,000$  cpm off IS;
    - Group 3:  $>40,000$  cpm on IS or  $>75,000$  cpm off IS.

- Circulating CD3+ T cells were  $>50/\text{mm}^3$  but CD45RA+ CD62L+ CD3+ T cells were  $<50/\text{mm}^3$  or  $<5\%$  of the total CD3 count.
5. *Study 950.1 only*, the single subject was required to meet the following key criteria: Circulating CD3+ T cells were  $>50/\text{mm}^3$  but CD45RA+ CD62L+ CD3+ T cells were  $<50/\text{mm}^3$  or  $<5\%$  of the total CD3 count.

#### Exclusion

1. Heart surgery  $<4$  weeks prior to projected transplantation date;
2. Heart surgery anticipated within 3 months after the proposed time of transplant;
3. Rejection by the surgeon or anesthesiologist as surgical candidate;
4. Lack of sufficient muscle tissue to accept a transplant of  $4 \text{ g}/\text{m}^2$  body surface area;
5. Human immunodeficiency virus (HIV) infection;
6. CMV infection by  $>500$  copies/mL in blood by polymerase chain reaction (PCR) on 2 consecutive assays;
7. Ventilator dependence: subjects had to be off ventilator or other pressure support such as continuous positive airway pressure or bi-level positive airway pressure support for 2 weeks prior to enrollment;
8. *Study 950 Only*: Prior attempts at immune reconstitution, such as bone marrow transplant or previous thymus transplantation.

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

The investigational product was allogeneic cultured postnatal thymus tissue product from unrelated donors under the age of 9 months. The minimum dose of RVT-802 was  $4 \text{ g}/\text{m}^2$  and the maximum dose was  $18 \text{ g}/\text{m}^2$  of subject BSA. However, in 2015, the IND was updated to define a dose range of 2,000 – 20,000  $\text{mm}^2$  of thymus tissue per recipient BSA in  $\text{m}^2$  (IND 9836, Serial Number 0209).

The immunosuppression regimen used in these two protocols were

- Study 950
  - RATGAM: All subjects received 3 IV doses of 2 mg/kg of RATGAM pre-transplant on Days -5, -4, and -3 followed by 2 days of rest prior to transplantation. Each dose was given over  $\sim 12$  hours with RVT-802 transplanted within 7 days of the last dose of RATGAM, otherwise the T cell count was repeated, and additional RATGAM was given.
  - Methylprednisolone: All subjects received IV methylprednisolone (2 mg/kg) beginning  $\sim 4$  hours prior to the first dose of RATGAM. Dose was then reduced to 0.5 mg/kg every 6 hours until 24 hours after the last dose of RATGAM. Subjects in Group 1 did not receive additional methylprednisolone but was resumed 24 hours after the last dose of RATGAM in Groups 2 and 3.
  - Cyclosporine (CSA)/Tacrolimus: Subjects in Group 1 did not receive cyclosporine. Subjects in Group 2 and Group 3 received CSA (except Subject <sup>(b) (6)</sup> because of that subject was on cidofovir for adenovirus). CSA was started as soon as the diagnosis of cDGA was made or at least 7 days prior to RATGAM administration.
  - Daclizumab: Subjects in Group 3 received this agent (1 mg/kg IV) if T cells  $>200/\text{mm}^3$  and  $>50\%$  were CD25<sup>+</sup> on Day -1 or 0.
  - Mycophenolate mofetil (MMF): This was dosed at 15 mg/kg IV every 8 hours if the T cell count was  $>5000/\text{mm}^3$  after Day 5 and stopped at Day 35 if there was

no extensive rash, AST and ALT were <3 times the upper limit of normal, and if T cells were <5000/mm<sup>3</sup>. MMF could have been continued for up to 6 months if these parameters were not met.

- Study 950.1: This protocol was developed for a single subject who was treated under an expanded access protocol. The subject was initially thought to have SCID and was treated with 2 paternal stem cell transplants without the development of normal naïve T cells. Subsequent testing determined the subject had athymia of undetermined etiology but not associated with SCID or cDGA. The immunosuppression regimen was based on Study 950 but was modified to administer higher doses including 4 doses of RATGAM
  - RATGAM (2.5 mg/kg/dose) on Days -6, -5, -4, and -3
  - Cyclosporine targeting trough levels of 120 to 150 ng/mL was initiated at least 7 days prior to RATGAM.
  - Methylprednisolone (2 mg/kg IV) approximately 4 hours prior to the first dose of RATGAM. The dose was reduced to 0.5 mg/kg IV every 6 hours during administration of RATGAM and continued until 24 hours after the last dose of RATGAM. Steroid therapy was resumed after RVT-802 transplantation.
  - Basiliximab (5 mg IV) was given within 24 hours of transplantation if the subject had T cells >200/mm<sup>3</sup> and were CD25<sup>+</sup> >50%.
  - MMF (15 mg/kg IV) was given every 8 hours if the T cell count was >5000/mm<sup>3</sup> after Day 5. MMF was stopped at 35 days if there was no extensive rash, AST and ALT were <3 times the upper limit of normal, and T cells <5000/mm<sup>3</sup>. MMF was continued for up to 6 months if these parameters were not met.

#### **6.1.5.5 Sites and Centers**

This study was conducted at a single center, Duke University Medical Center.

#### **6.1.5.6 Surveillance/Monitoring**

Subjects were screened at DUMC over a period of 2-8 weeks. Pre-transplantation medical testing in Study 950 included a renal ultrasound, cardiac evaluation, and a PTH assay with simultaneous ionized calcium to assess for hypoparathyroidism. Immunologic studies (ie: TREC, TCRV $\beta$ , flow cytometry, etc) was performed to characterize the subject's cDGA phenotype. Eligible subjects were transplanted with RVT-802 and parathyroid tissue (Study 950 only) in the quadriceps muscle under general anesthesia.

Subjects were followed as inpatients at DUMC through the time of graft biopsy at 8 to 12 weeks post-transplantation. The RVT-802 allograft was biopsied and stained with antibodies to keratin, CD3, CD1a (cortical thymocytes), and Ki-67 (proliferation marker of cortical thymocytes) to assess thymopoiesis. Subjects who were medically stable were then discharged to the care of their referring physician. After discharge, blood samples were scheduled to be obtained for immune testing (flow cytometry, TRECs, immunoglobulins, T cell proliferative response to mitogen/antigen, etc) at 3, 6, 9, 12, 18 and 24 months. However, adherence to the study evaluations was dependent upon the cooperation of the primary physician and parent(s)/legal guardian(s) of the subject.

#### **6.1.5.7 Statistical Considerations & Statistical Analysis Plan**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this and the 9 other clinical studies planned for inclusion in this BLA given the legacy data status and similarities across the 10 clinical studies in the RVT-802 program. The endpoints specified in the program-wide SAP were given precedence over the analyses

originally planned for this study (See Sec 6.1.5.7.4 Endpoints and Criteria for Study Success).

Summary statistics (n, mean, SD, median, quartiles, and ranges) were presented for continuous variables and frequencies and percentages were presented for categorical variables. As applicable, continuous variables were dichotomized to reflect whether they achieved preset threshold values and then summarized using methods for categorical variables as discussed above. Descriptive summaries were provided for the overall sample.

#### **6.1.5.7.1 Analysis Population and Disposition**

Subjects who received RVT-802 were included in the full analysis set (FAS). The efficacy analysis set (EAS) included all subjects with athymia associated with cDGA or FOYN1 deficiency, who had no prior HSCT and were treated with RVT-802 administered once by transplantation. An EAS-cDGA analysis set was defined to include all EAS subjects except those who had FOYN1 deficiency.

Study 950 was expected to recruit at least 1 to 5 subjects per year while a single subject was planned for enrollment in Study 950.1. Fourteen subjects received RVT-802 in Study 950; 13 subjects in Group 2 and one subject in Group 3. No subjects were treated in Group 1. The single subject treated in Group 3 did not require additional rescue therapy although this subject did receive the post-RATGAM steroids per protocol. In Study 950.1, one subject received RVT-802. Therefore, a total 15 subjects were analyzed in the FAS.

There were 14 subjects (93%) who were diagnosed with cDGA and had no prior HSCT that were included in the EAS, EAS-cDGA, and FAS analysis sets. One subject (Subject (b) (6) from Study 950.1) was excluded from the EAS and EAS-cDGA analysis sets because this subject was treated with 2 stem cell transplants and was diagnosed as having athymia of undetermined etiology. This subject was included in the FAS.

#### **6.1.5.7.2 Protocol Deviations**

There were 2 major protocol deviations reported for this study but neither impacted subject safety or the integrity of study results.

- Subject (b) (6)'s informed consent was not signed by the mother of the subject prior to having the mother's blood drawn for a research procedure. The informed consent form was signed one day after the blood draw but was then misplaced. A second informed consent form was signed 11 days after the first.
- Subject (b) (6) was given one dose of RATGAM in preparation for the thymus transplant. However, results of the CMV testing for the donor thymus were misinterpreted and the thymus was not suitable for transplantation. The transplantation was postponed until a suitable thymus was available.

#### **6.1.5.7.3 Demographics & Disease Characteristics**

The majority of subjects were male (9/15 subjects, 60%) and white (9/15 subjects, 60%) in the FAS. No subjects were Hispanic or Latino. The median age of subjects was 215 days (range: 83 to 1050) on the day of RVT-802 transplantation. The oldest subject was Subject (b) (6) (in Study 950.1) who was transplanted at age 1050 days after having received 2 stem cell transplants prior to RVT-802. The demographic and baseline characteristics were similar for the EAS.

All 14 subjects treated in Study 950 had atypical cDGA. Subject <sup>(b) (6)</sup> in Study 950.1 presented with diminished T cell counts for age and hypocalcemia but was diagnosed with athymia of unknown etiology. This subject's mother had gestational diabetes but the subject did not have the clinical phenotype typically associated with cDGA in infants of diabetic mothers. All 15 subjects had diminished T cell counts for their age, and the majority (>50%) of subjects had hypocalcemia (14 subjects) and congenital cardiothoracic vascular anomalies (11 subjects). At the time of cardiac repair, 4 subjects had no visualized thymus, and visualization of the thymus was unknown or not applicable for 5 subjects and 6 subjects, respectively

Four of 15 subjects in the FAS (27%) had hemizygous deletion of chromosome 22q11.2 and 4 subjects (27%) had CHARGE syndrome with an associated *CHD7* mutation. Four subjects had no known genetic mutations reported and 3 subjects had no data as genetic sequencing was not performed at the time of RVT-802 implantation. Notably, Subject <sup>(b) (6)</sup>, had a variant in T-box transcription factor (*TBX*)2 identified post-transplant. The mothers of 4 subjects had diabetes (2 with type II and 2 with gestational). One subject of a mother with gestational diabetes (Subject <sup>(b) (6)</sup>) also had 22q11.2DS. One subject (Subject <sup>(b) (6)</sup>) had exposure to his mother's anti-epileptic medications but also had 22q11.2DS.

The median age at diagnosis was 52.0 days of life (range: 0 to 832). All 15 subjects in the FAS had a history of gastrointestinal disorders, metabolism and nutrition disorders, and skin and subcutaneous tissue disorders, which were expected in subjects with atypical cDGA. By PT, the majority of subjects had a history of hypocalcemia (14 subjects), gastroesophageal reflux disease, central venous catheterization, and hypoparathyroidism (10 subjects each), diarrhea and vomiting (9 subjects each), and eczema, lymphadenopathy, atrial septal defect, gastrostomy, and pyrexia (8 subjects each). These conditions were expected in subjects with cDGA.

Thirteen subjects had a pre-transplant history of infection. Infections reported by >1 subject included device related infection (6 subjects), staphylococcal bacteremia (4 subjects), eye infection bacterial (3 subjects), and bacteremia, *Enterobacter* bacteremia, *pseudomonas* bacteremia, viremia, and *enterococcus* urinary tract infection (2 subjects each).

All 15 subjects received RATGAM and methylprednisolone, as required by the protocol. Fourteen subjects (93%) were prescribed CSA and tacrolimus was received by 1 subject (7%). Subject <sup>(b) (6)</sup> did not receive the protocol-dictated cyclosporine/tacrolimus because this subject was being treated with cidofovir for an adenovirus infection. Most subjects were on glucocorticoids including prednisolone (10 subjects), prednisone (3 subjects), and dexamethasone (2 subjects). One subject (Subject <sup>(b) (6)</sup>) received MMF.

#### **6.1.5.7.4 Endpoints and Criteria for Study Success**

The primary endpoints as defined in the SAP were survival at 1-year and 2-year post-transplant >50% using a binomial exact test. Furthermore, a Kaplan-Meier survival analysis was also performed with median follow-up time post-transplant for all subjects and median survival time post-transplant for the subjects who died during the study being reported.

The secondary efficacy endpoints included CD3, CD4, CD8, naïve CD4; and naïve CD8 cell counts; proliferative T cell responses to mitogens/antigens (PHA, ConA, Sol CD3, Immo CD3, tetanus toxoid, and *Candida*); TREC; TREG, TCR repertoire variability; and biopsy of

RVT-802. Descriptive summaries were calculated at baseline, Year 1 and Year 2 post-transplantation as data permitted.

#### **6.1.5.8 Efficacy Analyses**

##### **6.1.5.8.1 Primary Endpoint**

Ten of 14 subjects (71.4%) were alive at 1 year after RVT-802 transplantation in the EAS. The exact binomial test with null hypothesis that no greater than 50% of subjects would survive at Year 1 gave a 95% confidence interval (CI) of [0.42, 0.92] with a p-value of 0.0898. The results of the exact binomial exact at Year 2 were the same as Year 1 because all subjects who survived at least one-year were also alive at 2 years post-transplant.

Four subjects died within the first year with a median survival of 231.5 days (range 103 to 252 days) after transplantation. The median follow-up time for all subjects in the EAS was 8 years and ranged from 103 to 3979 days (10 years and 10 months) after receiving RVT-802. In the EAS, the estimated Kaplan-Meier survival rate at Year 1 post-transplant was 0.71 with a 95% CI of [0.406, 0.882]. Because all subjects who survived at least 1-year post-transplant were still alive through at least 5 years, with 1 subject being censored at Year 5, the Kaplan-Meier estimates of survival were the same at Years 1, 2, 3, 4, and 5 post-transplantation.

##### **6.1.5.8.2 Secondary Endpoints**

###### **Naïve CD3, CD4, and CD8 T Cell Counts**

The median naïve CD3, CD4, and CD8 T cell counts at baseline in the EAS were 1.6 cells/mm<sup>3</sup> (N=5, range: 1 to 6), 0.6 cells/mm<sup>3</sup> (N=13, range: 0 to 16), and 0.7 cells/mm<sup>3</sup> (N=12, ranges 0 to 26), respectively, which was consistent with the absence of thymic function. Follow-up results were reported for 9 subjects at 1-year post-transplant. The median counts at Year 1 were 155.6 cells/mm<sup>3</sup> (range: 23 to 751) for naïve CD4 cells and 36.9 cells/mm<sup>3</sup> (range: 4 to 217) for naïve CD8 cells. Naïve CD3 T cell counts within the Year 1 analysis window were not reported. At Year 2 (N=7), the median naïve CD4 and CD8 T cell counts further increased to 219.3 cells/mm<sup>3</sup> (range: 40 to 564) for naïve CD4 cells and 57.7 cells/mm<sup>3</sup> (range: 6 to 384) for naïve CD8 cells. At Year 2, a total median naïve CD3 count of 300.3 cells/mm<sup>3</sup> (N=3; range: 43 to 485) was reported. The naïve T cell counts were similar in the FAS.

###### **Total CD3, CD4, and CD8 T Cell Counts**

The median total CD3, CD4, and CD8 T cell counts at baseline in the EAS were 382 cells/mm<sup>3</sup> (range: 52 to 4059), 204 cells/mm<sup>3</sup> (range: 9 to 2458), and 98 cells/mm<sup>3</sup> (range: 1 to 1834), respectively. These counts are relatively high for this patient population but was expected in atypical cDGA which is characterized by the presence of oligoclonal T cells. Despite the presence of relatively high total CD3, CD4, and CD8 cells at baseline, no subject had greater than 50 naïve (CD45RA+ CD62L+) T cells/mm<sup>3</sup> or naïve T cells constituting >5% of total T cells indicating the absence of thymic function.

Subjects were initiated on immunosuppressive therapy to deplete the total T cell counts prior to receiving RVT-802. Following RVT-802 transplantation, total T cell counts increased at Year 1 with total CD3, CD4, and CD8 values of 726 cells/mm<sup>3</sup> (range: 345 to 1866), 593 cells/mm<sup>3</sup> (range: 230 to 1780), and 145 cells/mm<sup>3</sup> (range: 22 to 360), respectively. Similar values were also observed at Year 2. The results of total T cell counts were similar in the FAS.

There were two surviving subjects (Subjects (b) (6) ) who had lower than expected total T cell counts (<500/mm<sup>3</sup>) within 2 years post-transplant. These subjects also had lower than expected naïve T cell counts (<10% naïve T cells). The cause of these low T cell counts is unknown but may have been related to weaning cyclosporine too soon (Subject (b) (6) was weaned from cyclosporine when 5% of T cells were naïve) or frequent infections combined with a tracheostomy dependency at the time of transplantation and poor pulmonary status (Subject (b) (6) ). While both subjects reported lower than expected T cell counts, both subjects developed normal (Subject (b) (6) ) to near normal (Subject (b) (6) ) responses to PHA and were able to survive post-transplant infections suggesting the T cell counts were sufficient to respond to antigens. The protocol was subsequently amended to continue cyclosporine until 10% of T cells are naïve.

**Other Lymphocyte Subsets**

The median values for ALC, B, NK, αβ, γδ, and DN T cells were within the normal reference range for age at 1- and 2-years post-transplant in the EAS (Table 18):

**Table 18: Lymphocyte Subsets (Median in cells/mm<sup>3</sup>)**  
(Reviewer’s Table)

	ALC	B-cell	NK-cell	αβ T cell	γδ T cell	DN T cell
<b>Baseline</b>	3180 (n=14)	807 (n=14)	352 (n=14)	355 (n=14)	25 (n=14)	49 (n=14)
<b>Year 1</b>	2063 (n=10)	598 (n=10)	437 (n=10)	528 (n=9)	74 (n=4)	68 (n=9)
<b>Year 2</b>	1978 (n=7)	569 (n=7)	397 (n=7)	785 (n=7)	105 (n=3)	86 (n=7)

**6.1.5.8.3 Subpopulation, Exploratory and Post Hoc Analyses**

There was no subpopulation, exploratory and post hoc analyses conducted for this study.

**6.1.5.8.4 Dropouts and/or Discontinuations**

Study discontinuation was defined as completing at least 2 years of follow-up. There were 4 subjects (Subject (b) (6) ) in Study 950 who died within the first year after transplantation and were discontinued from the study.

**6.1.5.9 Safety Analyses**

**6.1.5.9.1 Methods**

The statistical summary of safety included all subjects who received RVT-802. Summaries of safety parameters included available data reported within 2 years of transplantation. Baseline is defined as the last value obtained prior to thymus transplantation and Day 0 was the day of transplantation. If there were multiple visits within an analysis window, the visit closest to the target date was used for analysis; if 2 visits were equidistant from the target date, the later visit was used.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. AEs and SAEs were summarized separately by presenting the number and percentage of subjects having any event, having a related event, having an event in each MedDRA system organ class (SOC) and preferred term (PT), having each individual event and the intensity, relationship and outcome of each event. The number of events was also presented.

A subject with >1 occurrence of the same AE in a particular SOC was counted only once in the total of those with AEs in that particular SOC. If a subject had the same AE at >1 severity, or with >1 relationship to study drug, the most severe rating or the stronger causal relationship to study drug was given precedence. Any missing severity, causality, or outcome was not imputed and classified as unknown.

Summaries classifying events according to severity and relationship were presented. Related events were defined as events that were possible, probable, or definitely related to study treatment or with an unknown relationship. The severity of non-infection-related AEs and SAEs were graded (Grades 1-5) according to the National Cancer Institute's CTCAE Version 3. Infection-related AEs were evaluated using either CTCAE criteria or criteria defined in the BMTCTN definitions of infection severity. Infection-related AEs with BMTCTN severity  $\geq$  severe were included in the analysis of AEs of Grade  $\geq$  3. Life-threatening infection related AEs with an outcome of fatal were reported as Grade 5 events in the summary tables.

AESIs were summarized by SOC and PT, and included infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas.

#### **6.1.5.9.2 Overview of Adverse Events**

All 15 subjects received RVT-802 with a median dose of 15,987 mm<sup>2</sup>/m<sup>2</sup> (range: 8223 to 23,755) based on the subject's BSA which ranged from 0.25 to 0.60 m<sup>2</sup> (median: 0.33). The number of RVT-802 thymus slices sutured into the subject's quadriceps muscle ranged from 14 to 48 (median: 32). In 2007, the maximum dose of RVT-802 was set at 18 g/m<sup>2</sup> which is approximately equivalent to the current maximum recommended dose of 20,000 mm<sup>2</sup>/m<sup>2</sup> BSA. Prior to the implementation of this dosing limit, a single subject in Study 950 (Subject (b) (6)) received a dose of 23,755 mm<sup>2</sup>/m<sup>2</sup> (equivalent to approximately 24 g/m<sup>2</sup>).

All 15 subjects in the study had at least 1 AE and 14 subjects had at least 1 SAE. In the FAS, 13 subjects had an AE  $\geq$  Grade 3 in severity. By maximum severity, 2 subjects had moderate AEs, 8 subjects had severe AEs, and 1 subject had life-threatening AEs. Four subjects had fatal AEs.

All 15 subjects in the study had at least 1 treatment-related AE. By maximum severity, treatment-related AEs were moderate for 5 subjects, severe for 6 subjects, and life-threatening for 2 subjects. Two subjects had a fatal treatment-related AEs.

All 15 subjects in the study had at least 1 infection-related AE. By maximum severity, infection-related AEs were moderate for 3 subjects, severe for 8 subjects, and life-threatening for 1 subject. Three subjects (Subject's (b) (6)) died from infection-related AEs and 1 subject (Subject (b) (6)) died from complications secondary to an infection prior to the development of thymic function.

There were 300 AEs reported within 2 years of transplantation in the FAS. By PT, the most frequent AEs in the FAS (>50% of subjects) were device related infection (11 subjects, 34 AEs), hypertension (11 subjects, 12 AEs) and cytokine release syndrome (8 subjects, 9 AEs). All 15 subjects in the study had an AE in the infections and infestations SOC. The majority (>50%) of subjects also had AEs related to metabolism and nutrition disorders (12 subjects, 24 AEs), investigations (11 subjects, 29 AEs), skin and subcutaneous tissue disorders (11 subjects, 24 AEs), gastrointestinal disorders (11 subjects, 19 AEs), vascular disorders (11 subjects, 15 AEs), respiratory, thoracic and mediastinal disorders (10 subjects, 21 AEs),

blood and lymphatic system disorders (9 subjects, 17 AEs), and immune system disorders (8 subjects, 13 AEs).

Most of the AEs were not treatment-related (235 of the 300 events) but there were 65 treatment-related events reported within 2 years of transplantation in the FAS. All 15 subjects in the study had at least 1 treatment-related AE. Two subjects had a fatal AEs that was possibly related to the study treatment. Subject (b) (6) died from a CMV infection that was possibly related to RVT-802.

Treatment-related AEs by PT reported for >1 subject included hypertension (9 subjects, 10 AEs), cytokine release syndrome (8 subjects, 9 AEs), hypomagnesemia (6 subjects, 6 AEs), rash, neutropenia (each 3 subjects, 3 AEs), thrombosis, hyperglycemia, proteinuria, renal failure, CMV infection, wound dehiscence, and hypoxia (each 2 subjects, 2 AEs).

The majority of treatment-related AEs by SOC (>50% of subjects) included vascular disorders (9 subjects, 12 AEs), metabolism and nutrition disorders (8 subjects, 12 AEs), and immune system disorders (8 subjects, 9 AEs).

The AEs related to RVT-802 implantation or biopsy, protocol required immuno-suppression, or supportive care associated with these procedures included a fatal CMV infection, cytokine release syndrome, hypertension, rash, hypoxia, fluid retention, seizure, and sinus tachycardia.

A total of 111 Grade  $\geq 3$  events were reported within 2 years of transplantation in the FAS. Thirteen subjects had AEs reported as Grade  $\geq 3$  although the majority were of mild or moderate severity (189 of the 300 events). The most frequent (>20% of subjects) Grade  $\geq 3$  AEs by PT were device related infection (11 subjects, 31 events) and neutropenia (4 subjects, 4 AEs). By SOC, infections and infestations that were Grade  $\geq 3$  were reported in more than 50% of subjects (12 subjects, 43 AEs).

There were 30 treatment-related Grade  $\geq 3$  events were reported within 2 years in the FAS but the majority were not treatment-related (81 of the 111 AEs). Ten subjects had at least one Grade  $\geq 3$  treatment-related AE. The treatment-related PT Grade  $\geq 3$  AEs reported by >1 subject included neutropenia and cytokine release syndrome (each 3 subjects, 3 AEs), and thrombosis, hypertension, renal failure, CMV infection, hypoxia, and rash (each 2 subjects, 2 AEs). By SOC, the most frequent (>20% of subjects) treatment-related Grade  $\geq 3$  AEs were blood and lymphatic system disorders (4 subjects, 7 AEs).

Two subjects had life-threatening AEs related to study treatment. Two subjects had fatal AEs possibly related to the study treatment.

There were 86 infection-related AEs reported within 2 years of transplantation in the FAS with all 15 subjects having at least 1 infection-related AE. The most frequent infection-related AEs by PT were device related infection (11 subjects, 34 events) and urinary tract infection bacterial (4 subjects, 6 events). Three subjects died due to infection-related AEs and one subject died from complications secondary to an infection.

**6.1.5.9.3 Deaths**

There were 4 deaths (Subject (b) (6) ) that were possibly related to RVT-802 during this study.

- Subject (b) (6) died of CMV infection considered possibly related to RATGAM. The latter immunosuppressive agent may have reactivated this subject's CMV, which was under control prior to therapy
- Subject (b) (6) tested positive for CMV 38 days after RVT-802 transplantation and the infection persisted until the subject died of respiratory complications from CMV 252 days after transplant. The thymus donor tested negative for CMV pre-transplant (negative urine culture, negative PCR) and had acceptable antibodies (CMV IgM negative, CMV IgG positive). The thymus donor was re-tested 49 days post-transplant and the urine culture for CMV was negative, CMV antibodies had not changed, but a CMV PCR test was now positive. However, the positive CMV PCR in the thymus donor was too low to quantitate or amplify for a DNA sequence comparison with that of the CMV infecting Subject (b) (6). Furthermore, repeat PCR testing of the pre-transplant frozen donor plasma was again negative. Thus, the origin of the CMV infection in Subject (b) (6) remained unknown but it was concluded that the potential risk of CMV transmission from the donor could not be excluded, and the death of Subject (b) (6) was considered possibly related to RVT-802.

Deaths unrelated to RVT-802

- Subject (b) (6) died of device related infections (*Candida parapsilosis* and *Candida tropicalis*) and lower respiratory tract fungal infection
- Subject (b) (6) died due to respiratory failure secondary to adenovirus infection.

**6.1.5.9.4 Nonfatal Serious Adverse Events**

There were 88 SAEs reported within 2 years of transplantation in the FAS with 14 subjects having at least 1 SAE. The SAEs by PT observed in >1 subject included device related infection (11 subjects, 34 SAEs), cytokine release syndrome, pyrexia (each 3 subjects, 3 SAEs), tachypnea (2 subjects, 3 SAEs), and CMV infection, neutropenia (each 2 subjects, 2 SAEs). By SOC, infections and infestations were reported in the majority (>50%) of subjects (13 subjects, 47 SAEs) and were expected in this study population.

There were 19 treatment-related SAE reported within 2 years of transplantation in the FAS with 8 subjects having at least 1 treatment-related SAE. By PT, treatment-related SAEs observed in >1 subject included cytokine release syndrome (3 subjects, 3 SAEs), neutropenia and CMV infection (each 2 subjects, 2 SAEs). By SOC, >1 subject had treatment-related SAEs of blood and lymphatic system disorders (3 subjects, 5 SAEs), immune system disorders (3 subjects, 3 SAEs), gastrointestinal disorders, and infections and infestations (each 2 subjects, 2 SAEs).

**6.1.5.9.5 Adverse Events of Special Interest (AESI)**

There were 43 AESI reported within 2 years of transplantation in the FAS with all 15 subjects having at least 1 AESI. By PT, the most frequent AESI was cytokine release syndrome, which was reported in the majority (>50%) of subjects (8 subjects, 9 AESI). These AESIs were considered likely related to RATGAM as cytokine release syndrome has been reported with the use of RATGAM. Other AESIs included hypothyroidism (5 subjects, 5 AESI), rash (4 subjects, 6 AESI), neutropenia and thrombocytopenia (each 4 subjects, 4 AESI), hypersensitivity (2 subjects, 3 AESI), autoimmune hemolytic anemia (1 subject, 2

AESI), alopecia, dermatitis atopic, exfoliative rash, granuloma skin, rash maculopapular, rash papular, rash pruritic, urticaria, disseminated intravascular coagulation, and hemolysis (each 1 subject, 1 event). By SOC, the majority (>50%) of subjects had AESIs related to skin and subcutaneous tissue disorders (8 subjects, 14 AESI) and immune system disorders (8 subjects, 12 AESI).

#### **6.1.5.9.6 Vital Signs & Physical Examination**

The vital signs measured in this protocol have limited utility in characterizing subject safety over the course of the study. There were no Grade 4 or Grade 5 vital sign AEs. The most frequent vital sign AE was hypertension, which was reported in most subjects (11 subjects, 12 events) in the FAS. Of these, 3 subjects had Grade 3 hypertension (3 events) and 9 subjects had treatment-related hypertension (10 events). Other abnormal vital sign AEs included pyrexia (6 subjects, 8 events), tachypnea (5 subjects, 8 events), sinus bradycardia (3 subjects, 4 events), sinus tachycardia (3 subjects, 3 events), and decreased weight (1 subject, 1 event). Of these AEs, sinus tachycardia (1 subject, 1 event) was assessed as treatment-related while pyrexia (2 subjects, 2 events) and tachypnea (1 subject, 2 events) were Grade 3.

Abnormal vital sign SAEs included pyrexia (3 subjects, 3 events) and tachypnea (2 subjects, 3 events).

Data regarding physical examinations were not collected in the database.

#### **6.1.5.9.7 Clinical Laboratory Results**

The most frequent abnormal laboratory AEs (>20% subjects) regardless of causality were hypomagnesemia (6 subjects, 6 AEs), hypothyroidism (5 subjects, 5 AEs), anemia, ALT increased (each 4 subjects, 5 AEs), neutropenia, and thrombocytopenia (each 4 subjects, 4 AEs). Of these AEs, Grade  $\geq 3$  AEs included neutropenia (4 subjects, 4 AEs), thrombocytopenia, anemia (3 subjects, 3 AEs), and ALT increased (1 subject, 1 event), and treatment-related AEs included hypomagnesemia (6 subjects, 6 AEs), neutropenia (3 subjects, 3 AEs) and thrombocytopenia (1 subject, 1 AE).

Abnormal laboratory results that were SAEs included neutropenia (2 subjects, 2 SAEs; both Grade 4), autoimmune hemolytic anemia (1 subject, 2 SAEs; both Grade 3), disseminated intravascular coagulation, hemolysis, thrombocytopenia, hyperkalemia, hypoalbuminemia, hypocalcemia, hyponatremia, and decreased blood bicarbonate (each 1 subject, 1 SAE; all Grade  $\leq 3$ )

#### **6.1.5.10 Study Summary and Conclusions**

The objective of Study 950 was to evaluate the safety of RVT-802 when administered with 3 different immunosuppression regimens. All 14 subjects enrolled in the study had a diagnosis of atypical cDGA. Their disease presentation was different from typical cDGA as they had relatively elevated total T cell counts ( $>50/\text{mm}^3$ ) and T cell proliferative responses to mitogen/antigens at baseline. The latter responses were concerning, as subjects could potentially reject RVT-802 without the use of immunosuppression. Therefore, subjects in this study were treated with CSA and/or steroids prior to RVT-802 transplantation to suppress the expansion of oligoclonal T cells and the associated morbidity from rash, lymphadenopathy, and hepatomegaly. RATGAM was administered prior to transplantation to deplete circulating T cells with the aim of preventing rejection in the peri-transplant period. By comparison, subjects with typical cDGA did not require immunosuppression.

Treatment assignment was based on each subject's baseline immune status with increasing levels of immunosuppression utilized for subjects with higher baseline proliferative responses to PHA. The protocol was designed with 3 treatment regimens, but no subjects were treated in Group 1 (RATGAM alone) and the single subject enrolled in Group 3 did not require rescue therapy with daclizumab or MMF. All 14 subjects received RATGAM and steroids (as clinically indicated) while 13 subjects received pre- and post-transplant CSA.

Study 950.1 was an expanded access study that was based on Study 950. This protocol was developed to provide higher doses of RATGAM and CSA to a single subject with athymia of unknown origin following 2 prior HSCT (one bone marrow and one peripheral blood).

Ten of the 14 subjects were alive at 1- and 2-year post-transplant (71.4%, 95% CI 0.42, 0.92) with a p-value of 0.0898 from the binomial exact test on survival >50%. The results of the binomial exact test at Year 2 were the same as Year 1 since all subjects who survived at least 1-year post-transplant were also alive after 2 years. The median follow-up for all subjects in the EAS was 8 years and ranged from 103 days to nearly 11 years after transplantation. Because all subjects who survived at least 1-year post-transplant were still alive through 5 years, with 1 subject being censored at Year 5, the estimated Kaplan-Meier survival rate at Years 1, 2, 3, 4 and 5 post-transplant was 0.71 (95% CI 0.406, 0.882).

RVT-802 transplantation resulted in the development of naïve T cells, improved proliferative response to mitogens, increased T cell receptor diversity, and evidence of thymopoiesis. The latter was noted in the thymic biopsy obtained at 2 to 3 months post-transplant for 7 of 10 subjects with evaluable samples. Naïve T cell counts increased markedly from baseline with median values increasing to ~10<sup>th</sup> percentile for age at 1- and 2-years post-transplant. These values were consistent with data reported in subjects with partial DGA who have not received RVT-802 and are considered sufficient to fight infection. T cell receptor diversity was assessed through immunoscope/spectratyping and flow cytometry. The available data while limited demonstrated a shift from an oligoclonal T cell population to a more Gaussian (normal) population at 1- and 2-year post-transplant. The presence of a broad TCR repertoire in combination with naïve T cell development supports the ability of RVT-802 to produce T cells capable of responding to a wide variety of antigens.

Subjects were required to have measurable T cell responses to PHA >20-fold higher than background or >5,000 cpm to participate in this study. These responses were from oligoclonal T cells that did not develop in the thymus and hence were not able to fight infection but rather could cause autoimmunity. Following RVT-802 treatment, the median T cell proliferative response to PHA normalized (>75,000 cpm) within 1 year indicating the ability to respond to mitogen/antigens. Similar results were observed for other antigens including Con A, sol CD3, immob CD3, and tetanus toxoid indicating the development of a functional T cell population. The only antigen that did not develop a normal T cell response post-transplantation was *Candida* skin test antigen, which was likely due to the lack of environmental exposure in these subjects.

The AE profile of RVT-802 was consistent with the expectation for pediatric, immunocompromised subjects with extensive individual histories of serious medical conditions. Any AE related to the RVT-802 implantation or biopsy, protocol required immunosuppression, or supportive care associated with these procedures to be related to study treatment. Fourteen subjects in the study had at least 1 SAE with a total of 88 events reported within 2 years of

transplantation. The most common SAEs included device related infection (73%), cytokine release syndrome, and pyrexia (20% each). These events were expected given the disease under study. The most common treatment-related AEs included those related to the use of immunosuppression such as hypertension (60%) related to calcineurin inhibitor therapy, cytokine release syndrome (53%) related to RATGAM, and hypomagnesemia (40%) related to calcineurin inhibitor therapy.

Four subjects died within the first post-transplant year (median survival of 231.5 days after RVT-802 transplantation), prior to the development of thymic function. The deaths were due to infections or infection-related complications. Two deaths (both CMV infections) were possibly related to the study treatment. One of these deaths was possibly related to RATGAM, and one death (Subject <sup>(b) (6)</sup>) possibly related to RVT-802. The remaining 2 deaths were unrelated to study treatment.

The safety and efficacy data from this study supports the use of RVT-802 with immunosuppression in subjects with congenital athymia, including subjects with atypical cDGA.

### **6.1.6 Study 25966: Safety and efficacy of thymus transplantation in complete DiGeorge anomaly.**

#### **6.1.6.1 Objectives**

The original objectives of this study were to assess survival, naïve CD4 T cell counts, and the effect of thymus graft dose on naïve CD4 T cell counts at 1 year after transplantation in subjects with cDGA. However, a single Statistical Analysis Plan, (dated 28 Sept 2017 and updated on 19 Sept 2018, was created to support the 10 clinical studies planned for inclusion in the BLA and the objectives were changed to include one- and two-years post-transplant.

#### **6.1.6.2 Design Overview**

This was a Phase 1/2, single-site, open-label, non-randomized clinical trial to treat subjects with typical or atypical cDGA. The study was designed to generate data on the safety and efficacy of RVT-802 as well as an expanded access protocol to allow continued treatment of subjects with RVT-802. Therefore, the protocol remains open and continues to enroll patients.

#### **6.1.6.3 Study Population**

Male or female subjects of any age who met the following criteria were eligible to be included in the study:

##### **Inclusion Criteria**

1. A parent or guardian of the cDGA subject signed the consent form.
2. Medical screening was completed.
3. For a diagnosis of DGA, the subject had to have 1 of the following:
  - Congenital heart disease
  - Hypocalcemia requiring replacement
  - 22q11.2 hemizyosity or 10p13 hemizyosity
  - CHARGE association or *CHD7* mutation
  - A subject with abnormal ears whose mother had diabetes (type I, type II, or gestational) had this risk factor recorded, but it was not sufficient to make the diagnosis of cDGA.
4. To meet criteria of typical cDGA, the subject had to have circulating CD3+ CD45RA+ CD62L+ T cell count <50/mm<sup>3</sup> or <5% of the total T cell count. The

phenotypic evaluation of T cells was done by flow cytometry, which was performed twice; the 2 studies had to show similar immunological findings for a subject to qualify. One assay had to be done within 3 months and the other within 1 month of transplantation.

PHA proliferative response

- For Group 1: T cell proliferative response to PHA of <5,000 cpm or <20-fold above background.
- For Group 2: T cell proliferative response to PHA of >5,000 cpm and <50,000 cpm or >20-fold over background.
- For Group 3: T cell proliferative response to PHA of >50,000 cpm.

For all 3 groups, 2 assays of T cell numbers and PHA responses had to show similar immunological findings [e.g., both had to meet naïve T cell criteria] for a subject to qualify for this study. One assay had to be done within 3 months and the other assay had to be done within 1 month of transplantation. The latter assay was used to assign the subject to a group.

5. To meet criteria of atypical cDGA, the subject had a rash at screening or had previously had a rash. If a rash was present, a biopsy of the rash had to show T cells in the skin. If the rash and adenopathy had resolved, the subject had to still have >50/mm<sup>3</sup> T cells and the naïve T cell (CD45RA+ CD62L+ CD3+ T cells) count had to be <50/mm<sup>3</sup> or <5% of the T cells.

PHA proliferative response

- Group 3: the PHA proliferative response had to be <40,000 cpm on immunosuppression or <75,000 cpm off immunosuppression.
- Group 4: the PHA proliferative response had to be >40,000 cpm on immunosuppression or >75,000 cpm off immunosuppression.

The assay had to be done twice. One assay had to be done within 3 months and the other assay had to be done within 1 month of transplantation. The last assay was used to assign the subject to a group.

Circulating CD3+ T cells

Circulating CD3+ T cells were expected to be >50/mm<sup>3</sup>, but CD45RA+ CD62L+ CD3+ T cells had to be <50/mm<sup>3</sup> or <5% of the total CD3 count. The phenotypic evaluation of T cells was done twice by flow cytometry. One assay within 3 months and the other assay within 1 month of transplantation.

If there was an increase in T cell numbers or activation status, this assay was to be

Exclusion Criteria

1. Heart surgery performed less than 4 weeks prior to projected transplantation date.
2. Heart surgery anticipated within 3 months after the proposed time of transplantation.
3. Rejection by the surgeon or anesthesiologist as surgical candidate.
4. Lack of sufficient muscle tissue to accept a transplant of 4 grams/m<sup>2</sup> BSA.
5. Human immunodeficiency virus (HIV) infection.
6. Prior attempts at immune reconstitution, such as bone marrow transplantation or previous thymus transplantation.

7. CMV infection: For Groups 2, 3, and 4, CMV infection documented by >500 copies/mL in blood by polymerase chain reaction (PCR) on 2 consecutive assays or by 2 positive urine cultures.
8. Ventilator support or positive pressure support such as continuous positive airway pressure or bi-level positive airway pressure support for a condition that was deemed by the Investigator to be severe or irreversible or which renders the subject too clinically unstable to undergo the procedures.

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

All subjects were transplanted with RVT-802 under general anesthesia.

Subjects were treated with 1 of 4 different immunosuppression regimens depending on cDGA phenotype and T cell proliferative response to PHA pre-transplantation. The groups were as follows:

- Group 1: Subjects with typical cDGA (PHA response <5,000 cpm) received no Immunosuppression
- Group 2: Subjects with typical cDGA (PHA response >5,000 cpm but ≤ 50,000 cpm) received RATGAM alone
- Group 3: Subjects with typical (PHA response >5,000 cpm) or atypical cDGA (PHA response ≤ 40,000 cpm on immunosuppression or ≤ 75,000 cpm without immunosuppression) received RATGAM plus cyclosporine (or tacrolimus)
- Group 4: Subjects with atypical cDGA (PHA response >40,000 cpm on immunosuppression or >75,000 cpm without immunosuppression) or maternal engraftment received RATGAM plus cyclosporine (or tacrolimus) plus basiliximab and/or MMF.

#### **6.1.6.5 Sites and Centers**

This study was conducted at a single center (Duke University Medical center) in the United States.

#### **6.1.6.6 Surveillance/Monitoring**

Subjects were followed for 24 months after RVT-802 transplantation. A thymus allograft biopsy was planned for approximately 2 to 3 months post-transplantation. However, a biopsy was not performed if the subject was at significant risk for pulmonary, cardiac, or infectious complications. In addition, biopsies were no longer performed starting January 2016. The thymic biopsy was examined for thymopoiesis and graft rejection for the presence of cytokeratin (marker of thymic epithelium) and for T cells by immunohistochemistry. The subject's immune status was monitored by blood sampling for the number and phenotype of T cells and the proliferative response of the T cells to mitogens and antigens, such as tetanus toxoid.

Most subjects were discharged to home/local hospital with their medical care provided by local pediatric immunologist) following the thymic biopsy at ~2 months post-transplant, unless medically unstable. After transferring the Subject's care to the referring pediatric immunologist, the subject was monitored for AEs by requesting information from the referring physician per the assessment schedule. Requests were also submitted to the referring pediatric immunologist for follow-up testing/blood samples per the protocol schedule of events. However, obtaining the testing/blood samples was dependent upon the parent(s), the referring/local physicians, and the subject's medical condition.

**6.1.6.7 Statistical Considerations & Statistical Analysis Plan**

A single SAP (dated 28 September 2017 and updated on 19 September 2018) was created to support this and the 9 other clinical studies planned for inclusion in this BLA given the legacy data status and similarities across the 10 clinical studies in the RVT-802 program. The endpoints specified in the program-wide SAP were given precedence over the analyses originally planned for this study (See Sec 6.1.6.7.4 Endpoints and Criteria for Study Success).

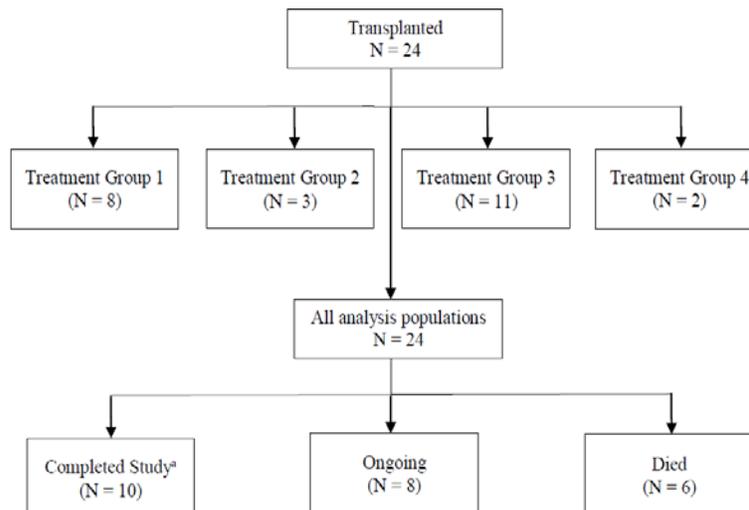
**6.1.6.7.1 Analysis Population and Disposition**

Twenty-four subjects transplanted with RVT-802 as of 15 July 2017 with available data reported through 16 July 2018 are included. All 24 subjects met the criteria for inclusion in the EAS-cDGA, EAS, and FAS analysis populations. Data are presented using the FAS since the analysis populations were identical. As of the data cut-off date for this interim report, 10 subjects (41.7%) had completed at least 2 years of study follow-up and study follow-up was ongoing for 8 subjects (33.3%). A total of 6 subjects (25%) discontinued from the study due to death (Figure 5).

The 6 subjects and their causes of death are listed below:

- Subject (b) (6) sudden catastrophic intracranial hemorrhage.
- Subject (b) (6) respiratory failure from disseminated mycobacterial infection.
- Subject (b) (6) multiorgan system failure as seen in severe septic shock.
- Subject (b) (6) progression of underlying parainfluenza virus 3 pneumonia.
- Subject (b) (6) cardiorespiratory arrest related to anasarca.
- Subject (b) (6); death secondary to disseminated *Candida*.

**Figure 5: Subject Disposition**  
(Applicant's Figure)



#### 6.1.6.7.2 Protocol Deviations

There were no major protocol deviations that impacted subject safety or the integrity of study results.

#### 6.1.6.7.3 Demographics & Disease Characteristics

Most subjects were male (63%) and white (71%) while 21% were black or African American. A third of the population (33%) were of Hispanic/Latino ethnicity.

All subjects had cDGA and was divided evenly between the atypical and typical cDGA. The median time of diagnosis was 12.5 days (range: 0 to 537). Diagnosis on Day 0 was based on the presence of clinical features consistent with DGA; however, the presence of athymia which is required for the diagnosis of cDGA was not confirmed until later using flow cytometry. Nine subjects had open heart surgery at which time the thymus was examined. In 7 of these 9 subjects (29.2%), the thymus was absent. The surgeon visualized hypoplastic thymus in 2 subjects; there was “essentially no thymus present” in Subject (b) (6) and there was a “very small thymic remnant” in Subject (b) (6). Six additional subjects had cardiac surgery prior to enrollment but no comment was made in the operative note regarding the evaluation of thymus (N=3) or it was unknown if the thymus was evaluated (N=3).

Gene mutations or syndromes associated with cDGA included hemizygous deletion of chromosome 22q11.2 (11 subjects, 46%) and CHARGE with a documented *CHD7* mutation (5 subjects, 21%). No gene mutations were identified for 8 subjects (33%) including 5 infants of diabetic mothers (IDM). The mothers of 6 subjects had diabetes (2 mothers each of type I, II, and gestational). One infant (Subject (b) (6)) also had 22q11.2DS while the other 5 IDM had no genetic mutations identified. “Other” types of potential fetal toxin exposure included treatment for typhoid during pregnancy (mother of Subject (b) (6)) and polyhydramnios complications (mother of Subject (b) (6)).

All subjects had congenital cardiac or cardiothoracic vascular anomalies and diminished T cell counts for age. Other frequent disease histories included hypocalcemia (22 subjects, 92%), deafness or ear pinnae anomalies (17 subjects, 71%), growth or mental retardation (15 subjects, 63%), and dysmorphic facies (14 subjects, 58%).

Most subjects (21 subjects, 88%) had a history of infection prior to transplantation. Oral candidiasis was the most frequent infection (9 subjects, 38%), followed by viral upper respiratory tract infection (8 subjects, 33%), Staphylococcal bacteremia (7 subjects, 29%) and pneumonia (6 subjects, 25%). The following were each reported for 5 subjects: bacteremia and device-related infection (e.g., infection detected in catheter). Other pre-transplant infections were reported for 3 subjects or fewer.

Nineteen of the 24 subjects underwent a skin biopsy with T cells detected in 14 of those 19 subjects (74%). The presence of T cells in skin biopsies was expected in atypical cDGA. Nineteen subjects were receiving at least 1 immunosuppressive medication according to the assigned study treatment group. The most common medications ( $\geq 50\%$  of subjects) were cyclosporine (17 subjects, 71%), methylprednisolone (17 subjects, 71%), RATGAM (16 subjects, 67%), and prednisolone (12 subjects, 50%).

#### **6.1.6.7.4 Endpoints and Criteria for Study Success**

The primary efficacy endpoints were survival at 1- and 2-years post-transplant since the profound immunodeficiency of cDGA usually leads to death from infection before the age of 2 years. The only hypotheses that was tested was survival at Years 1 and 2 exceeded 50%, using a binomial exact test. Kaplan-Meier survival analysis was also performed with median follow-up time post-transplantation for all subjects and median survival time post-transplantation for the subjects who died during the study being reported.

The secondary efficacy endpoints included CD3, CD4, CD8, naïve CD4, and naïve CD8 cell counts; proliferative T cell responses to antigens/mitogens (PHA, ConA, Sol CD3, Immob CD3, tetanus toxoid, and *Candida* skin test antigen); TREC; TREG, TCR variability; and biopsy of RVT-802. However, soluble CD3, Immob CD3, TREG, and TRECs were not consistently measured) in this study. Available data on other flow cytometry parameters (DB Neg, TCR $\alpha\beta$ , TCR $\gamma\delta$ , B, NK cells), serum immunoglobulins, isohemagglutinins, and B cell antibody responses to antigens, were also reported as data permitted.

#### **6.1.6.8 Efficacy Analyses**

##### **6.1.6.8.1 Primary Endpoint**

A total of 24 subjects received RVT-802 but one subject had not yet completed one year of follow-up at the time of data cut-off on 16 July 2018. With this subject censored, 18 of 23 subjects (78.3%) were alive at 1 year after transplantation. The binomial exact test with a null hypothesis that no greater than 50% of subjects would survive at Year 1 gave a 95% CI of [0.56, 0.93] with a p-value of 0.0053.

There were 8 subjects who had not completed 2 years of follow-up post-RVT-802. With these 8 subjects censored, 10 of 16 subjects (62.5%) were alive at Year 2 after RVT-802 transplantation. The binomial exact test with a null hypothesis that no greater than 50% of subjects would survive at Year 2 gave a 95% CI of [0.35, 0.85] with a p-value of 0.2272.

Six subjects died within 2 years of transplantation with five subjects dying within the first year. The median survival time for the 6 subjects who died was 128.5 days and ranged from 24 to 480 days after RVT-802 transplantation. The median follow-up time for all 24 subjects was 693 days (approximately 1.9 years) and ranged from 24 to 2103 days (5.8 years) after RVT-802 transplantation. The estimated Kaplan-Meier survival rate at Year 1 was 0.79 with a 95% CI of [0.570, 0.908]. The estimated Kaplan-Meier survival rate at Years 2, 3, 4, and 5 post-transplant was 0.74 (95% CI: 0.506, 0.874).

**6.1.6.8.2 Secondary Endpoints**

**Naïve CD3, CD4, and CD8 Cell Counts**

The median naïve CD3, CD4 and CD8 cell counts at baseline were 2 cells/mm<sup>3</sup> (N=23, range: 0 to 16), 0.65 cells/mm<sup>3</sup> (N=21, range: 0 to 12) and 0 cells/mm<sup>3</sup> (N=21, range: 0 to 6), respectively. At Month 6, these median cell counts increased to 18 (N=16), 10 (N=17), and 3 (N=16) cells/mm<sup>3</sup>, respectively and continued increasing at Year 1 with respective counts of 197 (N=11), 170 (N=11) and 39 (N=11) cells/mm<sup>3</sup>. While flow cytometry data was limited after Year 1, further increases were observed only for naïve CD8 cell count at Year 2 (49 cells/mm<sup>3</sup>, N=4), while naïve CD3 and CD4 cell counts were maintained at the Year 2 assessment (190 [n= 3] and 133 [N=4] cells/mm<sup>3</sup>, respectively). Despite the slight drop in median nave T cell counts at Year 2, the median naïve T cell count was still >100 cells/mm<sup>3</sup>, which is generally considered sufficient to prevent/control infection.

**Total CD3, CD4, and CD8 Cell Counts**

Subjects enrolled in Groups 3 (RATGAM plus cyclosporine [or tacrolimus]) and 4 (RATGAM plus cyclosporine [or tacrolimus] plus basiliximab and/or MMF) had atypical cDGA. They had elevated T cell counts, usually due to an oligoclonal T cell population that was not thymically derived. Therefore, the change in CD3, CD4 and CD8 counts from baseline were not considered clinically meaningful given the elevated total T cell counts at baseline. Despite the elevated total T cell counts observed at baseline among atypical cDGA subjects, the median CD3 and CD4 cell counts increased markedly from baseline (N=24, 183 and N=22, 135 cells/mm<sup>3</sup>, respectively) to Month 6 (N=20, 307 and N=20, 205 cells/mm<sup>3</sup>, respectively) and from Month 6 to Year 1 (N=15, 540 and N=15, 349 cells/mm<sup>3</sup>, respectively). While data were limited at Year 2, the median CD3 and CD4 cell counts (N=5, 396 and N=5, 264 cells/mm<sup>3</sup>, respectively) remained well above the median baseline values. A small increase in median CD8 cell count was observed from baseline (N=22, 18 cells/mm<sup>3</sup>) to Month 6 (N=20, 21 cells/mm<sup>3</sup>) and moderately increased thereafter at Year 1 (N=15, 72 cells/mm<sup>3</sup>) and through Year 2 (N=5, 105 cells/mm<sup>3</sup>).

**Other Lymphocyte Counts (Table 19)**

The median absolute lymphocyte counts fluctuated over time remaining below the 10<sup>th</sup> percentile for age at Years 1 and 2 post-transplantation. Total B and NK cells generally remained normal throughout the course of the study for age and gender. There was an increase in the median total αβ T cells from baseline to Year 2 while the number of γδ T cells fluctuated over time but generally remained within normal limits for age. The double negative T cells remained normal throughout the course of the study for age and gender.

**Table 19: Lymphocyte Subsets (Median in cells/mm<sup>3</sup>)**  
(Reviewer’s Table)

	<b>ALC</b>	<b>B-cell</b>	<b>NK-cell</b>	<b>αβ T cell</b>	<b>γδ T cell</b>	<b>DN T cell</b>
<b>Baseline</b>	1924 (n=24)	987 (n=24)	508 (n=24)	170 (n=23)	33 (n=23)	41 (n=11)
<b>Month 6</b>	1287 (n=17)	627 (n=19)	335 (n=19)	281 (n=16)	14 (n=16)	22 (n=4)
<b>Year 1</b>	1802 (n=14)	724 (n=15)	340 (n=15)	442 (n=12)	38 (n=12)	46 (n=5)
<b>Year 2</b>	1343 (n=4)	557 (n=5)	308 (n=5)	336 (n=3)	13 (n=3)	25 (n=1)

**T Cell Proliferative Response to Phytohemagglutinin**

The median proliferative response to PHA at baseline was 4343 cpm (N=24), which was below the normal PHA response of >75,000 cpm (Table 19). There was data available on only one subject (Subject (b) (6) at 6 months (77,878 cpm). Ten subjects had a PHA response at 1-year with a median of 119,807 cpm; 8 subjects had a normal PHA response >75,000 cpm. Subject (b) (6) had the lowest PHA response at Year 1 (67,172 cpm on 333 days post-transplant) but the response normalized at 215,403 cpm on 404 days post-transplant. Subject (b) (6) was the other subject with a slightly subnormal PHA response (73,231 cpm on Day 414). There were only two subjects with a PHA response reported at Year 2 post-transplant (median 37,816 cpm). One of the 2 subjects (Subject (b) (6) with a low PHA response (PHA response of 5822 cpm on Day 728), was still on immunosuppression for the treatment of pre-existing maternal GVHD.

**Table 20: T cell Proliferative Response to PHA**  
(Reviewer’s Table)

Visit	Response (cpm)	
	Median	Range
Baseline (n=24)	4343	108-73646
Month 6 (n=1)	77878	77878-77878
Year 1 (n=10)	119808	67172-300547
Year 2 (n=2)	37816	5822-69811

**T Cell Proliferative Response to Other Antigens**

The T cell proliferative response to ConA at baseline was available in 7 subjects with a median of 8777 cpm (range: 705 to 59,072) and increased to 44,605 cpm (N=4, range: 27,065 to 112,494) at Year 1. There were only 2 subjects with a ConA response at Year 2 ranging from 735 to 19,606 cpm with no baseline data collected. Thus, a conclusion regarding the response to ConA was not possible given the limited data. Similarly, the post-baseline data collected on T cell proliferation to *Candida* skin test and tetanus toxoid were too sparse to provide information for evaluating the efficacy of RVT-802.

**T Cell Receptor Diversity – Immunoscope/Spectratyping**

There were no data on TCR diversity (TCRVβ repertoire as measured by immunoscope/spectratyping) collected in this study.

**11.1.2.7 T Cell Receptor Repertoire Variability – Flow Cytometry**

The CD4 and CD3 TCR repertoire in subjects treated with RVT-802 was evaluated by flow cytometry using the standard repertoire of 24 Vβ families and compared with the reference normal range. T cell receptor repertoire on CD4 cells was only available for 4 to 5 subjects within the first year post-transplant. The available data showed that 24 of 24 Vβ families (100%) were within the normal reference range at Year 1 post-transplant. A similar pattern was observed with CD3 cells. These data indicate the development of a more diverse T cell repertoire for these subjects within one year of transplantation.

**T Cell Receptor Excision Circles**

The presence of TRECs indicates the presence of recent thymic emigrants and thus implies active thymopoiesis. However, no conclusion could be drawn on the development of TREC in this study given the limited data. Subject (b) (6) had normal TRECs level on CD3 cells (733.5/100,000 cells) on post-transplant Day 423.

**Regulatory T Cells**

There were no data on regulatory T cells collected in this study.

**B Cell Function**

B cell function was measured through the analysis of serum immunoglobulins (IgG, IgA, IgM, and IgE). However, IgG levels were affected by the monthly IGIV replacement therapy (for up to 2 years post-transplant) that subjects were receiving and were not representative of the subjects' endogenous IgG production. Nonetheless, IGIV does not impact the synthesis of IgA, IgE, and IgM and these values are representative of endogenous immunoglobulin levels. The percentage of subjects reporting low levels of IgA and IgM at baseline generally decreased with a higher percentage of subjects reporting normal values at Month 6, Year 1 and Year 2 post-transplant. Despite a shift to a more normal levels over time, 17% and 25% of subjects still reported low values for IgA and IgM at Year 1.

**RVT-802 Biopsy**

Thymopoiesis in RVT-802 biopsies was defined as the presence of a lacy pattern of cytokeratin-positive thymic epithelial cells and the presence of CD3+CD1a+Ki-67+ cells. Biopsy results were available for 9 subjects and there was evidence of thymopoiesis for 8 subjects (88.9%). Subject (b) (6) did not have evidence of thymopoiesis at the time of biopsy but had naïve CD4 T cells (172 cells/mm<sup>3</sup>) at Year 1. There was no evidence of rejection in the biopsies of these 9 subjects.

**Cytomegalovirus and Epstein-Barr Virus Infection Status**

Two subjects who were not immunosuppressed in Group 1 developed CMV infection post-transplantation that were reported as SAEs in this study. No other subjects tested positive for CMV during this study.

- Subject (b) (6) was hospitalized with Grade 3 CMV viremia (~2000 copies) 195 days after RVT-802 transplantation. He was treated with ganciclovir with resolution on Day 225.
- Subject (b) (6) was hospitalized with Grade 3 CMV viremia (viral copies unknown) 158 days after transplantation. Subject was treated with ganciclovir and CMV immune globulin. CMV remained detectable in the blood at 146 copies/mL and <500 copies/mL on Days 265 and 405, respectively. On Day 476 after transplantation, the subject had been off ganciclovir for 3 months and CMV was undetectable.

There was one subject who developed an EBV infection while on the study. Subject (b) (6) had received combination RATGAM, MMF, and cyclosporine (Group 4) prior to RVT-802 transplantation and was hospitalized for tachypnea on Day 39. The PCR for EBV viral load (VL) was positive at 84,900 copies/mL with an increase in ALC from 5029 cells/mm<sup>3</sup> on Day 39 to 19,173 cells/mm<sup>3</sup> on Day 41. The CD4 and CD8 ratio which had been normal prior to transplantation had inverted on Day 40 (CD4 288 cells/mm<sup>3</sup>, CD8 1135 cells/mm<sup>3</sup>, CD4/CD8 ratio 0.25). On Day 40, chimerism testing showed that 87% of the T cells were now maternal, up from 29% prior to the transplant. The EBV VL on Day 44 was 92,000 copies/mL and the subject was treated with ganciclovir from Day 44 to Day 53. By Day 45, the ALC had declined to 2604 cells/mm<sup>3</sup> with the VL declining to 5977 copies/mL on Day 49, which dropped further to 2 copies/mL by Day 77 without any additional treatment. After Day 55, the subject's ALC increased slightly to approximately 5000 cells/mm<sup>3</sup>. Chimerism studies showed that 97% of the T cells were maternal on Day 70, up from 29% on day 44 and 87% from Day 40. EBV remain detectable in multiple blood and tissue samples (liver, sigmoid colon, duodenal biopsies, and BAL) after discharge to the referring hospital on Day 126. The

maternal T cells resulted in GVHD and the subject was treated with potent immunosuppressants leading to reactivation of EBV with a maximum VL >375,000 copies/mL detected on Day 295 that fluctuated over time. A blood culture of EBV was <375 copies/mL on Day 350, a level below the linear range of the assay. EBV VL was still detectable at Day 804 post-transplant but the subject was reported alive at 1979 days (5.4 years). This was significant as this infection would have likely been fatal prior to RVT-802.

#### **6.1.6.8.3 Subpopulation, Exploratory and Post Hoc Analyses**

There was no subpopulation, exploratory or post-hoc analyses conducted in this study.

#### **6.1.6.8.4 Dropouts and/or Discontinuations**

There were no subjects who dropped out of this study. Discontinuation was defined as completing less than two years of follow-up after transplantation with 6 subjects who discontinued due to death (See Section 6.1.6.9.3 Deaths).

### **6.1.6.9 Safety Analyses**

#### **6.1.6.9.1 Methods**

The statistical analyses of safety included all subjects who received RVT-802. Summaries of safety parameters included available data reported within 2 years of transplantation. Adverse events were reported through the data cut-off.

All AEs observed within 2 years of transplantation were included in event summary tables. They were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. The number of events was presented with AEs and SAEs summarized separately by presenting the number and percentage of subjects having any event, having a related event, having an event in each MedDRA system organ class (SOC) and preferred term (PT). Each individual event was evaluated for their intensity, relationship and outcome.

A subject with more than one occurrence of the same AE in a SOC was counted only once in the total of those experiencing AEs in that particular SOC. If a subject had the same AE at more than one severity or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug was given precedence. Any missing severity, causality, or outcome was not imputed and classified as unknown. The severity and relationship to study treatment were presented with related events defined as definitely, probably, or possibly related to study treatment or with an unknown relationship. Non-infection-related AEs and SAEs were graded (Grades 1-5) according to the National Cancer Institute's CTCAE; Version 3). Infection-related AEs were evaluated using either CTCAE criteria or criteria defined in the BMTCTN definitions of infection severity. Infection-related AEs with BMTCTN severity  $\geq$  severe were included in the analysis of AEs of Grade  $\geq$  3. Life-threatening infection-related AEs with an outcome of fatal were reported as Grade 5 events in the summary tables. For the purposes of summarization, all AEs, including infection-related AEs reported in the first 2 years post-transplantation were included in AE summary tables, unless otherwise specified.

Adverse events of special interest (AESI) included infection-related, autoimmune diseases, GVHD, rashes, and granulomas and were summarized by SOC and PT. Infection-related AEs were of interest as the ability to respond to and control infections was indicative of the development of thymic function. Autoimmune diseases, GVHD, and granulomas were potential AEs that may have been related to study therapy given the ability of RVT-802 to reconstitute the immune system. Granulomas were of particular interest as they may be

indicative of the development of sarcoidosis. If granulomas were found, evidence of sarcoidosis including ACE level and eye examinations were performed. Rashes were of interest as they may have been indicative of new onset or flare of pre-existing features associated with the atypical cDGA. Rashes persisting more than 2 weeks were biopsied to assess the etiology of the rash. Finally, subjects were followed for the development of cancers given the risk of malignancy in subjects with poor T cell function.

#### **6.1.6.9.2 Overview of Adverse Events**

The baseline median BSA of the 24 subjects used to calculate the RVT-802 dose was 0.37 m<sup>2</sup> (range 0.27 to 0.46 m<sup>2</sup>). The median number of RVT-802 slices transplanted was 25 (range: 10 to 52) corresponding to a median of 12,268 mm<sup>2</sup>/m<sup>2</sup> (range: 7104 to 21,734). In 2015, the recommended RVT-802 dose range was set to a maximum dose of 20,000 mm<sup>2</sup>/m<sup>2</sup> BSA. Three years prior to the implementation of this dosing range, 2 subjects received a dose greater than 20,000 mm<sup>2</sup>/m<sup>2</sup>. Subject <sup>(b) (6)</sup> received a dose of 20,328 mm<sup>2</sup>/m<sup>2</sup> (45 RVT-802 slices) and Subject <sup>(b) (6)</sup> received 21,734 mm<sup>2</sup>/m<sup>2</sup> (52 RVT-802 slices).

All 24 subjects in the study had at least 1 AE with 19 subjects reporting at least 1 SAE (79.2%). Overall, 20 subjects (83.3%) had at least 1 AE ≥ Grade 3 including AEs that were severe in intensity for 4 subjects (16.7%), life-threatening for 10 subjects (41.7%), and fatal for 6 subjects (25%). There were 15 subjects (62.5%) with at least 1 AE related to study treatment, including AEs graded as severe for 3 subjects (12.5%) and life-threatening for 4 subjects (16.7%). No subject had a fatal event that was related to treatment.

#### **Frequency of Adverse Events**

There were 411 AEs observed in this study. The most frequently observed AEs were in the following SOCs: infections and infestations (24 subjects, 100%), general disorders and administrative conditions (15 subjects, 62.5%), gastrointestinal disorders (14 subjects, 58.3%), respiratory, thoracic and mediastinal disorders (14 subjects, 58.3%), skin and subcutaneous disorders (14 subjects, 58.3%), blood and lymphatic system disorders (14 subjects, 58.3%), investigations (13 subjects, 54.2%), and metabolism and nutrition disorders (13 subjects, 54.2%).

The most frequent AEs (>20% of subjects) within 2 years of transplantation were pyrexia (13 subjects [54.2%], 17 events) followed by device-related infection (12 subjects [50%], 33 events), rash (10 subjects [41.7%], 14 events), and diarrhea (10 subjects [41.7%], 11 events). Most of the other AEs were infection-related (AESIs of viral and lower respiratory tract, pneumonia, and oropharyngeal candidiasis) or associated with laboratory (increased ALT, anemia, neutropenia, thrombocytopenia) or vital sign abnormalities (hypertension).

#### **Severity of Adverse Events**

There were 187 AEs of Grade ≥ 3 with 20 subjects (83.3%) having at least 1 AE that was Grade ≥ 3 in intensity. The SOCs in which Grade ≥ 3 AEs were most frequent (on the basis of subject count) was infections and infestations (19 subjects, 79 AEs), blood and lymphatic system disorders (11 subjects, 16 AEs), respiratory, thoracic and mediastinal disorders (10 subjects, 19 AEs), and investigations (8 subjects, 16 AEs). In these SOCs, device-related infection and increase of AST were the most noted PT for 10 (28 AEs) and 7 (7 AEs) subjects, respectively followed by anemia, neutropenia, and respiratory failure for 6 subjects each.

### Relationship to Investigational Product

The AEs related to the RVT-802 implantation procedure or biopsy, RVT-802 implantation, protocol required immunosuppression, or supportive care associated with these procedures were assessed as TEAEs. Autoimmune diseases diagnosed after RVT-802 transplantation was considered possibly related to RVT-802 transplantation given the development of thymic function after transplantation. Treatment-related autoimmune diseases included autoimmune cytopenias (3 subjects, 12.5%) and transverse myelitis (1 subject, 4.2%). Hypothyroidism (4 subjects, 16.7%) was considered unlikely related because some subjects with cDGA present with hypothyroidism prior to transplantation and ~20% of subjects with partial DGA develop hypothyroidism in adulthood.

Fifteen subjects had 43 AEs that were related to treatment. There was no concentration of study treatment-related events in any SOC. The most frequent study treatment-related AEs (>2 subjects) were cytokine release syndrome (5 subjects [20.8%], 5 events) and hypomagnesemia (4 subjects [16.7%], 4 events). Cytokine release syndrome was considered related to RATGAM administration while hypomagnesemia was considered related to calcineurin inhibitor therapy.

There were 7 subjects (29.2%) with 14 AEs of Grade  $\geq 3$  that were considered study treatment related but none was observed in more than 1 subject. The treatment-related, Grade  $\geq 3$  AEs were reported for single subjects were increased ALT, increased AST, anemia, neutropenia, proteinuria, renal failure, renal tubular acidosis, hemolytic anemia, immune thrombocytopenic purpura, gastrointestinal hemorrhage, cytokine release syndrome, acidosis, transverse myelitis and hypertension.

#### 6.1.6.9.3 Deaths

There were 6 subjects who died in this study. A brief narrative of each is provided:

- Subject <sup>(b) (6)</sup> is a white male with typical cDGA with congenital anal/rectal anomalies, cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, esophageal anomalies, renal anomalies, hypocalcemia, and limb anomalies. He was 502 days of age at the time of RVT-802 transplantation (total dose 15,731 mm<sup>2</sup>/m<sup>2</sup>). Subject's post-op course was complicated by the development of Omenn syndrome, multiple infections, seizures, pneumonia with respiratory arrest, cardiac arrest, and renal insufficiency. The subject received immunosuppressive therapy including CSA (from 242 to 266 days), methylprednisolone (from 242 to 311 days, from 354 to 404 days, and from 460 to 479 days), tacrolimus (from 267 to 464 days), azathioprine (from 306 to 358 days), prednisolone (from 312 to 353 days), and MMF (from 358 to 461 days) for Omenn syndrome. The subject suffered a cerebral hemorrhage on Day 478 post-transplant likely due to uremic associated coagulopathy and the subject's family withdrew life support on Day 480.
- Subject <sup>(b) (6)</sup> is a white male who was transplanted with RVT-802 (total dose 8326 mm<sup>2</sup>/m<sup>2</sup>) on Day 201 of life. Phenotypic features included coloboma, congenital cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, dysmorphic facies, genital hypoplasia, growth or mental retardation, hypocalcemia, and rib or vertebral anomalies with a DGA gene mutation of CHARGE syndrome and *CHD7*. The subject received CSA (from 14 to 4 days prior to transplant, from 1 to 2 days and 44 to 125 days post-transplant), methylprednisolone (from 4 days prior to 1 day post-transplant and ~91 to 146 days post-transplant), RATGAM (3 doses

from 4 days to 1 day prior to transplant), prednisolone (from 97 to 100 days post-transplant), and rituximab (on day 143 post-transplant). The subject was hospitalized for bacteremia and blood cultures grew *Mycobacterium avium* complex (MAC) 59 days after transplantation. He developed respiratory failure at 120 days post-transplant, required bilevel positive airway pressure ventilation and was intubated on Day 126 and transitioned to an oscillator on Day 127. Subject was continued on various types of mechanical ventilation until his death on Day 149 when ventilatory support was withdrawn. An autopsy indicated the cause of death was respiratory failure from disseminated MAC.

- Subject <sup>(b) (6)</sup> was a male subject with atypical cDGA who received RVT-802 (total dose of 10,277 mm<sup>2</sup>/m<sup>2</sup>) on Day 541 of life. Phenotypic features included congenital cardiac/thoracic vascular anomaly, diminished T cell counts for age, dysmorphic facies, growth or mental retardation, hypocalcemia, rib or vertebral anomalies, and tracheal anomalies. His DGA gene mutation was a hemizygous deletion of chromosome 22q11.2. He received CSA (from 224 days prior to 178 days post-transplant), methylprednisolone (from 5 days to 1 day prior to transplant), RATGAM (3 doses from 5 days to 2 days prior to transplant), prednisolone (from 37 to 69 days, and then Day 100 until death), prednisone (from 69 to 99 days) and sirolimus (from 131 days post-transplant until death). The post-op course was complicated by *S epidermidis* central line infection, pancreatitis, pneumonia (trach cultures positive for *Pseudomonas* and *Stenotrophomonas*), and renal failure. The subject developed septic shock and multiple organ dysfunction 263 days after transplantation and died. The cause of death was reported as multi-organ system failure due to septic shock. Infection in the lungs was also noted during autopsy.
- Subject <sup>(b) (6)</sup> was a male with atypical cDGA manifesting as congenital cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, and renal anomalies. The subject was transplanted with RVT-802 (total dose 13,098 mm<sup>2</sup>/m<sup>2</sup>) on Day 447 of life. He received CSA (from 280 days to 55 days prior to transplantation and from 14 days prior to 22 days after transplantation), methylprednisolone (from 280 days to 265 days prior to transplantation and from 5 days to 1 day prior to transplantation), and RATGAM (3 doses from 5 days to 2 days prior to transplantation). The subject developed Grade 3 hypoxia 3 days after transplantation. He had been extubated the previous day and had a history of parainfluenza virus 3 upper respiratory tract infection and *Varicella-zoster*. The subject also developed severe fluid retention, anasarca, and worsening renal function and died on Day 24 after transplantation. The cause of death was reported as progression of underlying parainfluenza virus 3 pneumonia.
- Subject <sup>(b) (6)</sup> was a male with atypical cDGA presenting with congenital anal/rectal anomalies, cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, dysmorphic facies, growth or mental retardation, hypocalcemia, limb anomalies, renal anomalies, rib or vertebral anomalies, and tracheal anomalies. He received RVT-802 (total dose 11,437 mm<sup>2</sup>/m<sup>2</sup>) on Day 429 of life. The subject was immunosuppressed with MMF (from 284 to 1 day prior to transplant), prednisolone (from 296 to 41 days prior to transplant, from 23 to 19 days prior to transplant, and from 47 to 81 days post-transplant), CSA (from 71 days prior to 21 days post-transplant), methylprednisolone (from 40 to 24 days prior to transplant, from 19 to

1 day prior to transplant, Day 3, and from 30 to 46 days post-transplant), RATGAM (3 doses from 5 days to 3 days prior to transplant), and tacrolimus (from 21 to 106 days post-transplant). The post-op course was complicated by bacteremia with blood cultures from his central line positive for *E faecalis*, *K pneumoniae*, *S epidermidis*, and *S mitis* on Day 91 post-transplant. He was intubated for respiratory failure on Day 100. Subject had multiple cardiac arrest and anasarca. The subject developed significant head and neck swelling and had a complex airway that required an emergency tracheostomy. The edema was possibly related to blockage of vessel emptying into the heart. The subject failed to diurese and died of a cardiorespiratory arrest related to anasarca on Day 108.

- Subject <sup>(b) (6)</sup> was a male with atypical cDGA manifesting as congenital cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, dysmorphic facies, genital hypoplasia, growth or mental retardation, hypocalcemia, limb anomalies, rib or vertebral anomalies, and tracheal anomalies. The subject was transplanted with RVT-802 (total dose 8034 mm<sup>2</sup>/m<sup>2</sup>) on Day 497 of life. He was immunosuppressed with CSA (ongoing from 30 days prior to transplant), methylprednisolone (from 30 to 25 days prior to transplant, from 6 to 1 day prior to transplant, and from 8 to 75 days post-transplant), prednisolone (from 21 to 6 days prior to transplant), RATGAM (3 doses from 4 to 1 day prior to transplant) and basiliximab (from 6 to 7 days post-transplant). The post-op course was complicated by respiratory infection (BAL culture positive for *Stenotrophomonas maltophilia*), cardiac failure, systemic fungal infection, pancreatitis, acute respiratory and renal failure. A skin culture of a diaper rash was positive for rare *Candida albicans* and rare gram-negative rods on Day 74. He died of systemic Candidiasis 89 days after transplantation. A pancreatic biopsy obtained at autopsy was positive for *Candida lucitenia* and *Candida albicans* although the liver and spleen were negative for *Candida*.

#### **6.1.6.9.4 Nonfatal Serious Adverse Events**

Nineteen subjects (79.2%) had at least 1 SAE within the first 2 years of transplantation. There were 123 SAEs with the most frequent by SOC being infections and infestations (18 [75%] subjects, 61 events) and respiratory, thoracic and mediastinal disorders (12 [50%] subjects, 20 events). Device-related infection (infected central venous catheter) was the most frequent SAE (12 subjects, 50%) followed by respiratory failure and pyrexia for 6 subjects each (25%). Eight of the 123 SAEs were treatment-related. These included transverse myelitis, immune thrombocytopenic purpura, neutropenia, device-related infection (e.g., central catheter infection), proteinuria, pancreatitis, renal failure, and hemolytic anemia.

#### **6.1.6.9.5 Adverse Events of Special Interest (AESI)**

AESI were defined as infections, cancers, autoimmune diseases, GVHD, rashes, and granulomas. Nineteen subjects (79.2%) had 57 non-infection-related AESIs. The most frequent AESI were rash (10 subjects, 14 AEs), neutropenia (6 subjects, 6 AEs), thrombocytopenia (6 subjects, 6 AEs), cytokine release syndrome (5 subjects, 6 AEs), hypothyroidism (4 subjects, 4 AEs), urticaria (3 subjects, 5 AEs), and Omenn syndrome (autologous GVHD) (3 subjects, 3 AEs). All other AESIs occurred in 2 subjects or fewer. There were 4 AESIs that were treatment-related: rash (N=2), cytokine release syndrome (N=5), urticaria (N=2), and thrombocytopenia (N=1).

Three subjects developed Omenn syndrome (autologous GVHD). Subject <sup>(b) (6)</sup> had a flare of pre-existing Omenn syndrome associated with atypical cDGA which required prolonged

immunosuppression including alemtuzumab. Two other subjects (Subjects (b) (6) ) developed Omenn syndrome post-transplant that was considered related to their atypical cDGA and not RVT-802. The disease may have been present but undetected prior to transplantation. Subject (b) (6) had chronic diarrhea prior to RVT-802 which may have been due to Omenn syndrome although the diagnosis of Omenn syndrome was not confirmed until 35 days after transplantation.

All subjects had at least 1 infection-related AE for a total of 146 infection-related events (Table 20). The most frequent infection-related AE was device-related infection, which was observed for 50% of study subjects. Infection-related AEs of respiratory failure due to mycobacterial infection, parainfluenzae pneumonia, and systemic *Candida* reported by a single subject each (Subjects (b) (6) ), respectively) were SAEs that resulted in death.

**6.1.6.9.6 Vital Signs & Physical Examination**

The most frequent vital sign AE was pyrexia (13 subjects, 54.2%) and was the only AE that was rated Grade ≥ 3 for more than 1 subject (2 subjects, 8.3%). There were only two vital sign AEs (8.3%) that were treatment-related. Pyrexia in Subject (b) (6) and hypertension due to calcineurin therapy. Vital sign related SAEs included pyrexia (6 subjects, 25%).

There were no data available for findings on physical examination in this study.

**Table 21: Infection-Related AEs (>1 Subject)**  
(Applicant’s Table)

Preferred Term	FAS	
	(N = 24)	
	N	(%) E
Number of infection-related AEs	24	(100.0) 146
Device-related infection	12	(50.0) 33
Viral upper respiratory tract infection	7	(29.2) 7
Lower respiratory tract infection bacterial	6	(25.0) 12
Oropharyngeal candidiasis	5	(20.8) 6
Pneumonia	5	(20.8) 6
Upper respiratory tract infection	3	(12.5) 4
<i>Enterobacter</i> pneumonia	3	(12.5) 3
Fungal skin infection	3	(12.5) 3
Gastroenteritis norovirus	3	(12.5) 3
Urinary tract infection bacterial	2	(8.3) 5
<i>Klebsiella</i> bacteraemia	2	(8.3) 3
<i>Cytomegalovirus</i> viraemia	2	(8.3) 2
Oral candidiasis	2	(8.3) 2
Pneumonia pseudomonal	2	(8.3) 2
Sinusitis bacterial	2	(8.3) 2

**6.1.6.9.7 Clinical Laboratory Results**

This study population of infants with cDGA, who were approximately 5 months to 1.8 years at the time of RVT-802 transplantation, had a history of abnormal laboratory results that continued during the study. Analyses of individual safety laboratory parameters assessed in the study showed no clinically meaningful overall changes from baseline.

The most frequent laboratory AEs included increased AST (7 subjects, all of which were Grade  $\geq 3$  in intensity), anemia (7 subjects), increased ALT, neutropenia, and thrombocytopenia for 6 subjects each. Hypomagnesemia (4 subjects, 16.7%) was the most frequent laboratory AE that was related to study treatment (calcineurin therapy), followed by increased AST and increased ALT reported for 2 subjects each. Single occurrences of anemia, thrombocytopenia, neutropenia, and increased blood creatinine were considered treatment-related and were reported in one subject each.

Abnormal laboratory AEs that were  $\geq$ Grade 3 intensity included increased AST (5 subjects, 20.8%), anemia (5 subjects, 20.8%), increased ALT (2 subjects, 8.3%). Abnormal laboratory AEs reported in single subjects (4.2%) were neutropenia, increased amylase, decreased blood albumin, GGT, and hypokalemia.

There were several abnormal laboratory results that were considered life-threatening SAEs and included neutropenia (5 subjects, 20.8%), increased AST, increased ALT, and hypernatremia, each of which was reported for 2 subjects (8.3%). Other abnormal laboratory results that were considered SAEs included increased ALT and AST, anemia, neutropenia, hyperkalemia, and hypoglycemia, all reported for single subjects (4.2%).

#### **6.1.6.10 Study Summary and Conclusions**

Study 25966 was designed to evaluate the safety and efficacy of RVT-802 in subjects with cDGA. Twenty-four subjects were enrolled in 1 of 4 treatment groups depending on their cDGA phenotype (12 typical and 12 atypical subjects) and pre-transplant T cell proliferative response to PHA:

- Group 1 – no immunosuppression (N=8)
- Group 2 – RATGAM alone (N=3)
- Group 3 – RATGAM plus cyclosporine (or tacrolimus) (N=11)
- Group 4 – RATGAM plus cyclosporine (or tacrolimus) plus basiliximab and/or mycophenylate (N=2).

The median age of the population on the day of RVT-802 transplantation was 388 days. Most subjects (71%) were white; 21% of subjects were black or African American, and more than 60% of study subjects were male. All subjects were included in the 3 analysis populations defined for the study (EAS-cDGA, EAS, and FAS).

The primary endpoint was survival at 1- and 2-years post-transplant. However, the analysis is incomplete since 1 subject had not reached the 1-year timepoint and 8 subjects had not reached the 2-year timepoint at the time of data cut-off. At 1-year post-transplant, 18 of 23 subjects (78.3%) were alive, with a 95% CI of [0.56, 0.93] and a p-value of 0.0053 from the binomial exact test on survival  $>50\%$ . Survival at Year 2 post-transplantation was 62.5% (10 of 16 subjects; 8 subjects were censored) with a 95% CI of [0.35, 0.85] and a p-value of 0.2272 from the binomial exact test on survival  $>50\%$ . The estimated Kaplan-Meier survival rate was 0.79 (95% CI: 0.570, 0.908) at Year 1 and 0.74 (95% CI: 0.506, 0.874) at 2, 3, 4, and 5-years post-transplant.

For the secondary efficacy assessments, there were improvement from baseline in immune function at Month 6, Year 1, and Year 2. The median naïve CD3, CD4, and CD8 cell counts increased markedly from baseline to Month 6, Year 1, and were sustained at Year 2. Similarly, the median total CD3, CD4, and CD8 T cell counts showed marked increases from baseline through Year 1.

T cell proliferative response to PHA normalized at 1-year post-transplant in 8 of 10 subjects with available data; the remaining 2 subjects developed near normal PHA responses (67,172 and 73,231 cpm). At Year 2, the median response to PHA decreased to 37,816 cpm, but this result was based on data from only 2 subjects. The values for both subjects were below normal (>75,000 cpm), but Subject (b) (6) was still on immunosuppression for pre-existing maternal GVHD.

Improvements in T cell function was corroborated by histologic evidence of thymopoiesis for 8 of 9 subjects at 2 months post-transplant. While one subject (Subject (b) (6)) did not have definitive evidence of thymopoiesis at the time of biopsy, flow cytometry showed that the subject developed naïve T cells at Year 1 (172 cells/mm<sup>3</sup>) indicating thymopoiesis.

Thymic regeneration was further corroborated by 2 subjects (Subject (b) (6) and Subject (b) (6)) who developed CMV infections approximately 5- and 6-months post-transplant. Both subjects survived these infections, demonstrating the robustness of the immune response enabled by RVT-802. Another subject (Subject (b) (6)) developed EBV post-transplantation. While this event was still ongoing at the time of this Application as EBV could still be detected at low levels, the subject remained alive at the time of the latest follow-up at 5.4 years after transplantation. These findings are significant since the infections would likely have been fatal without RVI-802 transplantation.

The AE profile was consistent with that expected in this population of pediatric, immunocompromised subjects. Nineteen subjects had at least 1 SAE, most of which were in the infections and infestations SOC. Device-related infection (i.e., catheter associated infection) was the most frequently observed SAE and most frequently observed infection-related AE. Of the 123 SAEs, 8 were considered related to study treatment and included transverse myelitis, neutropenia, device-related infection, immune thrombocytopenic purpura, proteinuria, pancreatitis, renal failure, and hemolytic anemia.

The most frequent AE in this study was pyrexia. The most common Grade  $\geq 3$  AEs were device-related infection and increased AST. Grade  $\geq 3$  AEs related to study treatment was seen in 7 subjects. In general, the overall incidence of any individual study TEAE was low. The most frequent study TEAEs were cytokine release syndrome and hypomagnesemia, which were considered related to RATGAM administration and calcineurin inhibitor therapy, respectively.

Autoimmune conditions secondary to an abnormal distribution of T cells was expected since RVT-802 does not immediately correct the T cell repertoire. All post-transplant autoimmune conditions were considered treatment-related and included autoimmune cytopenias (blood and lymphatic system disorders in 3 subjects, 12.5%) and transverse myelitis (1 subject 4.2%). The etiology of the transverse myelitis is unknown. The subject had a C77G polymorphism in the PTPRC (CD45) gene which has been reported to be associated with multiple sclerosis, autoimmunity and infectious diseases. The role of this mutation in this subject's disease is unknown. Hypothyroidism (4 subjects, 16.7%) was also considered unlikely related because ~20% of partial DGA subjects develop hypothyroidism as adults.

There were 6 deaths in this study (25%); 5 subjects died in the first-year post-transplant and one subject within the second year. The causes of death included cerebral hemorrhage, respiratory failure, multiple organ dysfunction syndrome, viral parainfluenza pneumonia,

generalized edema, and systemic *Candidiasis*. None of these deaths were considered related to study treatment.

These safety and efficacy data support the use of RVT-802 in subjects with congenital athymia, including cDGA, with or without the use of immunosuppression.

## **6.2 Supporting Studies**

### **6.2.1 Study 51692: Thymus Transplantation for Immunodeficiency, Hematologic Malignancies, and Autoimmune Disease Related to Poor Thymic Function**

#### **6.2.1.1 Objectives**

To make thymus transplantation available on an expanded access basis to patients with immunodeficiency, malignancies, and/or severe autoimmune disease related to poor thymic function.

#### **6.2.1.2 Design Overview**

This was a single-site, open-label, nonrandomized, study to provide expanded access to athymic patients (other than DGA) in whom the development of naïve T cells would be expected to lead to clinical improvement. This would include patients with malignancies, immunodeficiency, and/or severe autoimmune disease related to poor thymus function secondary to primary or acquired thymus deficiency.

#### **6.2.1.3 Study Population**

##### **Inclusion Criteria**

1. Have had an immunodeficiency, malignancy, or severe autoimmunity for which development of naïve T cells would be expected to lead to clinical improvement. Examples of eligible underlying conditions included the following:
  - a. Immunodeficiency secondary to primary or acquired thymus deficiency;
  - b. EBV or CMV related lymphoma secondary to primary or acquired thymus deficiency;
  - c. Autoimmune disease likely secondary to primary or acquired thymus deficiency.
2. Have given written consent (or consent of parent/legal guardian as applicable).

##### **Exclusion Criteria**

1. Unrepaired cyanotic congenital heart disease;
2. Uncontrolled infections defined as requiring a ventilator, dialysis, or vasopressor support or potentially requiring such support within 6 months;
3. Pregnancy
4. Tested positive for HIV

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

Subjects received RVT-802 surgically implanted into their quadriceps muscles in an open procedure under general anesthesia. The RVT-802 doses that were transplanted:

Subject <sup>(b) (6)</sup>: 6489 mm<sup>2</sup>/m<sup>2</sup> in 15 slices.

Subject <sup>(b) (6)</sup>: 4523 mm<sup>2</sup>/m<sup>2</sup> in 19 slices.

In preparation for RVT-802 treatment, subjects received immunosuppression depending on their immune status. These regimens were based on standard of care practices, subject condition, and history of other chemotherapy administration. Adjunctive chemotherapy was allowed for subjects with malignancy.

**6.2.1.5 Sites and Centers**

This was conducted by a single Sponsor/Investigator at DUMC. Subjects transplanted between 05 August 2014 (IRB approval date) and 15 July 2017 were included in this report. Study data were included through 31 December 2017.

**6.2.1.6 Surveillance/Monitoring**

Subjects were followed as inpatients or outpatients at DUMC for 2 months following RVT-802 transplantation. Subjects received SOC monitoring while at DUMC with the schedule tailored to the subject's underlying medical condition. Standard blood counts were done at least once a week for 2 months, or for as long as the subject was on immunosuppression. After 2 months, and after immunosuppression had stopped, standard blood counts were assessed once a month for the first year after transplant.

A thymus allograft biopsy was planned for ~2 months after transplantation with the biopsied tissue examined for thymopoiesis by immunohistochemical staining. Concurrent with this, the blood was evaluated for T cell chimerism. The chimerism test was repeated at 6 months after transplantation if thymic donor T cells were present. Blood samples were also collected for flow cytometry, including CD3, CD4, CD8 and naïve T cell numbers at 6 months and 1 year after transplantation.

Prophylactic medications were given as clinically indicated to prevent infection and subjects received supportive care such as blood components, antibiotics, immunoglobulin replacement, and other interventions as appropriate for their medical care.

**6.2.1.7 Statistical Considerations & Statistical Analysis Plan**

This was an expanded access study and thus, no formal hypothesis testing or statistical analyses were performed. Narratives were presented for the two subjects in this study.

**6.2.1.7.1 Study Population and Disposition**

The protocol design did not specify a planned enrollment number, as the Applicant could not predict the exact number of subjects available for enrollment. The Applicant anticipated that 2 subjects could be treated per year under this protocol. As of 15 July 2017, two subjects had received RVT-802 under this protocol and available data through 31 December 2017 were included in this report. This study was ongoing at the time of reporting and a full study report is planned upon study closure.

**6.2.1.7.2 Protocol Deviations**

There were no protocol deviations reported.

**6.2.1.7.3 Demographics & Disease Characteristics**

Two subjects had been treated in Study 51692 at the time of this Application. Both subjects completed at least two years of follow-up post-transplant. Subjects (b) (6) were 1017 (~2 years and 9 months) and 6163 (~16 years, 10 months) days old, respectively, on the day of transplantation. The Subjects' background characteristics and treatment are summarized in Table 21.

Subject (b) (6) was a white male with typical cDGA who was born without T cells and abnormally low T cell excision circles (TRECs). In the first 3 months of life, extensive genetic testing ruled out all known genetic defects for severe combined immunodeficiency (SCID) and DiGeorge Syndrome, including 22q11.2 deletion syndrome and it was concluded that he had an unknown form of SCID. Subsequently, after 2 cord blood transplants, it was

recognized that he had cDGA based on the clinical presentation of heart defect (atrial septal defect), hypoparathyroidism and the absence of T cells. There was no familial history of cDGA.

**Table 22: Subject Demographics and Disease Characteristics**

(Applicant's Table)		
	Subject <sup>(b) (6)</sup>	Subject <sup>(b) (6)</sup>
Age at time of transplantation (days)	1017	6163
Gender	Male	Male
Race	White	White
Diagnosis	cDGA	cDGA (atypical)
Previous treatment	Cord blood transplantation x 2	Cord blood transplantation
Immunosuppression prior to transplantation	Methylprednisolone, 22 mg once, Day -5; Methylprednisolone, 5.5 mg every 6 h, Days -5 to -2; RATGAM 22 mg daily on Days -5 to -3	Fludarabine, 25 mg/m <sup>2</sup> daily, Days -4 to -2; CSA (dosing to target level 200 to 300 ng/ml), Days -4 to 0

The subject received an allogeneic unrelated 10/10 cord blood transplant at 4 months of age. Although he initially had detectable donor T-cells, these disappeared without evidence of sustained T cell engraftment. Because he remained T cell lymphopenic (13 cells/mm<sup>3</sup> T cells at 7 months post-CBT), he received a second unrelated cord blood transplant. After each transplant, the subject had successful engraftment of all lineages except T cells. When the subject was 1.5 years old, the transplant was considered unsuccessful and he was referred to the Investigator at DUMC.

His medical history included an atrial septal defect, hip dysplasia, hypoparathyroidism, hypospadias, diarrhea, gastroesophageal reflux disease, failure to thrive, hyperphosphatemia, hypocalcemia, atopic dermatitis, central venous catheterization and CBT. He had been immunized for hepatitis B, presumably at birth. His pre-transplantation infection history included a gastroenteritis enteroviral and upper respiratory tract viral infection (coronavirus, enterovirus and rhinovirus). The cDGA phenotype at screening included congenital cardiac/thoracic vascular anomaly, diminished T cell counts for age, genital hypoplasia and hypocalcemia.

At screening on Day -18, few CD3 (6 cells/mm<sup>3</sup>), CD4 (0 cells/mm<sup>3</sup>) and CD8 (1 cells/mm<sup>3</sup>) T cells were detected. There were no naïve CD3, CD4 or CD8 cells detected by flow cytometry. There were 21 cells/mm<sup>3</sup> NK cells and 1,111/mm<sup>3</sup> B cells. His PHA response was 370 cpm with a background of 121 cpm, compared to a control value of 97,614 cpm with a background of 224 cpm. No CMV or EBV was detected in blood samples.

Subject <sup>(b) (6)</sup> is a white male who was diagnosed with atypical cDGA in infancy. His phenotype at screening included congenital cardiac anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, growth or mental retardation, hypocalcemia, genital hypoplasia and rib or vertebral anomalies. He also had many of the symptoms of CHARGE syndrome but subsequent sequencing of CHD7 (Day -9) did not reveal any mutations in CHD7. However, he was the infant of a diabetic mother (Type I maternal diabetes).

The subject received a CBT on Day 79 of life. However, there was poor engraftment and the subject had low (4%) naïve CD4 T cell counts with an inverted CD4 to CD8 ratio within 5 years. He had recurrent EBV lymphoma (3 times over 4 years) as an adolescent. The

expected prognosis was recurrent lymphoma that would be refractory to chemotherapy. Therefore, the subject was enrolled in Study 51692 with the anticipation that treatment with RVT-802 would enable the subject to develop thymic function to control his recurrent EBV lymphoma.

His medical history at screening included ear malformation, heart disease, lymphopenia, hypogammaglobulinemia, micropenis, patent ductus arteriosus, spina bifida, hypoacusis, hypoparathyroidism, diarrhea, gastroesophageal reflux disease, intestinal mass, large intestinal ulcer, stomatitis, sinusitis, body height below normal, weight decreased, decreased WBC, decreased appetite, hypocalcemia, vitamin D deficiency, rib deformity, EBV associated lymphoma, speech disorder, asthma, bronchiectasis, alopecia, rash, rash erythematous, seborrheic dermatitis, cardiac operation, central venous catheterization, cord blood transplant therapy, graft versus host disease (GVHD) after cord blood transplantation, gastrostomy, esophagogastric fundoplasty, splenectomy and hypertension. His pre-transplantation infection history included a respiratory syncytial virus infection (detected at screening), upper respiratory tract infection bacterial (pseudomonas infection in nasal and sinus cultures), pneumonia, EBV viremia, pseudomonal bacteremia, and systemic bacterial infection (*Klebsiella pneumoniae* and *Enterobacter cloacae*).

The total CD3, CD4 and CD8 counts at screening on Day -11 were 1434, 112 and 1320 CD8 cells/mm<sup>3</sup>, respectively. There were no naïve CD4 or CD8 cells consistent with a lack of thymic function. Similarly, there were no B cells but NK cells were 109 cells/mm<sup>3</sup>. His PHA response was 4454 cpm with a background of 26 cpm compared to a control value of 185,891 cpm with a background of 30 cpm. No CMV or EBV viruses were detected in blood or plasma samples.

#### **6.2.1.7.4 Endpoints and Criteria for Study Success**

The primary efficacy endpoints as defined in the SAP were survival at Year 1 and Year 2 post-transplantation.

The secondary efficacy endpoints (at Year 1 and Year 2 [as data permitted]) were:

- Total CD3, CD4, CD8 cell counts;
- Total naïve CD3, naïve CD4, and naïve CD8 cell counts;
- Proliferative T cell responses to antigens (PHA, ConA, Sol CD3, Immo CD3, tetanus toxoid, and *Candida* skin test antigen);
- TCR repertoire variability;
- TREC; regulatory T cells (TREG);
- Biopsy of transplanted thymus.

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

#### **6.2.1.8 Efficacy Analyses**

##### **6.2.1.8.1 Primary Endpoint**

Both subjects were alive at 1-year and 2-years after transplantation. At the time of this Application:

- Subject (b) (6) was alive 1183 days (~3 years, 3 months) post-transplant
- Subject (b) (6) was alive 1057 days (~2 years, 11 months) post-transplant

**6.2.1.8.2 Secondary Endpoints****Total CD3, CD4 and CD8 T cells**

- Subject (b) (6) CD4, CD8 and CD3 cells remained  $<150$  cells/mm<sup>3</sup> with counts of 137, 27, and 173 cells/mm<sup>3</sup> recorded on Day 164. The cell counts fluctuated thereafter with 254 CD4 cells, 97 CD8 cells and 373 CD3 cells/mm<sup>3</sup> on Day 416 post-transplant. At the last assessment on Day 621 post-transplant, he had 798 CD4 cells/mm<sup>3</sup> (normal for age), 190 CD8 cells/mm<sup>3</sup> and 1026 CD3 cells/mm<sup>3</sup>. The CD8 and CD3 counts were below the 10<sup>th</sup> percentile for age.
- Subject (b) (6) CD4, CD8 and CD3 cells were 56, 80 and 136 cells/mm<sup>3</sup>, respectively, on Day 0. The number of CD3, CD4 and CD8 cells remained below 150 cells/mm<sup>3</sup> until Day 130, at which time 235 CD4, 124 CD8 and 369 CD3 cells/mm<sup>3</sup> were recorded. These values fell below 100 cells/mm<sup>3</sup> on Day 163 and fluctuated thereafter, reaching a high of 141 CD4 cells/mm<sup>3</sup>, 419 CD8 cells/mm<sup>3</sup> and 560 CD3 cells/mm<sup>3</sup> on Day 262 and with all three cell lines maintained at  $>100$  cells/mm<sup>3</sup> thereafter. The values were below the 10<sup>th</sup> percentiles for age on the last assessment on Day 1057 post-transplant with 516 CD4 cells/mm<sup>3</sup>, 158 CD8 cells/mm<sup>3</sup> and 712 CD3 cells/mm<sup>3</sup>.

**Naive CD3, CD4 and CD8 T cells**

- Subject (b) (6) naïve CD4, CD8 and CD3 cells first appeared 132 days after transplant; they were 11, 5 and 13 cells/mm<sup>3</sup>, respectively. There was a slight increase in his naïve CD4 (16 cells/mm<sup>3</sup>), CD8 (18 cells/mm<sup>3</sup>) and CD3 (32 cells/mm<sup>3</sup>) on Day 187.
- Subject (b) (6) naïve CD4, CD8 and CD3 cells remained below 10 cells/mm<sup>3</sup> until Day 619 at which time, there were 218 naïve CD4 cells/mm<sup>3</sup>, 61 naïve CD8 cells/mm<sup>3</sup> and 310 naïve CD3 cells/mm<sup>3</sup>. On Day 880, his naïve CD4, CD8, and CD3 counts were 201, 40 and 265 cell/mm<sup>3</sup>, respectively.

**NK and B cells**

- Subject (b) (6) had 82 NK cells/mm<sup>3</sup> and 527 B cells/mm<sup>3</sup> on Day 132 that increased to 135 and 1235 cells/mm<sup>3</sup>, respectively on Day 187. Assessments on Day 416 showed 146 NK cells/mm<sup>3</sup> but B cells were absent ( $<5$  cells/mm<sup>3</sup>) because of the use of rituximab for treatment of thrombocytopenia. The NK (133 cells/mm<sup>3</sup>) and B (741 cells/mm<sup>3</sup>) cell counts had normalized by 621 days post-transplant.
- Subject (b) (6) had 3 NK cells/mm<sup>3</sup> on Day 0. These values fluctuated throughout the study from a high of 766 cells/mm<sup>3</sup> on Day 130 to a low of 2 cells/mm<sup>3</sup> on Day 410. There were no B cells detected on Day 0 because of previous rituximab therapy. The number of B cells remained at or close to 0 cells/mm<sup>3</sup> until Day 163, at which time 143 B cells/mm<sup>3</sup> were recorded. The number of B cells fluctuated thereafter, with a low of 3 cells/mm<sup>3</sup> on Day 262. However, the number of B cells increased at each assessment timepoint from Day 262 onwards. On Day 880, 480 B cells/mm<sup>3</sup> were recorded.

**Biopsy of RVT-802**

Subjects (b) (6) were biopsied on Days 63 and 68 post-transplant, respectively. There were no signs of rejection and the thymic tissue was positive for CD3, Ki-67, CD1a and Ck14 confirming thymopoiesis.

**CMV and EBV**

CMV was not detected after transplantation in either subject. EBV was not detected in Subject (b) (6) after transplantation but was detected in Subject (b) (6) (2096 copies) 781 days after transplantation.

**6.2.1.8.3 Subpopulation, Exploratory and Post Hoc Analyses**

There was no subpopulation, exploratory or post-hoc analyses conducted for this study.

**6.2.1.8.4 Dropouts and/or Discontinuations**

No subjects dropped out or discontinued from this study.

**6.2.1.9 Safety Analyses****6.2.1.9.1 Methods**

Safety assessments (AEs, laboratory evaluations, vital signs measurements, and physical examinations) were assessed while the subject was hospitalized following transplantation. Additional assessments were scheduled through 2 years post-transplant. Adverse events were reported through 31 December 2017.

Non-infection related AEs and SAEs were graded (Grades 1 to 5) according to the CTCAE version 4.0. Infection related AEs were evaluated using criteria defined in the BMTCTN definitions of infection severity. An unexpected AE was any event not listed in either the protocol or the consent form, or not associated with expected events given a subject's underlying condition. Assessment of the relationship of an adverse event to transplantation (i.e. 'possible', 'probable', or 'definitely related') was a clinical decision based on all available information.

**6.2.1.9.2 Overview of Adverse Events**

Subject (b) (6) had 8 AEs with 6 AEs assessed as possibly or probably related to Treatment including:

- Pyrexia (onset Day 1 after transplantation): This was most likely post-operative fever as all cultures were negative.
- Hypomagnesemia (onset Day 45 after transplantation): This was possibly related to CSA or hypocalcemia (subject had a history of hypoparathyroidism which often is associated with hypomagnesemia). Subject was treated with an IV magnesium bolus after failure of oral supplements due to diarrhea.
- Lymphadenopathy (Onset Day 71 after transplantation): This event remains unresolved at the time of the most recent ultrasound on Day 1100.
- Urticaria (onset Day 103 after transplantation): This was considered a food allergy and not GVHD. The subject continued to experience intermittent hives at discharge which, per parental confirmation on Day 1183, had since ceased and the subject was not receiving medication for this event.
- Hepatomegaly (onset Day 196 after transplantation): An abdominal ultrasound on Day 196 showed mild hepatosplenomegaly and was unchanged on days 238 and 1100. This event had not resolved at the time of reporting.
- Hypokalemia (onset Day 292 after transplantation): This was possibly related to sirolimus used to treat cytopenias.

The remaining two AEs that were assessed as unrelated to study treatment were aphthous ulcer and macular papular rash. There were no infection related AEs.

Subject <sup>(b) (6)</sup> had 14 AEs but only 4 of the AEs were assessed as possibly or probably related to treatment. The latter 4 AEs included:

- Hypertension (onset Day 12 after transplantation): This was considered related to treatment with tacrolimus and/or steroids.
- Glycosuria (onset Day 86 after transplantation): This was likely related to the subject's hyperglycemia.
- Acidosis (onset day 91 after transplantation): This was likely related to the subject's hyperglycemia but may also have been caused by the GVHD from the CBT and an intestinal adenovirus infection leading to diarrhea.
- Weight decreased (onset Day 291 after transplantation) that recovered to his pre-transplantation weight on Day 544.

Subject <sup>(b) (6)</sup> also had 8 infection-related AEs (norovirus gastroenteritis, bacterial sinusitis, chronic otitis media, fungal ear infection, esophageal candidiasis, enterocolitis, pyrexia, and abdominal pain) but none were assessed as related to treatment.

#### **6.2.1.9.3 Deaths**

There were no deaths in this study.

#### **6.2.1.9.4 Nonfatal Serious Adverse Events**

Subject <sup>(b) (6)</sup> had 6 SAEs (Table 22). He developed splenomegaly and thrombocytopenia as 2 concurrent, life-threatening SAEs. An ultrasound showed mild hepatosplenomegaly on Day 196 post-transplant. A bone marrow aspirate was obtained on Day 200 as the platelet count had dropped to 10,000/mm<sup>3</sup>. The bone marrow showed multiple small non-necrotizing granulomas as well as histiocytosis. Stains for mycobacteria (acid-fast bacillus, Fites) and fungus (Gomori Methenamine Silver) were negative. The investigator felt, despite the negative stains, that infection was likely because of the granuloma. Thus, steroids were not initiated. A lymph node was biopsied on Day 202 to obtain tissue for 16S and 28S DNA testing. He was treated with intravenous immunoglobulin, rituximab, and romiplostim. On Day 226, the DNA results did not detect infection and steroids were started as the diagnosis was autoimmune disease. A splenectomy was performed on Day 228 post-transplant. This SAE occurred at the same time as a serious neutropenia which was considered to be associated with the thrombocytopenia and Coomb's positive anemia. The neutropenia required treatment with granulocyte colony stimulating factor until after the above-mentioned splenectomy. The SAEs of thrombocytopenia, neutropenia, and Coomb's positive anemia were assessed as probably related to treatment. These events were expected as severe cytopenias had been seen in other cDGA patients in the first year after transplantation and most likely reflected an immature immune system that was not yet functioning.

**Table 23: SAE in Subject (b) (6)**  
(Applicant’s table)

Preferred Term	Start Day <sup>a</sup>	End Day <sup>a</sup>	CTCAE Grade / Seriousness category	Related? <sup>b</sup>	Outcome
Subject (b) (6)					
Splenomegaly	196	238	4 / Life threatening	Probably	Recovered / Resolved
Coombs positive hemolytic anemia	196	239	4 / Caused/Prolonged hospitalization, other medically important event	Probably	Recovered / Resolved
Neutropenia	196	239	4 / Caused/Prolonged hospitalization, other medically important event	Probably	Recovered / Resolved
Thrombocytopenia	196	239	4 / Life threatening	Probably	Recovered / Resolved
Pulmonary mass	889	-	3 / Caused/Prolonged hospitalization	Unrelated	Ongoing / Not recovered / Not resolved
Pyrexia	1095	1104	2 / Caused/Prolonged hospitalization	Unrelated	Recovered / Resolved

Subject (b) (6) had six SAEs; four that were infection-related (gastroenteritis adenovirus, viremia, pneumonia and sinusitis fungal). None of the infectious SAEs were considered related to study treatment. The subject also developed GVHD on Days 12 to 544 after transplantation. This was considered to have been triggered by his CBT, not donor cells, and resulted in diarrhea, rash, decreased platelets, anemia, decreased WBC, alopecia and abdominal pain. The subject was initially treated with steroids. However, the subject developed treatment-related hyperglycemia on Days 84 to 104 after transplantation. The subject recovered following hospitalization and treatment with insulin. Steroids were stopped because of the side effects and infliximab was used to control the diarrhea from the GVHD through Day 523. The SAEs of GVHD and hyperglycemia were assessed as being possibly related to treatment.

**6.2.1.10 Study Summary and Conclusions**

This is an ongoing study that had enrolled only 2 subjects with cDGA at the time of this report (November 6, 2018). Subject (b) (6) was initially diagnosed with SCID and had received two CBT prior to the diagnosis of cDGA. Subject (b) (6) was a cDGA patient who had received a CBT in childhood but developed EBV lymphoma 13 years later prior to entering the study. Both subjects are alive at 1183 (~3 years, 3 months) and 1057 days (~2 years, 11 months) post-transplant demonstrating the effectiveness of RVT-802. Notably, Subject (b) (6) was able to develop adequate thymic function to overcome his pre-existing EBV lymphoma. Furthermore, the development of naïve T cells is indicative of thymic function. The AEs recorded after transplantation were consistent with those expected in this clinical population. These data demonstrate the safety and effectiveness of RVT-802.

**6.2.2. Study (b) (6): Single Subject Treatment Plan: Thymus Transplantation for EBV Lymphoma**

**6.2.2.1 Objectives**

This study was designed to treat a single, pre-identified subject with cDGA and EBV-lymphoma. The objective of RVT-802 transplantation was the development of EBV-specific cytotoxic T cells (CTLs) that could suppress the subject’s EBV infection and lymphoma. The hypothesis was that CTLs would only develop if RVT-802 engrafted and produced naïve T cells by thymopoiesis.

#### **6.2.2.2 Design Overview**

This was a single-subject, open-label, non-randomized, expanded access study conducted by a single Sponsor/Investigator at DUMC.

#### **6.2.2.3 Study Population**

Subject <sup>(b) (6)</sup> was a 15-year old white male at study enrollment, who was diagnosed in infancy with cDGA. The latter was characterized by athymia, hypoparathyroidism, atrial and ventricular septal defects, and an interrupted aortic arch with bicuspid aortic valve. There was no family history of DiGeorge syndrome.

The subject's medical history included drug hypersensitivity, thrombocytopenia, seizure, right bundle branch block, interruption of aortic arch, hyperbilirubinemia (due to biliary obstruction secondary to EBV), elevated international normalized ratio, psoriasis, hypocalcemia, hypoparathyroidism, diarrhea, malnutrition, gastrostomy, gastroesophageal reflux disease, vocal cord paralysis, elevated ALT and AST, hypoalbuminemia, clubbing, kyphosis, bronchiectasis, multiple cardiac operations, and central venous catheterization

He was treated twice with infusions of peripheral blood mononuclear cells (adoptive T cell transfer) from his HLA-identical brother (on Day 43 and Day 184 of life). However, this resulted in lymphopenia, suboptimal lymphocyte function, and borderline humoral immunocompetence. He had several episodes of pneumococcal pneumonia, an episode of pneumococcal bacteremia, bronchiectasis and chronic sinusitis. Other infections included EBV infection and associated lymphoma/lymphoproliferative disorder, *Staphylococcus* infection, tympanic membrane perforation, abscess, and *Clostridium difficile* colitis.

The subject developed EBV lymphoproliferative disease at 14 years of age. The EBV-related lymphoma was widespread with diffuse adenopathy (neck, chest, abdomen, and pelvis), dilated biliary system, multiple liver and splenic lesions and hypermetabolic foci involving the bones. Prior to enrolling in this Study, he was treated with gemcitabine, vinorelbine, rituximab, and multiple cycles of EBV-specific CTLs. He also received radiation for a tonsillar mass, followed by chemotherapy.

The subject had very low CD4 counts upon entry into this study with an inverted CD4 to CD8 ratio. Chimerism testing performed 8 days prior to transplantation showed that >98% of the subject's T cells was from the sibling donor. There were no detectable B cells (secondary to prior rituximab therapy), almost no NK cells, and hypogammaglobulinemia.

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

The planned pre-transplantation immunosuppressive conditioning regimen included fludarabine 34 mg/day intravenously (IV) on Days -6 to -2 and dexamethasone 18 mg IV every 8 hours on Days -5 to -2.

The subject received RVT-802 (4915 mm<sup>2</sup>/m<sup>2</sup> BSA from 46 slices) sutured into the subject's quadriceps muscles in a single, open procedure under general anesthesia.

#### **6.2.2.5 Sites and Centers**

This was a single center study conducted at Duke University Medical Center.

**6.2.2.6 Surveillance/Monitoring**

The subject was transferred back to the referring medical center 4 days after transplantation for further management of his EBV lymphoma. The subject did not have a post-transplant thymus biopsy because of his critical condition.

**6.2.2.7 Statistical Considerations & Statistical Analysis Plan**

There was no SAP as this was a single subject study.

**6.2.2.8 Efficacy Analyses**

The subject died approximately 4 months after receiving the RVT-802 transplant due to progressive EBV lymphoma, which had an onset date 24 days after RVT-802 transplantation. No conclusion about the effect of RVT-802 on the development of EBV-specific CTLs could be drawn since the subject died before the development of thymic function.

Flow cytometry tests were conducted on post-transplant Day 52, prior to the time that thymic function would have been expected to develop.

**6.2.2.9 Safety Analyses**

There were 5 AEs and 2 SAEs for this subject (Table 24). The latter included a life-threatening episode of torsade de pointes and fatal progression of EBV-associated lymphoma. The episode of torsade de pointes was associated with hypomagnesemia occurred on post-transplant Day 25. He was treated with chest compressions and a lidocaine drip. The SAE was unlikely related to study treatment.

The subject’s EBV lymphoma progressed beginning on post-transplant Day 24, resulting in many symptoms (details were not provided by the Applicant) related to disease progression. The EBV viral load which had been 1500 copies/mL 18 days prior to transplantation had increased to 4100 copies/mL on Day 3, 13,300 copies/mL on Day 11, 113,00 copies/mL on Day 24, and 31,800 copies/mL on Day 51 post-transplant. The subject’s clinical condition deteriorated over several weeks as his EBV lymphoma progressed and he died of an intracranial bleed ~4 months after receiving RVT-802. This fatal SAE was possibly related to study treatment.

**Table 24: Safety Assessment for Subject <sup>(b) (6)</sup>**  
(Applicant’s Table)

Preferred Term	Start Day <sup>a</sup>	End Day <sup>a</sup>	CTCAE Grade/Intensity	Serious?	Related? <sup>b</sup>	Outcome
Nausea	-2	4	1/Mild	No	Yes <sup>c</sup>	Resolved
Graft haemorrhage	0	2	1/Mild	No	Yes	Resolved
Pyrexia	0	1	1/Mild	No	No	Resolved
Neutropenia	10	33	4/Life-threatening	No	Yes	Resolved
Epstein-Barr virus associated lymphoma	24	--	5/Fatal	Yes	Yes	Fatal
Hypomagnesaemia	25	25	1/Mild	No	No	Resolved
Torsade de pointes	25	25	4/Life-threatening	Yes	No	Resolved

**6.2.2.10 Study Summary and Conclusions**

This study enrolled a single subject who died ~4 months after receiving RVT-802 due to progression of his EBV lymphoma, which had an onset 24 days after receiving RVT-802. No conclusion about the effect of RVT-802 on the development of EBV-specific CTLs could be

drawn since death occurred prior to the development of thymic function. However, it was possible that conditioning regimen (fludarabine and dexamethasone) may have led to faster progression of the EBV lymphoma than would have occurred without participation in this study. However, no mechanism by which the study treatment could have hastened lymphoma progression was identified.

### **6.2.3 Study 735: Thymic Transplantation in Partial DiGeorge Syndrome**

#### **6.2.3.1 Objectives**

Many patients with partial DiGeorge syndrome have spontaneous improvement in immune system function. However, some patients with partial DiGeorge syndrome continue to have significant T cell dysfunction with recurrent infections and autoimmune disease. The objectives of this study were to evaluate the following in subjects with partial DiGeorge syndrome:

- Effect of treatment with RVT-802 on T cell proliferation and function
- Safety of treatment with RVT-802

#### **6.2.3.2 Design Overview**

This was a single-center, open-label, non-randomized study intended to evaluate subjects with partial DGA. The protocol did not specify the number of subjects planned for enrollment but only one subject was treated in this study.

#### **6.2.3.3 Study Population**

This study enrolled a single subject with a presumed diagnosis of partial DGA at the time of RVT-802 transplantation but was subsequently determined to have atypical DGA. The study did not enroll any additional partial DiGeorge subjects because the RVT-802 development program shifted focus to subjects with cDGA with athymia.

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

The subject received RVT-802 in a single surgery. The total dose of RVT-802 implanted was not measured. Approximately 5 petri dishes of RVT-802 were transplanted according to the operating room notes at the time of the procedure. The subject did not receive immunosuppressive therapy as the guardian declined.

#### **6.2.3.5 Sites and Centers**

This study was conducted at DUMC between 03 February 1995 (IRB approval date) and 08 January 1999 (enrollment closure date).

#### **6.2.3.6 Surveillance/Monitoring**

Multiple blood draws were taken post-transplant to evaluate the subject's immune system. The number of T cells was also determined by flow cytometry in addition to T cell function by mitogen and antigen responsiveness. The subject had a thymus graft biopsy approximately 3 months post-transplant.

#### **6.2.3.7 Statistical Considerations & Statistical Analysis Plan**

There was no statistical analysis plan as this was a single subject study.

##### **6.2.3.7.1 Analysis Population and Disposition**

The was a single subject study. The subject was considered lost-to-follow-up at ~2 years after transplantation. However, in the preparation of this report, the Investigator confirmed the subject was still alive 8172 days (22.4 years) post-transplant.

#### **6.2.3.7.2 Protocol Deviations**

There were no protocol deviations.

#### **6.2.3.7.3 Demographics & Disease Characteristics**

Subject (b) (6) (also referred to as (b) (6)) was a 625 days old female at informed consent. She presented with thymic hypoplasia as evidenced by a low number of circulating T cells, significant T cell dysfunction, and recurrent infections. The subject's medical history included anemia, lymphadenopathy, lymphopenia, cardiomegaly, atrial septal defect, hypoparathyroidism, hypothyroidism, low set ears, intestinal malrotation, diarrhea, vomiting, developmental delay, pyrexia, short stature, occult blood positive, failure to thrive, feeding disorder, glucose tolerance impaired, hyperphosphatemia, hypocalcemia, hypocalcemic seizure, lethargy, pulmonary edema, respiratory distress, drug eruption, exfoliative rash, central venous catheterization, gastrointestinal tube insertion, oxygen supplementation, and parenteral nutrition. The referring physicians noted that on presentation the patient had Omenn syndrome.

The subject had many infections consistent with profound immunodeficiency. Her pre-transplant infection history included bronchiolitis (chronic parainfluenza I, enterovirus infection), otitis media, device related infection, *candida* infection, sinusitis, *clostridium difficile* colitis (due to antibiotic use), gastroenteritis *enteroviral*, and gastroenteritis *salmonella*.

The subject was thought to have partial DGA upon enrollment in this study. The phenotype included congenital cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, growth or mental retardation, and hypocalcemia. The subject's family history of DiGeorge syndrome was unknown. At the time this study was initiated, the category of "atypical DiGeorge anomaly" would not be identified for another 9 years. The available data suggested that this subject had developed T cells but the numbers were low. Antibodies for detecting naïve T cells had been developed but were not available to the Investigator. Similarly, there were no assays to assess TCR repertoire by flow cytometry or spectratyping. Therefore, the subject was initially believed to have partial DGA on the basis of circulating T cells. However, in reviewing this subject's records at the time of this report, the Investigator believes that the subject likely had atypical complete DGA.

#### **6.2.3.8 Efficacy Analyses**

##### **6.2.3.8.1 Primary Endpoint**

The subject remains alive 8172 days (22.4 years) after RVT-802 transplantation

##### **6.2.3.8.2 Secondary Endpoints**

There were only limited flow cytometry data from this subject as antibodies to detect naïve T cells were not available at the time of the study. The results of CD3, CD4, and CD8 cell counts for selected timepoints are presented in Table 25. The subject's CD3, CD4, and CD8 cell counts were lower than pretransplantation (Day -44) counts when assessed on post-transplantation Day 89 and were observed to have increased from Day 89 to Day 285 after transplantation. On Day 496, CD3 and CD4 counts were higher than the pre-transplant counts and the CD8 count was comparable to the pre-transplantation count. The inverted CD4 to CD8 T cell ratios show that the subject had poor thymic function on Days -44, 89, and 496.

**Table 25: CD3, CD4, and CD8 Counts for Subject (b) (6)**  
(Reviewer’s Table)

<b>Day</b>	<b>CD3</b> (cells/mm <sup>3</sup> )	<b>CD4</b> (cells/mm <sup>3</sup> )	<b>CD8</b> (cells/mm <sup>3</sup> )
<b>-44</b>	724	121	597
<b>89</b>	93	67	100
<b>285</b>	457	307	123
<b>496</b>	886	263	587

A thymus biopsy from the right and left quadriceps was performed 90 days after transplantation. However, thymus tissue was not identified in the biopsies.

**6.2.3.9 Safety Analyses**

The subject had three SAEs of hepatic infection (MAC), hyperphosphatemia, and *P. jirovecii* pneumonia, all of which were to be unrelated to study treatment.

The subject also had multiple (n=7) non-serious infection-related AEs that was considered unrelated to study treatment. These included *Clostridium difficile* colitis, bacterial gastrointestinal infection, lower respiratory tract infection (fungal), urinary tract infection (2 episodes, *Burkholderia cepacian* and *Enterobacter*), sinusitis (bacterial), and biliary tract infection (bacterial).

The subject also developed GVHD that was initially thought to be possibly related to RVT-802 treatment. However, the Investigator now believes that the GVHD was secondary to pre-existing Omenn syndrome (autologous GVHD) and not related to RVT-802 treatment.

**6.2.3.10 Study Summary and Conclusions**

This study treated a single subject (b) (6) who was a challenging case because at the time of enrollment in 1995, “atypical cDGA” had not been identified and would not be defined for another 9 years. She was also the first subject with Omenn syndrome which recurred after RVT-802 transplantation. This subject was not treated with immunosuppression but eventually developed T cells and she remains healthy. It was likely that her T cell numbers would have been higher if immunosuppression had been used, as is the current clinical practice for subjects with atypical cDGA who receive RVT-802.

The subject was alive when follow-up contact was made 22.4 years following RVT-802 transplantation. Her CD3, CD4, and CD8 cell counts initially decreased after RVT-802 treatment. But by Day 496, the last post-treatment timepoint for which cell counts are available, CD3 and CD4 counts were higher relative to pre-treatment counts and the CD8 cell count was comparable to the pre-treatment values. However, interpretation of these T cell numbers is not possible without antibodies to detect naïve T cell markers. Therefore, it is unknown if any of the T cells were formed in the thymus. Nonetheless, it is presumed that sufficient thymic function developed to enable survival.

The subject had 3 SAEs of hepatic MAC infection, hyperphosphatemia, and *P. jirovecii* pneumonia, all of which were unrelated to study treatment. In addition, she had multiple non-serious infection-related AEs unrelated to study treatment. The GVHD was initially thought to be possibly related to the RVT-802 treatment but is now presumed secondary to pre-existing Omenn syndrome (autologous GVHD) in the context of cDGA and not related to RVT-802.

**7.0 Integrated Overview of Efficacy**

**7.1 Indication**

RVT-802 is indicated for thymic transplantation to support immune reconstitution in patients with primary immunodeficiency resulting from congenital athymia.

**7.2 Method of Integration**

Data from the 10 clinical studies were combined in the pooled analyses to assess the efficacy and safety of RVT-802.

- Full Analysis Set (FAS): All 93 subjects treated with RVT-802. This includes all 85 subjects in the EAS plus 8 additional subjects.
- Efficacy Analysis Set (EAS): All 85 subjects with congenital athymia associated with cDGA or FOYN1 deficiency, with no prior HSCT and were treated with RVT-802.
- EAS-cDGA Analysis set (EAS-cDGA): All 83 subjects in the EAS except the two subjects with FOYN1 deficiency.

The primary and secondary endpoints that were assessed across studies and included in the Clinical Summary of Efficacy (CSE) analysis plan to facilitate cross-study comparisons and overall program analyses are presented in Table 26.

The primary endpoint was survival assessed at Year 1 and Year 2 post-implantation across all studies included in this CSE. Survival is a clinically meaningful endpoint since T cell immunodeficiency leads to death, usually from infections before the age of 2 years. The primary efficacy endpoint was analyzed using the EAS as well as with the EAS-cDGA and FAS populations. Kaplan-Meier estimates of survival at Year 1 and Year 2 were presented with the number of subjects at risk, the number of subjects with events and the estimated survival probability. Estimates of survival were also given annually until the last subject included in the current analysis was censored or died. The median survival time with 95% confidence interval (CI) was given, if possible; if not possible, then, the 75th percentile estimate was given, if possible. The Kaplan-Meier estimates were also plotted. Survival rate at Year 1 and Year 2 >50% was tested using the binomial exact test.

**Table 26: Primary and Secondary Endpoints**  
(Applicant’s Table)

	668 <sup>a</sup>	884	931	932	950	25966
<b>Primary Endpoints</b>						
Survival at Year 1	x	x	x	x	x	x
Survival at Year 2	x	x	x	x	x	x
<b>Secondary Endpoints (at Year 1 and Year 2)</b>						
CD3 cells	x	x		x	x	x
CD4 cells	x	x	x	x	x	
CD8 cells	x	x	x	x	x	
Naïve CD4 cells	x	x	x	x	x	x
Naïve CD8 cells	x	x	x	x	x	
Total TCRαβ cells						x
Total TCRγδ cells						x
Total B cells						x
Total NK cells						x
Proliferative T cell responses to mitogens, and antigens, including the following: PHA, ConA, sol CD3, immob CD3, TT, and <i>Candida</i>	x	x	x	x	x	x
Anti-tetanus toxoid antibody				x		
TCR repertoire variability	x	x	x	x	x	x
TREC/TREG <sup>b</sup>		x	x	x	x	x
Biopsy of implanted thymus	x	x	x	x	x	x

ConA = concanavalin A; immob = immobilized sol = soluble; NK = natural killer; PHA = phytohemagglutinin; TCR = T cell receptor; TT = tetanus toxoid; TREC = T cell receptor rearrangement excision circles; TREG = regulatory T cells  
<sup>a</sup>Study 668 was initially opened as a Phase 1 study. In 2001, the study was amended to form a Phase 2 study. The initial Phase 1 study is Study 668-1 and the later Phase 2 study is Study 668-2.  
<sup>b</sup>Summaries of TREC/TREG were done for trials where data were present in the database.

Secondary efficacy endpoints including immune outcomes and dose effect were assessed after RVT-802 implantation by:

- biopsies of the allografts by immunohistochemistry;
- peripheral blood for naïve T cells and other T cell phenotypes;
- variability of the TCRV $\beta$  region;
- T cell proliferative responses and
- B cell antibody responses to antigens.

Descriptive summaries were provided at 3-month intervals (when available) for up to 24 months after implantation. Univariate regression analyses were used to correlate dose with the T cell proliferative response to the mitogen PHA, and the number of naïve CD4 and naïve CD8 T cells at Year 1. The number of infections was assessed for the first 6 months after implantation versus 6 to 12 months and <12 months versus 12 to 24 months post-implant. The median naïve CD3, naïve CD4, and naïve CD8 cell counts were plotted over time. The median T cell proliferative response to PHA was also plotted over time.

### 7.3 Demographics and Baseline Characteristics

All subjects enrolled in the studies were males and females under 2 years of age at the time of implantation (Table 27). The subject's parent(s)/legal guardian(s) provided informed consent for the subject to participate in the studies. Subjects were required to have a diagnosis of congenital athymia for enrollment. The diagnosis of athymia was based on flow cytometry documenting <50 naïve T cells/mm<sup>3</sup> (CD45RA<sup>+</sup>, CD62L<sup>+</sup>) in the peripheral blood or <5% naïve T cells. In addition to athymia, subjects were required to have at least one of the following (criteria were similar across studies):

- Congenital heart defect
- Hypoparathyroidism (or hypocalcemia requiring replacement)
- 22q11.2 hemizyosity or 10p13 hemizyosity
- CHARGE syndrome or *CHD7* mutation

Genetic sequencing was often not performed in the early years of the RVT-802 development program as it was not widely available. However, gene mutations and syndromes associated with the 22q11.2 deletion (39.8%) and CHARGE syndromes (21.5%) were commonly observed once sequencing was initiated. Ten of the 20 subjects diagnosed with CHARGE had a documented *CHD7* mutation. Eleven subjects were missing data on cDGA gene mutations/syndrome associations as it was not applicable (subjects diagnosed with FOXN1 deficiency or SCID) or genetic sequencing was not performed. The two subjects with FOXN1 deficiency subjects were required to have a diagnosis of athymia and FOXN1 deficiency. They were enrolled as pre-planned, IRB-approved, single-patient enrollment exceptions in Study 668-2 (Subject (b) (6)) and Study 884 (Subject (b) (6)). One subject (Subject (b) (6)) had a variant in *TBX2* identified post-RVT-802 implantation. This subject was counted as “missing” as the genetic defect was not identified at the time of implantation. Three other subjects had other genetic mutations reported; however, these mutations have no known association with cDGA or athymia.

- Subject (b) (6) with 16p12.2 microdeletion syndrome
- Subject (b) (6) with mosaic partial trisomy as well as 22q11.2DS
- Subject (b) (6) with duplication of 1q44.

**Table 27: Baseline Disease Characteristics**  
(Applicant's Table)

	EAS N = 85	FAS N = 93
<b>Day of life at diagnosis (days)</b>		
Mean (SD)	57.2 (89.40)	79.6 (151.02)
Median (Minimum, Maximum)	26.0 (0, 537)	28.0 (0, 841)
<b>Diagnosis, n (%)<sup>a</sup></b>		
SCID	0	2 (2.2)
FOXN1	2 (2.4)	2 (2.2)
Partial DiGeorge anomaly	0	1 (1.1)
Complete DiGeorge anomaly	83 (97.6)	87 (93.5)
<b>DiGeorge phenotype, n (%)<sup>b</sup></b>		
Typical DiGeorge anomaly	43 (50.6)	45 (48.4)
Atypical DiGeorge anomaly	39 (45.9)	41 (44.1)
<b>DGA gene mutation / Syndromic Association, n (%)</b>		
Hemizygous deletion of chromosome 22q11.2	35 (41.2)	37 (39.8)
<i>CHD7</i> mutation <sup>c</sup>	10 (11.8)	10 (10.8)
CHARGE	20 (23.5)	20 (21.5)
None known	21 (24.7)	25 (26.9)
Missing <sup>d</sup>	9 (10.6)	11 (11.8)
<b>Phenotypic features, n (%)</b>		
Congenital cardiac anomaly or cardiothoracic vascular anomaly	76 (89.4)	82 (88.2)
Hypocalcaemia	73 (85.9)	80 (86.0)
Diminished T cell counts for age	85 (100.0)	93 (100.0)
Dysmorphic facies	39 (45.9)	39 (41.9)
Deafness or ear pinnae anomalies	44 (51.8)	48 (51.6)
Coloboma	17 (20.0)	17 (18.3)
Cleft lip	11 (12.9)	11 (11.8)
Cleft palate (frank cleft or submucous cleft)	16 (18.8)	16 (17.2)
Velopharyngeal insufficiency/hypernasal speech	3 (3.5)	4 (4.3)
Choanal atresia	10 (11.8)	10 (10.8)
Tracheal anomalies	22 (25.9)	22 (23.7)
Esophageal anomalies	8 (9.4)	8 (8.6)
Anal and/or rectal anomalies	4 (4.7)	4 (4.3)
Renal anomalies	23 (27.1)	24 (25.8)
Genital hypoplasia	11 (12.9)	13 (14.0)
Rib or vertebral anomalies	26 (30.6)	27 (29.0)
Limb anomalies	15 (17.6)	16 (17.2)
Growth or mental retardation	45 (52.9)	50 (53.8)
Other	4 (4.7)	5 (5.4)

The mothers of 24 subjects were diabetic. Of these, 6 were Type 1 diabetes, 11 were Type 2 diabetes, and 7 had gestational diabetes. Four subjects of diabetic mothers (gestational diabetes) also had a deletion in 22q11.2. The other 20 subjects with exposure to maternal diabetes had no known or no reported cDGA genetic mutations. Five subjects were exposed to other toxins in utero. These included: Group B strep (Subject (b) (6)), marijuana and amphetamines (Subject (b) (6)), antiepileptic medications (Subject (b) (6)), typhoid infection and treatment (Subject (b) (6)), and polyhydramnios (Subject (b) (6)).

A wide range of phenotypic features associated with athymia were observed given the disease heterogeneity. All subjects had a diminished T cell count for their age and most subjects reported a congenital cardiac/thoracic vascular anomaly (88%), hypocalcemia (86%), growth/mental retardation (54%), or deafness or ear pinnae anomalies (52%).

**7.4 Subject Disposition**

The Efficacy Analysis Set (EAS) included all 85 subjects with congenital athymia associated with cDGA or FOYN1 deficiency, who had no prior HSCT and were treated with RVT-802. The Full Analysis Set (FAS) included all 85 subjects in the EAS plus 8 additional subjects described below:

- Subject (b) (6) (Study 884) had cDGA with 2 prior fetal thymus transplants.
- Subject (b) (6) (Study 950.1) had an unknown form of athymia with 2 prior HSCTs.
- Subject (b) (6) (Study (b) (6)) had cDGA with a prior sibling PBMC transplant.
- Subject (b) (6) (Study 51692) had received 2 prior CBTs.
- Subject (b) (6) (Study 51692) had received a prior CBT.
- Subject (b) (6) (Study 668-2) had severe combined immunodeficiency (SCID).
- Subject (b) (6) (Study 932) was initially diagnosed with cDGA but was later confirmed (post-implantation) to have SCID.
- Subject (b) (6) (Study 735) was diagnosed with partial DGA at the time of enrollment but is now thought to have cDGA with autologous GVHD (Omenn Syndrome).

Two subjects were included in the EAS but not included in the EAS-cDGA. Both subjects had FOYN1 deficiency:

- Subject (b) (6) (Study 668-2);
- Subject (b) (6) (Study 884).

**7.5 Analysis of Primary Endpoint**

The median follow-up time for all subjects in the EAS was 2682 days (7.3 years) and ranged from 0 to 8569 days (23.5 years) after RVT-802 implantation. The Kaplan-Meier estimated survival rates at Years 1 and 2 post-implant were 76% (95% CI 0.659, 0.841) and 75% (95% CI 0.646, 0.831), respectively, in the EAS. The survival rates estimated on a year-by-year basis were similar from Year 2 to Year 9 (75% to 70%). The overall survival was 72% in the EAS and the estimated survival rates were similar across the 3 analysis populations (FAS, EAS, EAS-cGDA) at all time points (Table 28).

**Table 28: Summary of Kaplan-Meier Survival**  
(Applicant’s Table)

	EAS-cDGA N = 83	EAS N = 85	FAS N = 93
Number of subjects who died: n (%)	24 (28.9)	24 (28.2)	27 (29.0)
Number of subjects who did not die (censored): n (%)	59 (71.1)	61 (71.8)	66 (71.0)
Follow-up time <sup>a</sup> for subjects who died			
n	24	24	27
Mean (SD)	443.5 (833.73)	443.5 (833.73)	447.6 (793.13)
Median	133.5	133.5	137.0
Q1, Q3	85.5, 257.5	85.5, 257.5	89.0, 289.0
Minimum, maximum	0, 3116	0, 3116	0, 3116
Follow-up <sup>b</sup> (all subjects)			
n	83	85	93
Mean (SD)	2532.4 (2137.53)	2570.7 (2127.12)	2549.8 (2170.02)
Median	2103.0	2682.0	2103.0
Q1, Q3	348.0, 4368.0	400.0, 4368.0	400.0, 4368.0
Minimum, maximum	0, 8569	0, 8569	0, 8569

Source: Table 14.2.1.1.1

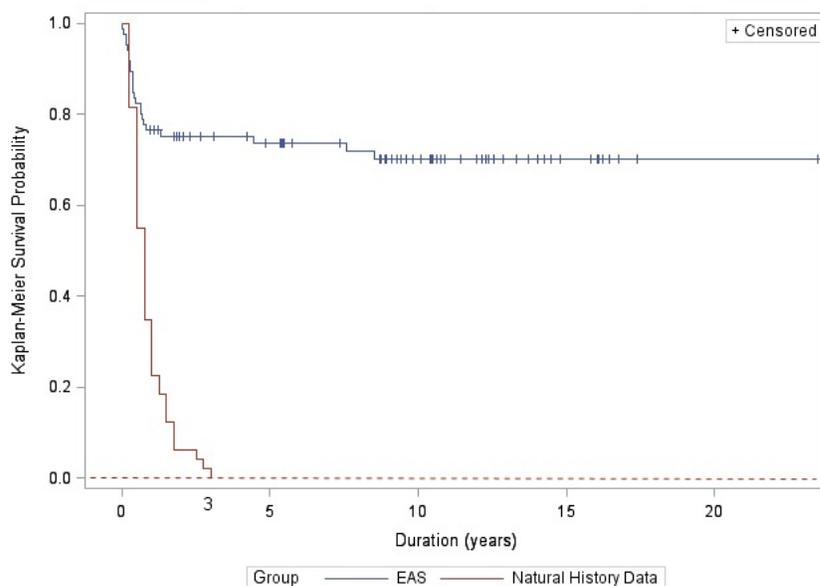
cDGA = complete DiGeorge anomaly; EAS = efficacy analysis set; EAS-cDGA = subset of EAS excluding FOYN1 subjects; FAS = full analysis set

<sup>a</sup> Days from date of implant to date of death.

<sup>b</sup> Days from date of implant to date of death or censor.

Most deaths occurred within the first year after implantation. No new death was observed after Year 9 before the last subject was censored at Year 24 post-implant. For the 24 subjects (28%) in the EAS who died, the median survival time was 134 days (range: 0 to 3116 days [8.5 years]) after RVT-802 implantation. Figure 6 shows a Kaplan-Meier survival curve of the EAS population and the cDGA natural history subjects.

**Figure 6. Kaplan-Meier Survival for EAS Population (n=85) and Natural History Population (n=49)**



Source: Figure made by FDA statistical reviewer.

Natural history data is based on unpublished data on cDGA patients who received standard of care therapy. Data obtained from Dr. Markert included in the BLA (section 2.7.3). We assumed no censoring of control subjects and conservatively assumed that all subjects died at the end of the 3 month window in which their deaths were reported.

## 7.6 Analysis of Secondary Endpoints

Data collection for some of the planned secondary endpoints was limited because obtaining follow-up blood samples was dependent upon the parent(s)/legal guardian(s), the referring local physicians, and the subject's medical condition. In addition, subjects contributing data at any given time point may not have been the same across time points because the visit windows for the secondary efficacy endpoints were not specified and, as such, study-related assessments were performed over a relatively wide timeframe.

### 7.6.1 Flow Cytometry

#### 7.6.1.1 Naïve CD3, CD4 and CD8 Cell Counts

Study subjects in the EAS were athymic at the time of study entry, which was defined as a naïve T cell count of  $<50$  cells/mm<sup>3</sup> or  $<5\%$  of the total T cell being naïve in phenotype. There were marked and sustained increases in Naïve CD3, CD4, and CD8 T cell counts, an indicator of thymic function, as the study progressed. The median naïve CD3 cell counts (cells/mm<sup>3</sup>) were 2.0 (N=33) at baseline, 16.0 at Month 6 (n= 21), 124.0 at Year 1 (N=10), and 227.0 at Year 2 (N=7).

A naïve CD4 count  $>100$  cells/mm<sup>3</sup> was generally considered sufficient to fight infection and immunosuppressive therapies were generally discontinued once subjects achieved at least 10% naïve T cells. Median naïve CD4 cell counts (cells/mm<sup>3</sup>) were 1.0 (N=57) at baseline, 23.0 at Month 6 (n= 62), 261.8 at Year 1 (N=39), and 273.0 at Year 2 (N=25).

Median naïve CD8 cell counts (cells/mm<sup>3</sup>) were 0.29 (N=51) at baseline, 6.7 at Month 6 (N=51), 58.7 at Year 1 (N=36), and 84.0 at Year 2 (N=25). In the EAS, 4 subjects failed to develop at least 50 cells/mm<sup>3</sup> naïve CD4 T cells within 2 years after RVT-802 implantation. A cut-off of  $<50$  cells/mm<sup>3</sup> was used as this was the eligibility criterion that defined athymia in the clinical studies. A brief summary of naïve CD4 T cell data for these subjects is included below:

- Subject (b) (6) had a maximal naïve CD4 count of 5 cells/mm<sup>3</sup> 218 days post implant. The reason RVT-802 did not promote naïve T cell development in this subject is unknown. However, this subject did achieve low levels of naïve T cells after the 2-year follow-up period, which has likely enabled this subject to survive more than 10 years after implantation.
- Subject (b) (6) achieved a naïve CD4 count of 44 cells/mm<sup>3</sup> 588 days post RVT-802 implantation. This subject also reported low total T cell counts (CD3 105/mm<sup>3</sup> on Day 588). It is unknown why this subject did not develop higher naïve CD4 counts with RVT-802. However, in addition to a deletion in 22q11.2, this subject had a genetic mutation (partial mosaic trisomy at 14.q) that may have played a role in T cell development. Despite the relatively low naïve T cell count, this subject was alive at the latest follow-up 11.4 years post-implant.
- Subject (b) (6) achieved a maximal naïve CD4 count of 0.26 cells/mm<sup>3</sup> (total CD3 count 67.98/mm<sup>3</sup>) 62 days after implantation. This subject developed autologous GVHD (Omenn's syndrome) 62 days after implantation which required prolonged immunosuppression including steroids, CSA/tacrolimus, and MMF. The subject initially presented with a Gianotti Crosti rash that was not considered related to autologous T cells, and thus, immunosuppression was not initiated. A skin biopsy performed 225 days post-implantation confirmed the presence of T cells and a diagnosis of autologous GVHD. The Investigator believed the autologous GVHD resulted in the rejection of RVT-802 but this was not confirmed by biopsy. This subject died 480 days after RVT-802 implantation from an intracranial hemorrhage.
- Subject (b) (6) achieved a maximal naïve CD4 count of 5 cells/mm<sup>3</sup> on Day 303. This subject had autologous GVHD (Omenn's syndrome) from atypical cDGA. This subject required prolonged immunosuppression including CAMPATH. The subject did not develop thymic function within 2 years of RVT-802 implantation but remained alive at the most recent follow-up on Day 679.

Eight additional subjects (Subjects (b) (6)) survived at least 1-year post-implant with maximal naïve CD4 count between 50 and 100 cells/mm<sup>3</sup> (range: 64 to 99 cells/mm<sup>3</sup>) within 2 years post-implantation. While these counts were lower than expected, all 8 subjects were alive at the latest follow-up, which ranged from 401 to 5850 days (1.1 to 16.0 years) post-implant, indicating a naïve CD4 count  $>50$  cells/mm<sup>3</sup> may be sufficient for survival.

**Reviewer's comments:** There were 20 subjects (29.4%) in the FAS who did not develop naïve CD4 cells of at least 50 cells/mm<sup>3</sup> within the first year (425 days) post-implantation. Eighteen of the subjects had DGA, I had SCID and the remaining subject had FOXN1

deficiency. Nine of these subjects (Subjects (b) (6)) went on to develop  $>50$  cells/mm<sup>3</sup> naïve CD4 cells within 2 years (790 days) post-implantation, whereas 11 did not. Of the latter, 6 subjects (Subjects (b) (6)) eventually developed naïve T cells more than 2 years post-implantation. Three subjects (Subjects (b) (6)) never developed naïve T cells post-implantation, and 2 subjects (Subjects (b) (6)) survived but did not have data available regarding naïve T cell development. Among the 3 subjects who survived at least 1-year post-RVT-802 implantation but did not develop thymic function, 1 (Subject (b) (6)) died 480 days post-implantation from an unrelated intracranial hemorrhage, 1 (Subject (b) (6)) was diagnosed with SCID after treatment with RVT-802 and subsequently died 950 days post-implant, and 1 subject (Subject (b) (6)) was withdrawn from the study after an RVT-802 biopsy noted evidence of RVT-802 rejection.

There were 9 additional subjects (13.2%) in the FAS whose naïve CD4 count within the first year were between 50 and 100 cells/mm<sup>3</sup>. Seven of the subjects (Subjects (b) (6)) naïve CD4 count increased to over 100 cells/mm<sup>3</sup> during the second year but 2 subjects (Subjects (b) (6)) did not. However, the latter two subjects had reported naïve CD4 counts of 281 and 149 cells/mm<sup>3</sup> on Days 1104 and 1055, respectively. While these values were reported more than 2 years post-implantation, it was possible these subjects had developed naïve CD4 counts  $>100$  cells/mm<sup>3</sup> earlier since flow cytometry was not assessed in these subjects between Year 1 and Year 3.

There were no discernible factors that predicted responders (naïve CD4 counts  $>100$  cells/mm<sup>3</sup>) from non-responders. Non-responders in the EAS at Year 1 and Year 2 were slightly older at the time of RVT-802 implantation (median age of 277.0 days and 279.5 days, respectively) as compared to responders at Year 1 and 2 (median age of 201.5 days and 206.0, respectively) Race and other baseline characteristics were generally similar across the two populations. The disease history was also generally similar across the responder and non-responder populations, with the exception of typical and atypical cDGA. There was a slightly higher percentage of responders who had typical cDGA (60.5% at Year 1 and 60.0% at Year 2) as compared to non-responders (44.0% at Year 1 and 40.0% Year 2). The dose of RVT-802 that was implanted was similar between the two groups as was the culture duration of RVT-802 (median 16 days for both groups).

There was no difference in survival between responders and non-responders. The Kaplan-Meier survival curves were similar for both responders and nonresponders defined at Year 1 and Year 2 post-implantation with RVT-802. Similarly, the AE and SAE profile for responders and non-responders were similar with no clear trends or safety concerns distinct from the overall population. These data suggest that even low levels of naïve CD4 T cells, as found in the non-responder population, may be sufficient to protect against serious infections until full immune reconstitution can be achieved.

The reason for this delayed response is not fully understood, it may be related to concurrent autologous GVHD (Omenn syndrome) requiring prolonged immunosuppression or other medical comorbidities impacting the subject's overall health.

**7.6.1.2 Total CD3, CD4, and CD8 T Cells**

The median total CD3, CD4, and CD8 cell counts in the EAS, showed marked and sustained increases over time as expected with the development of thymic function during the study (Table 30).

**Table 30: T-cell Counts**  
(Reviewer’s Table)

	<b>CD3</b>	<b>CD4</b>	<b>CD8</b>
<b>Baseline</b>	139 (n=85)	111.0 (N=75)	14.1 (N=72)
<b>Month 6</b>	346.0 (n= 70)	251.0 (N=70)	37.8 (N=70)
<b>Year 1</b>	731.0 (N=49)	526.0 (N=50)	140.0 (N=49)
<b>Year 2</b>	721.0 (N=27)	532.5 (N=28)	136.0 (N=28)

**7.7 Subpopulations**

**7.7.1 Primary Efficacy Endpoint**

Subgroup analyses of the primary efficacy endpoint were performed for 15 study subgroups. These covered a range of demographic (gender, race, age at transplant) and baseline disease characteristics (cDGA phenotype, 22q11.2 hemizyosity, CMV infection, mutation), as well as the use of immunosuppression, RVT-802 dose and manufacturer, study protocol, renal function, hepatic function, and maximum naïve CD4 count post-implantation. A Cox proportional hazards (PH) model was fitted to the survival data, using 1 covariate at a time. Each subgroup was tested to see if it had a significant effect on survival.

There were no statistically significant differences in survival for 12 of the 15 subgroups analyzed. A higher risk of death (p <0.05 from Cox PH analysis of survival) between pre-defined subject subgroups was observed for the following 3 subgroups:

- CMV infection prior to RVT-802 implantation - In the EAS, 3 of 4 subjects (75%) with CMV prior to implantation died, as compared with 18 of 74 subjects (24%) without CMV infection. The single surviving subject with pre-existing CMV was considered to have a false positive test for CMV prior to treatment as all subsequent testing was negative. The hazard ratio was 7.3 with a 95% CI of [2.21, 24.14] and a p-value of 0.0011. A Similar risk of death was observed in the EAS-cDGA and FAS. Subjects with pre-existing CMV infections died from their infection prior to the development of thymic function.
- Serum creatinine at Screening – In the EAS, 5 of 9 subjects (56%) with an elevated serum creatinine died, as compared with 18 of 75 subjects (24%) with no elevation of serum creatinine prior to RVT-802 implantation. The hazard ratio was 3.14 with a 95% CI of [1.18, 8.33] and a p-value of 0.0215. An increased risk of death was also observed in the EAS-cDGA and FAS. The clinical significance of this analysis is unclear as only 9 subjects had an elevated serum creatinine value at screening and only 1 subject had an elevated serum creatinine that persisted post-transplant.
- Maximal post-transplant naïve CD4 count – An increased risk of death was observed for subjects in the lowest quartile of post-transplant naïve T cell development (0 to 16 cells/mm<sup>3</sup>) as compared to the highest quartile of naïve T cell development (393 to 1836 cells/mm<sup>3</sup>). In the EAS, no subject in the highest quartile group (N=20) died, as compared to 12 deaths in 18 subjects (67%) in the lowest quartile. The hazard ratio was 1.55 with a 95% CI of [3.11, 1342.25] and a p-value of 0.0071. An increased risk of

death was also observed for subjects in the lowest quartile for naïve T cell development in the EAS-cDGA and FAS. For subjects in the second and third quartiles, there was no increased risk of death, as only 11% and 15% of subjects in these quartiles died. This suggests that even a moderate level of naïve T cell provides a survival benefit.

**Reviewer's comments:** There were two important subpopulations that were not included in the Applicant's analysis which may impact the safety and efficacy of RVT-802.

***1. Duration of thymic culture during the manufacturing process.***

The Kaplan-Meier estimated survival rates at Year 1 in the EAS were:

- Tissue cultured from 11 to 15 days (n=35): 83% (95% CI 0.658, 0.919)
- Tissue cultured for 16 days (n=14): 86% (95% CI 0.539, 0.962)
- Tissue cultured for 17 to 19 days (n=18): 88% (95% CI 0.586, 0.967)
- Tissue cultured for 20 to 21 days (n=18): 56% (95% CI 0.305, 0.748)

Most deaths (21 of 25 deaths in the EAS, 84%) occurred within the first year after implantation with most deaths in subjects receiving tissue cultured for the longest duration (8 deaths among 18 subjects receiving tissue cultured between 20 and 21 days). Overall, the survival rate was lowest among subjects receiving RVT-802 cultured from 20 to 21 days with a Kaplan-Meier estimated survival rate of 56%, with all subjects dying in the first-year post-implantation. Similar results were also observed when analyzed by the FAS and EAS-cDGA.

There was a trend towards decreased survival with increasing time in tissue culture using a Cox proportional hazards (PH) model but the difference was not statistically significant when compared against subjects receiving tissue cultured for 16 days, which was the most common duration of tissue culture used for implantation (Table A). Similar results were also observed when analyzed by the FAS and EAS-cDGA populations.

Most of the deaths in subjects who received RVT-802 cultured for 20 and 21 days were due to pre-existing infections or comorbidities. Six of the 8 subjects in the EAS (Subjects (b) (6) [REDACTED] who died following receipt of RVT-802 cultured for 20 to 21 days died from infections that were present prior to RVT-802. The remaining two subjects (Subjects (b) (6) [REDACTED] contracted serious viral infections in the early post-implantation period, prior to the development of thymic function. Furthermore, most deaths occurred within the first-year following implantation, including all 8 deaths reported in the longest tissue culture time quartile. The presence of pre-existing infections in combination with significant comorbidities and an older median age (304 days at the time of implantation versus 251 to 290 in the other tissue culture time quartiles) likely contributed to the higher incidence of deaths reported in this quartile. Therefore, it is difficult to determine the impact of tissue culture time on survival because these deaths occurred prior to the expected development of thymic function and as such were not indicative of the efficacy of RVT-802.

**Table 31: Cox PH Model for Survival by Time in Tissue Culture**

	RVT-802 (EAS) N = 90				
	Culture Time Q2	Culture Time Q1	Culture Time Q3	Culture Time Q4	Culture Time Missing or Excluded
	16 Days (N=14)	(11-15 Days) (N=35)	(17-19 days) (N=18)	(20-21 days) (N=18)	(N=5)[b]
Number of subjects who died: n (%)	2 (14.3)	8 (22.9)	4 (22.2)	8 (44.4)	3 (60.0)
Number of subjects who did not die (censored): n (%)	12 (85.7)	27 (77.1)	14 (77.8)	10 (55.6)	2 (40.0)
Hazard ratio Other dose groups vs. Q4 (16402.5 < - 23754.5 mm <sup>2</sup> /m <sup>2</sup> )		1.26	1.53	2.86	
Standard error		0.75	0.82	0.75	
95% CI <sup>a</sup>		(0.29, 5.50)	(0.30, 7.72)	(0.65, 12.50)	
One-sided p-value		0.7605	0.6044	0.1624	

**2. Hematopoietic stem cell (CD34) transplantation**

This analysis was conducted on the expanded data set from the 120-day safety update. There were 6 subjects who received RVT-802 after a prior hematopoietic cell transplantation; 5 subjects with congenital athymia and one subject with SCID (Subject (b) (6)). Among the former subjects, 3 had a diagnosis of cDGA (Subjects (b) (6) 1 had FOXN1 deficiency (Subject (b) (6)), and 1 had athymia of unknown etiology (Subject (b) (6)). These 5 subjects with congenital athymia who had received prior HSCT (prior HSCT; n = 5) were compared with those in the EAS with a diagnosis of athymia without prior HSCT (n = 90). The single subject with SCID who received RVT-802 after a prior HSCT (Subject (b) (6)) was excluded from this analysis as RVT-802 is not expected to benefit subjects with a diagnosis of SCID without athymia.

The baseline characteristics were generally similar between the two groups except for age at RVT-802 implantation and race. All 5 subjects in the prior HSCT group were white (100%) as compared to 70% of subjects in the EAS population without prior HSCT. Subjects with prior HSCT were older at the time of implantation with a median age of 1158 days (range 1017 to 6163) at the time of implantation as compared to subjects without prior HSCT (245 days; range 33 to 775).

Subject (b) (6) in the prior HSCT group died following treatment with RVT-802. The Kaplan-Meier estimated survival rates at Year 1 were 80% (95% CI [0.204, 0.969]) and 76% (95% CI [0.658, 0.838]) for subjects receiving RVT-802 after prior HSCT versus without prior HSCT, respectively. A Cox proportional hazards (PH) model for survival by receipt of prior HSCT showed no statistically significant differences in survival between the two groups (HR 1.15, 95% CI: 0.21, 6.17, p=0.87).

**7.7.2 Secondary Efficacy Endpoints**

The same 15 subgroups evaluated for the primary efficacy endpoint were analyzed against the secondary efficacy endpoints.

**7.7.2.1 T cell Counts**

Subjects who were <6 months of age at the time of transplantation had higher median naïve CD4 counts at 1-year post-implant as compared with subjects who were older. Similarly, subjects who received RVT-802 when >12 months of age had lower median CD4 counts, as compared with subjects <12 months of age. The significance of these findings is unknown although lower median T cell counts are observed with increasing age in normal healthy

children. There were no clinically relevant differences in survival despite the slight differences in naïve CD4 T cell counts observed based on age at the time of transplant.

The median naïve CD4 T cell counts at Years 1 and 2 post-transplant were slightly lower for subjects who received immunosuppressive therapies when compared with those who did not (Table 32). However, the naïve CD4 counts were still in the normal range (i.e., >100 cells/mm<sup>3</sup>) in subjects who were immunosuppressed.

**Table 32: Naïve CD4 T cell (median) vs Immunosuppression**

(Reviewer’s Table)

Immunosuppression	Baseline	Year 1	Year 2
Yes	1.0 (n=47)	222.3 (n=25)	247.7 (n=11)
No	0.0 (n=10)	289.8 (n=14)	273 (n=11)

The naïve CD4 counts were analyzed by the dose of RVT-802 (by quartiles) that was transplanted. Subjects receiving the lowest dose of RVT-802 (4523 - 9110 mm<sup>2</sup>/m<sup>2</sup>) had lower naïve CD4 counts at Year 1 post-implantation when compared with subjects in the 3 higher dose quartiles (Table 33). The number of subjects with Year 2 data available for analysis was too small to draw meaningful conclusions. However, these changes were unlikely to be clinically significant. The results of a univariate regression analyses found no significant effect of dose on naïve CD4 counts indicating the absence of a dose response relationship. Finally, all dose subgroups had median naïve T cell counts there were sufficient to fight infection (>100 cells/mm<sup>3</sup>).

**Table 33: Naïve CD4 T cell (median) vs RVT-802 Dose**

(Reviewer’s Table)

RVT-802 Dose	Baseline	Year 1	Year 2
Q1 (4522.7 - 9110.0)	0.7 (n=11)	117.5 (n=6)	244.5 (n=4)
Q2 (9110.0 - <13098.1)	1.0 (n=16)	282.9 (n=10)	205 (n=7)
Q3 (13098.1 - <16402.5)	1.9 (n=14)	268.9 (n=10)	318.5 (n=4)
Q4 (16402.5 - <23754.5)	0.7 (n=13)	271.1 (n=9)	246.2 (n=6)

No conclusion can be drawn regarding naïve CD4 T cell development based on manufacturing facility due to the limited number of subjects. As follow-up is ongoing in Study 25966, only 2 out of 5 subjects receiving RVT-802 manufactured at the (b) (4) facility had naïve CD4 counts reported at Year 1. The median reported for these 2 subjects was lower than that reported for subjects implanted with RVT-802 manufactured in (b) (4). In particular, Subject (b) (6) had a count of 1 naïve CD4 cell in the Year 1 analysis was likely due to the prolonged use of immunosuppression. Subject (b) (6) had a count of 68 naïve CD4 cells.

Analyses of naïve CD4 counts versus baseline disease characteristics were also inconclusive because of the limited number of subjects within each subgroup.

- cDGA phenotype - subjects with the typical cDGA phenotype had a higher median naïve CD4 count as compared to subjects with atypical cDGA at Year 1. This difference was likely related to the use of immunosuppression in atypical cDGA. However, naïve CD4 counts were similar between the cDGA phenotypes by Year 2.

- cDGA etiology/mutation - subjects with CHARGE had the lowest naïve CD4 counts at Year 1, as compared with other etiologies of cDGA; however, by Year 2, naïve CD4 counts were similar across the disease etiologies.
- CMV infection – Only 1 subject tested positive for CMV prior to RVT-802 implantation and was still alive at Year 1 (Subject (b) (6)). This subject had a naïve CD4 count of 677 cells/mm<sup>3</sup> at Year 1. However, it is likely the CMV test was a false positive, as all subsequent CMV tests were negative.
- Serum creatinine - there were only 3 subjects with an elevated creatinine at baseline and their naïve CD4 counts at Year 1 were lower than subjects with normal values. However, the naïve CD4 counts by Year 2 values were higher in subjects with elevated serum creatinine at baseline.
- Serum AST - subjects with elevated AST at baseline had lower naïve CD4 counts compared with subjects who had normal values. However, the naïve CD4 counts by Year 2 values were similar regardless of baseline AST.
- Serum ALT - the naïve CD4 counts were higher at Years 1 and 2 in subjects with elevated ALT levels at baseline relative to those with normal baseline values.

However, no conclusions can be drawn regarding these differences given the small sample size.

#### **7.7.2.2 PHA Response**

There were no trends in T cell proliferative responses to PHA when examined by subgroup.

#### **7.7.2.3 Thymic Histology**

RVT-802 biopsy results were available for 50 subjects in the EAS. Thymopoiesis was evident in 40 subjects (80%), rejection in 1 subject (2%), and 9 subjects had no evidence of thymopoiesis or rejection. Subgroup analysis by maximal achieved naïve CD4 count suggest thymopoiesis was more often observed in subjects that received higher doses of RVT-802. Only 6 of 10 subjects (60%) in the lowest RVT-802 dose quartile (0 - 16 cells/mm<sup>3</sup>) showed thymopoiesis versus 14 of 15 subjects (93%) receiving the highest quartile (393 < 1836 cells/mm<sup>3</sup>). There were no association between the other subgroups that were assessed.

#### **7.7.2.3 Other Secondary Endpoint Subgroup Analyses**

There were a variety of other secondary endpoints that were analyzed by subgroup including Immunoglobulins, B cell function, TRECs, TREGs, T cell receptor diversity (Immunoscope/Spectratyping), subject infection (CMV/EBV), and T cell receptor diversity (TCR Flow). Numerical differences were observed between subgroups, but they did not appear to be associated with any clinically relevant differences in the results for any subgroup.

**Reviewer's comments:** There were two important subpopulations that were not included in the Applicant's original analysis which may impact secondary efficacy endpoints:

##### **1. Duration of thymic culture during the manufacturing process.**

The effect of the duration that the thymic tissue was cultured during the manufacturing process on secondary endpoints was also assessed. The median naïve CD4 T cell counts were >100 cells/mm<sup>3</sup> at Year 1 and Year 2 post-implant in all tissue culture durations; this threshold is considered sufficient to combat infection (Table 34). In addition, the median CD4 count at 1 year was the highest in subjects that received RVT-802 cultured for 20-21 days (297 cells/mm<sup>3</sup>) although the number of subjects assessed is limited (6 of 14 subjects or 43%). Similarly, T cell proliferation in response to antigen/mitogen were not different

regardless of time in tissue culture as were evidence of thymopoiesis on RVT-802 biopsy. Similar results were also observed when analyzed by the FAS and EAScDGA populations.

**Table 34: Naïve CD4 Cell Count by Time in Tissue Culture**

Subgroup		EAS (N = 90) Naïve CD4 (cells/mm <sup>3</sup> )					
		Baseline		Year 1		Year 2	
		n	Median	n	Median	n	Median
Time in Tissue Culture	11 to 15 Days (N=35)	21	1.000	20	248.920	12	323.000
	16 Days (N=14)	10	0.825	9	171.830	7	273.000
	17-19 Days (N=18)	14	1.000	6	217.000	3	202.000
	20-21 Days (N=18)	14	1.250	6	297.410	4	135.695

**2. Hematopoietic stem cell (CD34) transplantation**

There were 6 subjects who received RVT-802 after a prior hematopoietic cell transplantation; 5 subjects with congenital athymia and one subject with SCID (Subject (b) (6)). The subject with SCID was excluded from this analysis. The median naïve CD4 T cell counts were 150 and 378 cells/mm<sup>3</sup> at Years 1 (N =2) and 2 (N =1) post-implant, respectively in subjects with prior HSCT. This exceeds the threshold (>100 cells/mm<sup>3</sup>) that is considered sufficient to fight infection. Similarly, subjects generally achieved normal responses to mitogens/antigens at Year 1 with or without a prior HSCT. Evidence of thymopoiesis was also noted on RVT-802 biopsy in all 4 of the prior HSCT subjects who were biopsied. By comparison, 41 of the 51 (80%) subjects without prior HSCT had evidence of thymopoiesis.

**7.8 Persistence of Efficacy**

There were 85 subjects who were implanted with RVT-802 in the EAS. Of these subjects, 84 and 77 subjects completed at least 1 and 2 years of follow-up, respectively. Survival at 1 year was 76% (64 of 84 subjects) and at Year 2 was 73% (56 of 77 subjects). In addition, there were no new deaths after Year 9 before the last subject was censored at Year 24 post-transplant. Furthermore, the incidence of infections significantly declined 12 to 24 months post-transplant as compared to the first 12 months. The survival benefit of RVT-802 was accompanied by the development of immune function that persisted for at least 2 years post-transplant.

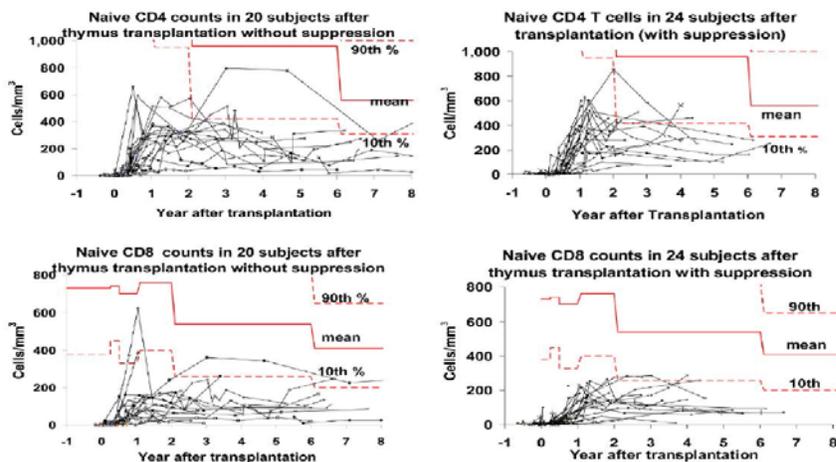
- Median naïve CD3, CD4, and CD8 cell counts increased through 2 years post-transplant.
- T cell proliferative responses to PHA, ConA, Sol CD3, Immob CD3, and tetanus toxoid were also sustained through 2 years post-transplant.
- TCRVβ repertoire variability as assessed by immunoscope/spectratyping and flow cytometry demonstrated a diverse TCR repertoire through 2 years after transplantation.

The clinical studies conducted in support of this application were limited to 2 years of follow-up. However, Dr Markert has evaluated the outcomes of these subjects beyond 2 years. With the use of general estimating equations analysis, she showed that naïve T cell counts peak around 1 to 2 years post-transplant and stabilize thereafter. Whereas naïve CD4 T cells begin to decrease 2 years after transplantation, naïve CD8 T cells remained stable

after Year 2. As observed in Figure 7, naïve CD4 and CD8 T cell counts generally remained below the 10<sup>th</sup> percentile for age but were sufficient to fight infection and enable survival.

**Figure 7: Naïve Cd4 and CD8 T-cells following RVT-802**

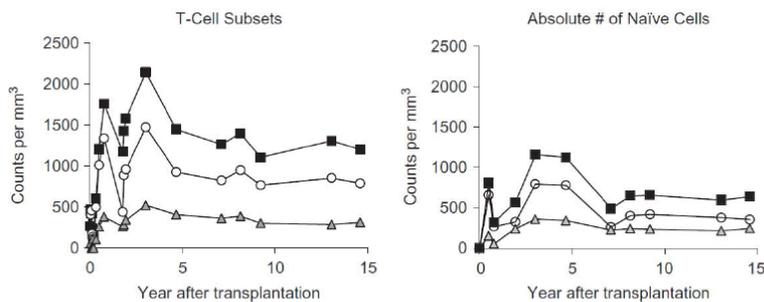
(Applicant's Figure)



In addition, a time course for the development and persistence of T cells for a single subject through 14.8 years post-transplant is shown in Figure 8. At the last assessment (14.8 years of age), the subject had normal CD3, CD4, naïve CD4, and naïve CD8 counts. T cell diversity was also maintained over time as well as T cell proliferative responses. These results demonstrate that the immune reconstitution is durable and persistent and complements the long-term survival benefit.

**Figure 8: T cell count following RVT-802 in a Subject**

(Applicant's Figure)



Left panel: CD3 (black square), CD4 (white circle), CD8 (gray triangle) counts/mm<sup>3</sup>. Right panel: total naïve CD3 (black square), naïve CD4 (white circle), and naïve CD8 (gray triangle) T cell counts.

Finally, the tolerance of the newly developed T cells to the allogeneic RVT-802 was confirmed using a mixed lymphocyte cultures test. Specifically, tolerance of recipient T cells toward their HLA-non-matched thymus (RVT-802) grafts was observed in a subset of 12 subjects ranging from 10.5 months to 6.4 years post-transplant (median 4.2 years).

**7.9 Product-Product Interactions**

There were no studies of potential drug-drug or drug-food interactions performed with RVT-802.

### 7.10 Efficacy Conclusions

The RVT-802 development program for the treatment of T cell immunodeficiency resulting from congenital athymia has been conducted at DUMC during the past 25 years. The primary clinical efficacy data included in this Application are derived from 7, single-site, open-label, non-randomized clinical studies in subjects with congenital athymia (Studies 668-1, 668-2, 884 [includes 884-1], 931, 932, 950 [includes 950-1], and 25966) and three supporting single-subject/expanded access studies (Studies 735, (b) (6), and 51692). These studies cumulatively treated 93 subjects with RVT-802 and constitute the FAS. Of these, 85 and 83 subjects, respectively, met the criteria for inclusion in the EAS and EAS-cDGA.

The EAS included all subjects with congenital athymia associated with cDGA or FOXP1 deficiency. In the EAS, 2 subjects had FOXP1 deficiency and 83 subjects had a diagnosis of cDGA, of whom 43 subjects had the typical cDGA phenotype and 39 subjects had the atypical cDGA phenotype. Eight additional subjects were included in the FAS and provide supportive efficacy data. These subjects included 2 subjects with SCID (N=2), 3 subjects with cDGA who had received prior HSCT, 1 cDGA subject who had 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 who is now considered to have had the atypical phenotype of cDGA.

The Kaplan-Meier estimated survival at Year 1 and Year 2 post-transplant in the EAS, were 76% (95% CI: 0.659, 0.841]) and 75% (95% CI: 0.646, 0.831]), respectively. Most deaths occurred within the first year after transplantation and the survival rate was essentially unchanged thereafter; 75% to 70% from Year 2 to Year 9, respectively. There were no deaths after Year 9 before the last subject was censored at Year 24 post-transplant. Sixty subjects (94%) remained alive at the latest follow-up, which extended up to 24 years post-implant. The survival rates were similar across analysis populations at all time points. The median follow-up time for all subjects in the EAS was 2682 days (7.3 years) and ranged from 0 to 8569 days (23.5 years) after RVT-802 transplantation. Kaplan-Meier analysis showed the overall survival rate in the EAS was 72%; the median survival time was 134 days (range: 0 to 3116 days [8.5 years]) for the 24 subjects (28%) who died in the EAS. By comparison, infants with congenital athymia generally survive less than 2 years.

To further investigate the survival benefit of RVT-802, survival at Year 1 and Year 2 >50% was tested using the binomial exact test. In the EAS, with 1 subject censored as follow-up was still ongoing, 64 of 84 subjects (76.2%) were alive at Year 1 post-implantation. The binomial exact test with null hypothesis that no greater than 50% of subjects would survive at Year 1 gave a 95% CI of 0.66, 0.85 ( $p < 0.0001$ ). At Year 2 post-implantation, with 56 of 77 subjects (72.7%) alive with 8 subjects censored as follow-up was still ongoing, the exact binomial test gave a 95% CI of 0.61, 0.82 ( $p < 0.0001$ ).

The clinical benefit of RVT-802 transplantation was supported by data from a number of secondary endpoints that were consistent with immune reconstitution.

- Naïve CD3, CD4, and CD8 T cells - immune profiles of most subjects implanted with RVT-802, changed from having no naïve T cells (or  $< 50$  cells/mm<sup>3</sup>) at baseline to having measurable cells within approximately 6 months after implantation and levels considered sufficient to fight infection within 1-year post-transplant.
- T cell proliferation in response to PHA was increased from baseline to Year 2 post-transplant. The median PHA response at Month 6 and afterward was greater than

75,000 cpm which was indicative of a normal response. Data for other antigens/mitogens including ConA, Candida, sol CD3, immob CD3, and tetanus toxoid were limited. Nonetheless, with the exception of *Candida* skin test antigen (due to a lack of environmental exposure), the median T cell proliferative response normalized for all other antigens/mitogens tested within ~1-year and were maintained through Year 2.

- TCRVβ repertoire - Flow cytometry and spectratyping data demonstrated an emergence of a diverse TCRVβ repertoire over time which was indicative of improved thymic function. These results are significant as the development of a diverse TCRVβ repertoire is necessary to recognize and respond to a broad range of antigens.
- Thymic biopsy - Thymopoiesis was noted for 40 of the 50 subjects (80%) in the EAS for whom biopsy results were available. Only one subject showed evidence of RVT-802 rejection despite the thymic tissues not being HLA matched. This subject had atypical cDGA with the presence of oligoclonal T cells at transplantation. He had received pentostatin prior to transplantation because he was too ill to receive RATGAM and was likely inadequately immunosuppressed.
- Infections - The incidence of infections significantly decreased over time as would be expected with the development of immune function. The Wilcoxon signed-rank test on the difference of the number of infection-related AEs with an onset within 6 months and >6 months to 12 months after transplantation was statistically significance (median difference = 2.0, p <0.001), with fewer infection-related AEs reported 6 to 12 months post-RVT-802 implantation. Similar results were observed when infections were evaluated within 12 months post-implantation versus 12 to 24 months post-implantation (median difference = 3.0, p <0.001). See Table 35 for additional details on number of infections.

**Table 35. Infections Over Time in EAS Subjects Treated with RVT-802**

	<6 months	6-12 months	12-24 months
<b># infection AEs</b>	312	88	83
<b># Subjects with infection</b>	78	37	31
<b>% Subjects with infection (95% CI)</b>	91.8% (83.8%, 96.6%)	43.5% (32.8%, 54.7%)	36.5% (26.3%, 47.6%)

Source: Table made by FDA Statistician.

The analyses of these secondary endpoints were limited by the variability in the amount of the data that was collected. This was because upon discharge from the primary study center (DUMC), the follow-up testing was dependent upon the parent(s)/legal guardian(s) of the subject, the referring local physicians, and the subject’s medical condition. Furthermore, the absence of protocol defined visit windows resulted in limited data reporting within the pre-defined analysis windows. Despite these limitations, the available data clearly support the reconstitution of thymic function following RVT-802.

In summary, transplantation of RVT-802 reconstituted a immunocompetent T cell population in subjects with congenital athymia. This resulted in a reduction in infections that enabled long-term survival in a population with an otherwise fatal disease.

## 8. INTEGRATED OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

The integrated overview of safety was analyzed based upon the data pooled from the 10 studies. The safety data were summarized using descriptive statistics and summary tabulations. Continuous variables were presented as minimum and maximum values, mean, median and standard deviation (SD). Categorical data (frequency tabulations) were presented by the number and percentage of subjects. The denominator for all percentages was the number of subjects that were pooled for the analysis set of interest, unless otherwise indicated.

Baseline was defined as the last value obtained prior to RVT-802 implantation. If multiple values were recorded on the same day, the average of all measurements taken on that day was used as the baseline value. The day of RVT-802 implantation was defined as Day 0 and was used to calculate days relative to implantation. Imputation of missing dates was done prior to entering the data into the database according to the eCRF completion guidelines. Consequently, no programmatic imputation was performed.

In the pooled analysis, the severities of all AEs were reported as collected in the individual studies using the CTCAE version used in that study. A tabular summary of AEs with severity  $\geq$  Grade 3 was generated. Adverse events were summarized separately by presenting the number and percentage of subjects having any event; having a related event; having an event in each MedDRA SOC and PT; and having each individual event and the severity, relationship, and outcome of each event. The number of events was also presented. Missing severities, relationship or outcomes were classified as unknown. For the purposes of summarization, all AEs including infection-related AEs were included in AE summary tables, unless otherwise specified.

A subject with more than one occurrence of the same AE in a particular SOC was counted only once in the total of subjects experiencing AEs in that particular SOC. If a subject had the same AE at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug was given precedence. Any missing severities, causalities, or outcomes were not imputed and were classified as unknown.

### 8.2 Safety Database

The Full Analysis Set (FAS) comprising of all 93 subjects treated with RVT-802 was used for the safety analyses. The EAS (N=85) included all subjects with congenital athymia associated with cDGA or FOXP1 deficiency, who had no prior HSCT and were treated with RVT-802. The EAS-cDGA analysis set (EAS-cDGA; N=83) included all subjects in the EAS except those with FOXP1 deficiency.

Safety assessments were generally conducted weekly for the first 12 weeks post-implantation while the subject was still hospitalized. Further safety assessments were summarized at Months 3, 6, 9, 12, 18, and 24. Additional AEs reported beyond 2 years were also summarized. However, the reporting of AEs beyond 2 years was limited given differences in the duration of subject follow-up and the return of subjects to their referring institution.

**8.2.1 Studies/Clinical Trials Used to Evaluate Safety**

The clinical safety data included in this Integrated Summary of Safety supporting the use of RVT-802 for the immune reconstitution of patients with congenital athymia are derived from the 10 clinical studies that comprised the development program.

- Seven core, single-site, open-label, non-randomized studies (Protocols 668-1, 668-2, 884 [includes Study 884.1], 931, 932, 950 [includes 950.1] and 25966),
- Two additional IND 9836 studies (Protocols (b) (6) and 51692), and
- One non-IND single subject study (Protocol 735).

**8.2.2 Demographics of Pooled Safety Populations**

The demographics of the FAS and EAS are presented in Table 36. The demographics of the subjects in the two analysis sets were very similar with the exception of age at the time of RVT-802 implantation. Subjects in the FAS had a median age at the time of implantation of

**Table 36: Subject Demographics**  
(Applicant’s Table)

	EAS N = 85	FAS N = 93
Age on day of implantation (days)		
N	85	93
Mean (SD)	249.9 (152.05)	449.1 (963.48)
Median	239.0	256.0
Minimum, Maximum	33, 664	33, 6163
Sex, n (%)		
Male	52 (61.2)	56 (60.2)
Female	33 (38.8)	37 (39.8)
Race, n (%)		
White	59 (69.4)	67 (72.0)
Black or African American	18 (21.2)	18 (19.4)
Asian	3 (3.5)	3 (3.2)
American Indian or Alaska Native	2 (2.4)	2 (2.2)
Native Hawaiian or Other Pacific Islander	1 (1.2)	1 (1.1)
More than one race	2 (2.4)	2 (2.2)
Unknown or not reported	0 (0.0)	0 (0.0)

Source: Table 14.1.4.1

Abbreviations: cDGA = complete DiGeorge anomaly; EAS = efficacy analysis set; FAS = full analysis set; N = number of subjects included in the analysis set; SD = standard deviation

256 days (range 33 to 6163 days), which was nominally greater than that in the EAS (239 days, range 33 to 664 days). All subjects in the EAS were <2 years old (<730 days) at the time of implantation while 5 subjects who were included only in the FAS ((b) (6)) were more than 2 years old. Subjects (b) (6) were 4741, 1050, 5763, 1017 and 6163 days old, respectively, at the time of implantation. A total of 64 subjects were <1-year old at the time of thymic implant. Of these 64 subjects, 35 (37.6%) were ≤ 6 months old and 29 (31.2%) were 6 to ≤ 12 months old. Most subjects were male (56 [60.2%]) and white (67 [72.0%]). Immunosuppressive medications were administered to 61 (65.6%) subjects during the study.

The diagnosis of DGA was confirmed based on the presence of characteristic clinical features, including congenital cardiac anomalies, a small thymus, and hypocalcemia secondary to hypoparathyroidism. The diagnosis of athymia, and subsequently cDGA, was confirmed via flow cytometry based upon <50 naïve T cells/mm<sup>3</sup> (CD45RA+, CD62L+) in the peripheral blood or <5% of total T cells being naïve in phenotype. The median age at diagnosis was 28 days (range: 0 to 841 days) with most subjects diagnosed before they were 6 months of age (≤ 185 days). Most subjects (87 [93.5%]) had a diagnosis of cDGA with a

similar number of subjects having the typical (45 subjects) and atypical (41 subjects) cDGA phenotypes.

A phenotype classification was missing for two subjects (Subjects (b) (6) ) with cDGA. Subject (b) (6) was enrolled after the development of GVHD from the donor of an unirradiated red blood cell transfusion. Due to the presence of GVHD, this subject's cDGA phenotype could not be determined. Subject (b) (6) was enrolled following two stem cell transplants. Because this subject had received prior stem cell transplants, his cDGA phenotype could not be determined.

One subject (b) (6) had what was thought to be partial DGA at the time of study enrollment as this subject was treated prior to the availability of reagents to assess naïve T cell markers. Given this diagnosis, this subject was included only in the FAS. However, in reviewing this subject's presentation at the time of this Application, the Investigator considered it likely this subject had what is now considered to be atypical cDGA, and thus this subject was reported as having an atypical phenotype.

For the remaining subjects, two subjects (2.2%) were diagnosed with FOXN1 deficiency (Subjects (b) (6) ). The only disease characteristic reported for subjects with FOXN1 deficiency was diminished T cell count for age. Both subjects also presented with alopecia which was consistent with FOXN1 deficiency. A diagnosis of SCID was reported in 2 (2.2%) subjects (Subjects (b) (6) ). Subject (b) (6), who was initially diagnosed with cDGA, had a hemizygous deletion of chromosome 22q11.2 and presented with congenital cardiac/thoracic vascular anomaly, deafness or ear pinnae anomalies, diminished T cell counts for age, growth or mental retardation, hypocalcemia, limb anomalies and renal anomalies. This subject was found to have SCID after treatment with RVT-802 and was subsequently withdrawn from the study. Subject (b) (6) had athymia of unknown etiology. This subject's mother had gestational diabetes and exhibited phenotypic features that included diminished T cell count for age and hypocalcemia.

### **8.2.3 Overall Exposure**

The median dose of RVT-802 implanted in subjects in the FAS was 13,098 mm<sup>2</sup>/m<sup>2</sup> (range: 4,523 to 23,755) with a median of 30 slices (range: 10 to 108). A total of 5 subjects received a dose greater than the current IND-recommended maximum dose of (b) (4) mm<sup>2</sup>/m<sup>2</sup>. The maximum dose implanted was 23,754.51 mm<sup>2</sup>/m<sup>2</sup>.

The duration of subject follow-up was limited to the first 2 years after implantation following a program-wide protocol amendment (31 July 2010). Prior to that, the protocols for studies 735, (b) (6), 668-1, 668-2, 884, 931, 932, and 950 were open-ended and did not include an end date for subject follow-up. This 2-year follow-up period was selected because immune reconstitution is usually achieved within 1 to 2 years after implantation. In addition, subjects returned to their referring institution shortly after implantation and, as such, were followed by their referring physician. Studies 25966 and 51692 also utilized a 2-year follow-up period.

Of the 93 subjects who received RVT-802 in the FAS, 65 (69.9%) were alive at the most recent follow-up, 25 (26.9%) were dead, and 3 (3.2%) had been withdrawn from the study, of whom 2 had subsequently died after study withdrawal (Table 37). The 3 subjects who were withdrawn from the study did so because of physician's decision. This included 2 subjects

**Table 37: Subject Disposition**  
(Applicant's Table)

	EAS N = 85	FAS N = 93
Number of subjects implanted	85	93
Status at the most recent follow-up:		
Alive	61 (71.8)	65 (69.9)
Dead	24 (28.2)	25 (26.9)
Withdrawn	0	3 (3.2) <sup>a</sup>
Number of subjects who completed at least 2 years of follow-up post-implantation, n (%)	56 (65.9)	61 (65.6)
Number of subjects ongoing	8 (9.4)	8 (8.6)
Number of subjects discontinued from study prior to 2 years after implantation, n (%)	21 (24.7)	24 (25.8)
Reasons for discontinuation from study prior to 2 years after implantation, n (%):		
Death	21 (24.7)	22 (23.7)
Parental decision	0	0
Physician decision	0	2 (2.2) <sup>b</sup>

Source: Table 14.1.2

Abbreviations: cDGA = complete DiGeorge anomaly; EAS = efficacy analysis set; FAS = full analysis set; N = number of subjects included in the analysis set

<sup>a</sup> 2 of 3 subjects (Subjects (b) (6) and (b) (6)) who were withdrawn due to physician decision died after study withdrawal.

<sup>b</sup> 1 additional subject (Subject (b) (6)) was withdrawn due to physician decision 6 years post-implantation.

with SCID (Subjects (b) (6)) who were withdrawn within 2 years of implantation and 1 subject (Subject (b) (6) with cDGA who had received prior fetal thymus transplants. Subject (b) (6) was withdrawn after the Investigator determined that RVT-802 had not engrafted. Subject (b) (6) was withdrawn after it was determined that the subject had SCID and not cDGA. Subject (b) (6) was withdrawn after evidence of thymus rejection on RVT-802 biopsy.

AEs were summarized within 2 years post-transplant to ensure consistency across the study protocols and in alignment with the 2-year follow-up period. Sixty-one of the 93 subjects (65.6%) had completed at least 2 years of follow-up while 8 subjects (8.6%) had not at the time of this report. Twenty-four subjects (25.8%) discontinued the study before completing at least 2 years of follow-up including 22 subjects who died and 2 subjects (Subjects (b) (6)) who were withdrawn within the first 2 years. Subjects (b) (6) died 375 and 950 days after implantation, respectively, following withdrawal from the study.

### 8.2.3 Categorization of Adverse Events

Medical history and AEs were coded according to MedDRA version 19.1. The severities of non-infection-related AEs and SAEs were graded (Grades 1 to 5) according to CTCAE version 3.0 and was used for Studies 668-1/668-2, 884/884.1, 931, 932, 950/950.1, 25966, (b) (6) and 735. CTCAE version 4.0 was used for Study 51692. Infection-related AEs were evaluated using either CTCAE criteria or criteria defined in the BMTCTN definitions of infection severity. Infection-related AEs with BMTCTN severity  $\geq$  severe were included in the analysis of AEs of Grade  $\geq$  3. Life-threatening infection-related AEs with an outcome of fatal were reported as Grade 5 events.

### 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

This integrated safety analysis was not affected by the pooling of data from clinical studies.

## 8.4 Safety Results

### 8.4.1 Deaths

There were 27 deaths following RVT-802 implantation including 23 deaths in the first two years after treatment and 4 deaths reported more than two years after implantation. Most deaths (21 deaths, 77.8%) occurred within the first-year (<365 days) after implantation which was prior to the development of thymic function. Most of these deaths were due to infections, complications associated with infection, or respiratory failure/hypoxia, and were consistent with the disease under study.

The causes of the 21 deaths reported in the first-year post-implantation included:

- Respiratory failure/hypoxia (N=5): Subjects (b) (6);
- Infection/sepsis/complication due to infection (N=12): Subjects (b) (6);
- Hemorrhagic events (N=3): Subjects (b) (6);
- Cardiorespiratory arrest (N=1): Subject (b) (6).

Six subjects died more than one year after implantation; none of the deaths were considered related to RVT-802 treatment.

- Respiratory failure (N=2): Subjects (b) (6) (Day 2769) (b) (6) (Day 3116);
- Cardiopulmonary arrest (N=1): Subject (b) (6) (Day 1617);
- Intracranial hemorrhage (N=1): Subject (b) (6) (Day 480);
- Infection (N=1): Subject (b) (6) (Day 375); subject died after study withdrawal;
- Unknown (N=1): Subject (b) (6) (Day 950); subject died after study withdrawal.

The causes of death were consistent with the clinical condition and medical histories of seriously ill, immunocompromised athymic subjects. The most common cause of death was infection as athymic subjects were prone to infections during the first year after implantation. However, there were 3 deaths that were considered possibly related to study treatment. All 3 deaths were due to infections or complications from infections and included:

- Subject (b) (6) died of progressive EBV lymphoma resulting in an intracranial hemorrhage considered possibly related to the use of immunosuppression;
- Subject (b) (6) died of CMV infection considered related to RATGAM;
- Subject (b) (6) died of CMV infection considered possibly related to RVT-802. The thymus donor had tested negative for CMV prior to tissue donation but both the subject and donor subsequently tested positive for CMV post-RVT-802 implantation. The origin of the CMV infection remained unknown.

The second most common cause of death was pre-existing respiratory and cardiovascular conditions associated with the disease. Seven subjects died of respiratory failure/hypoxia and none were considered related to study treatment. Of note, 89.2% of subjects entered RVT-802 studies with medical histories in the respiratory, thoracic, and mediastinal disorder SOC. All 7 subjects who died of respiratory failure/hypoxia had medical histories significant for prior respiratory distress and/or multiple prior respiratory related infections. Additionally, subjects entering the studies with pre-existing cardiovascular disorders likely had an increased risk of developing cardiovascular AEs. Finally, an increased risk of thrombocytopenia and associated bleeding events has been reported in subjects with 22q11.2DS.

#### **8.4.2 Serious Adverse Effects**

There were 443 SAEs reported in 79 (84.9%) subjects in the FAS within 2 years of RVT-802 implantation (Table 38). An additional 98 SAEs were reported > 2 years after RVT-802 implantation. The SAEs reported in the first 2 years after RVT-802 implantation were consistent with subjects' underlying conditions and medical histories.

The most frequent SAEs were in the infections and infestations SOC (n=67, 72.0%) but only device-related infection (n=41, 44.1%), pneumonia (n=8, 8.6%), lower respiratory tract infection (n=5, 5.4%) and viral upper respiratory tract infection (n=5, 5.4%) were reported in ≥ 5% of subjects. SAEs were also frequent in the respiratory and mediastinal disorders SOC

(n=37, 39.8%); the most frequent were respiratory failure (n=16, 17.2%), hypoxia (n=13, 14.0%) and respiratory distress (n=5, 5.4%). Pyrexia was also common (n=17, 18.3%).

**Table 38: SAEs Within 2 Years of Implantation (>5%)**  
(Applicant's Table)

System Organ Class Preferred Term	EAS N = 85		FAS N = 93	
	n (%)	E	n (%)	E
Number of subjects with SAEs	72 (84.7)	405	79 (84.9)	443
<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: Table 14.3.1.7.1  
Abbreviations: AE = adverse event; E = number of events; EAS = efficacy analysis set; FAS = full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the analysis set; n = number of subjects with events; PT = preferred term; SAE = serious AE; SOC = system organ class  
Note: If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count for a given SOC and PT. Adverse events were coded using MedDRA version 19.1.

**8.4.3 Adverse Effects**

All subjects reported at least one AE in the first 2 years after RVT-802 implantation (Table 39). A total of 1684 AEs were reported by the 93 subjects included in the FAS. Most subjects (n=84, 90.3%) had AEs that were Grade ≥ 3 including 22 (23.7%) subjects who died within the first 2 years after implantation. Nearly all subjects (n=89, 95.7%) reported at least one infection-related AE including 12 (12.9%) subjects with life-threatening and 10 (10.8%) subjects with fatal infections.

**Table 39: Overview of AEs (Within 2 Years Implantation)**  
(Applicant's Table)

	EAS N = 85	FAS N = 93
Number (%) of subjects with at least one AE	85 (100.0)	93 (100.0)
Number (%) of subjects with at least one AE by maximum severity <sup>a</sup> :		
Mild	1 (1.2)	1 (1.1)
Moderate	8 (9.4)	8 (8.6)
Severe	28 (32.9)	32 (34.4)
Life Threatening	27 (31.8)	30 (32.3)
Death	21 (24.7)	22 (23.7)
Number (%) of subjects with at least one related <sup>b</sup> AE	62 (72.9)	70 (75.3)
Number (%) of subjects with at least one related <sup>b</sup> AE by maximum severity:		
Mild	3 (3.5)	3 (3.2)
Moderate	21 (24.7)	21 (22.6)
Severe	24 (28.2)	29 (31.2)
Life Threatening	12 (14.1)	14 (15.1)
Death	2 (2.4)	3 (3.2)
Number (%) of subjects with at least one:		
SAE	72 (84.7)	79 (84.9)
AE with Grade ≥ 3 <sup>c</sup>	76 (89.4)	84 (90.3)
Infection-related AE	83 (97.6)	89 (95.7)
Number (%) of subjects with at least one infection-related <sup>b</sup> AE by maximum severity:		
Mild	2 (2.4)	2 (2.2)
Moderate	13 (15.3)	15 (16.1)
Severe	48 (56.5)	50 (53.8)
Life Threatening	10 (11.8)	12 (12.9)
Death	10 (11.8)	10 (10.8)

An additional 319 events were reported >2 years after implantation through the reporting period of 31 December 2017 for all studies except Study 25966 which had a data cut-off date of 16 July 2018, resulting in a total of 2003 AEs at the time of this report. The AE profile beyond 2 years after transplantation was consistent with that reported in the first 2 years.

**8.4.3.1 Adverse Events of Grade ≥ 3**

There were 1684 AEs reported in the FAS; 680 (40.4%) of the AEs in 84 (90.3%) subjects were Grade ≥3 in severity using either CTCAE or BMTCTN (Table 40). On the basis of subject count, Grade ≥3 AEs were most frequent in the infections and infestations SOC (n=72, 77.4%). However, only device-related infection was reported in ≥10% of subjects, and only CMV infection (n=2, 2.2%) was assessed as related to treatment in this SOC. Other Grade ≥3 AEs that were reported in ≥10% of subjects were thrombocytopenia, anemia, neutropenia, hypoxia, respiratory failure, diarrhea, AST increased, ALT increased, and pyrexia. This AE profile is consistent with the overall population under study.

There were 95 treatment-related AEs of Grade ≥ 3 in 46 (49.5%) subjects. However, no AEs were assessed as related to treatment in ≥10% of subjects. The most frequent TEAEs were thrombocytopenia and neutropenia which were reported in 8 (8.6%) subjects each.

**Table 40: AEs Grade ≥3 Within 2 Years of Implantation**  
(Applicant’s Table)

System Organ Class Preferred Term	EAS N = 85		FAS N = 93	
	n (%)	E	n (%)	E
<b>Number of subjects with AE Grade ≥ 3</b>	<b>76 (89.4)</b>	<b>633</b>	<b>84 (90.3)</b>	<b>680</b>
<b>Infections and Infestations</b>	<b>68 (80.0)</b>	<b>238</b>	<b>72 (77.4)</b>	<b>249</b>
Device-related infection	40 (47.1)	99	41 (44.1)	101
<b>Blood and lymphatic system disorders</b>	<b>36 (42.4)</b>	<b>52</b>	<b>41 (44.1)</b>	<b>64</b>
Anaemia	18 (21.2)	19	19 (20.4)	20
Neutropenia	13 (15.3)	13	16 (17.2)	16
Thrombocytopenia	9 (10.6)	11	10 (10.8)	12
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>36 (42.4)</b>	<b>81</b>	<b>36 (38.7)</b>	<b>81</b>
Hypoxia	19 (22.4)	24	19 (20.4)	24
Respiratory failure	16 (18.8)	20	16 (17.2)	20
<b>Gastrointestinal disorders</b>	<b>32 (37.6)</b>	<b>45</b>	<b>35 (37.6)</b>	<b>50</b>
Diarrhoea	11 (12.9)	13	11 (11.8)	13
<b>Metabolism and nutrition disorders</b>	<b>31 (36.5)</b>	<b>44</b>	<b>34 (36.6)</b>	<b>47</b>
<b>Investigations</b>	<b>24 (28.2)</b>	<b>42</b>	<b>27 (29.0)</b>	<b>46</b>
Aspartate aminotransferase increased	11 (12.9)	11	13 (14.0)	13
Alanine aminotransferase increased	11 (12.9)	12	12 (12.9)	13
<b>General disorders and administration site conditions</b>	<b>18 (21.2)</b>	<b>23</b>	<b>18 (19.4)</b>	<b>23</b>
Pyrexia	14 (16.5)	18	14 (15.1)	18
<b>Nervous system disorders</b>	<b>13 (15.3)</b>	<b>19</b>	<b>14 (15.1)</b>	<b>20</b>
<b>Immune system disorders</b>	<b>9 (10.6)</b>	<b>11</b>	<b>14 (15.1)</b>	<b>16</b>
<b>Renal and urinary disorders</b>	<b>10 (11.8)</b>	<b>16</b>	<b>10 (10.8)</b>	<b>16</b>
<b>Vascular disorders</b>	<b>10 (11.8)</b>	<b>16</b>	<b>10 (10.8)</b>	<b>16</b>

Source: Table 14.3.1.5

Abbreviations: E = number of events; EAS = efficacy analysis set; FAS = full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the analysis set; n = number of subjects with events; PT = preferred term; SOC = system organ class

Note: If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count for a given SOC and PT. Adverse events were coded using MedDRA version 19.1.

8.4.3.2 Adverse Events by Time of Onset

8.4.3.2.1 ≤ 2 Months versus > 2 Months after Implantation

The 2-month time point was selected as this typically coincided with the time subjects were most closely followed post-implantation. Most subjects were followed at DUMC for ~2 to 3 months following implantation until RVT-802 was biopsied. Medically stable subjects were then returned to their referring institution. This time point was also selected to capture the acute recovery period post-implantation prior to the development of thymic function.

There were 1684 AEs reported in the FAS; 694 AEs (41% of all reported AEs) were reported in the first 2 months after RVT-802 implantation (Table 41). Nearly all subjects (90 [96.8%]) had at least 1 AE in the first 2 months after RVT-802. This was not unexpected given the close follow-up required in the first few months following implantation. In addition, thymic function had not reconstituted, and a higher incidence of infections was expected. Finally, AEs captured in the first 2 months reflected the time-period of immunosuppression therapy.

**Table 41: AEs Reported ≤ 2 Months vs > 2 Months after Implantation**  
(Applicant’s Table)

	Within 2 Months N = 93 n (%) E	After 2 Months N = 93 n (%) E
Number of subjects with AEs	90 (96.8) 694	85 (91.4) 990
Number of subjects with SAEs	43 (46.2) 103	67 (72.0) 340
System Organ Class		
AE preferred term reported in ≥ 10% of subjects		
Infections and infestations	69 (74.2) 187	76 (81.7) 346
Device-related infection	22 (23.7) 39	34 (36.6) 83
Viral upper respiratory tract infection	4 (4.3) 4	13 (14.0) 14
Pneumonia	0	10 (10.8) 11
General disorders and administration site conditions	41 (44.1) 56	37 (39.8) 64
Pyrexia	38 (40.9) 47	33 (35.5) 54
Investigations	39 (41.9) 74	35 (37.6) 74
Alanine aminotransferase increased	12 (12.9) 13	15 (16.1) 16
Aspartate aminotransferase increased	10 (10.8) 10	14 (15.1) 14
Respiratory, thoracic and mediastinal disorders	39 (41.9) 60	37 (39.8) 79
Hypoxia	14 (15.1) 16	14 (15.1) 17
Respiratory failure	5 (5.4) 5	12 (12.9) 15
Gastrointestinal disorders	34 (36.6) 48	40 (43.0) 78
Diarrhoea	10 (10.8) 10	17 (18.3) 21
Vomiting	5 (5.4) 6	11 (11.8) 12
Skin and subcutaneous tissue disorders	34 (36.6) 44	37 (39.8) 65
Rash	18 (19.4) 22	21 (22.6) 24
Metabolism and nutrition disorders	30 (32.3) 40	33 (35.5) 55
Hypomagnesaemia	15 (16.1) 15	3 (3.2) 3
Blood and lymphatic system disorders	28 (30.1) 44	33 (35.5) 53
Anaemia	14 (15.1) 15	10 (10.8) 11
Thrombocytopenia	10 (10.8) 13	13 (14.0) 14
Vascular disorders	26 (28.0) 32	10 (10.8) 12
Hypertension	21 (22.6) 22	7 (7.5) 7
Immune system disorders	21 (22.6) 27	12 (12.9) 14
Cytokine release syndrome	18 (19.4) 20	0
Cardiac disorders	17 (18.3) 21	12 (12.9) 17
Injury, poisoning and procedural complications	14 (15.1) 15	10 (10.8) 10
Renal and urinary disorders	11 (11.8) 15	21 (22.6) 29
Nervous system disorders	8 (8.6) 14	19 (20.4) 28
Hepatobiliary disorders	7 (7.5) 7	18 (19.4) 21
Hepatomegaly	3 (3.2) 3	10 (10.8) 10
Congenital, familial and genetic disorders	2 (2.2) 2	8 (8.6) 8
Eye disorders	2 (2.2) 2	5 (5.4) 6
Endocrine disorders	1 (1.1) 2	18 (19.4) 19
Hypothyroidism	1 (1.1) 1	16 (17.2) 16
Reproductive system and breast disorders	1 (1.1) 2	0
Ear and labyrinth disorders	1 (1.1) 1	5 (5.4) 5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.1) 1	3 (3.2) 4
Musculoskeletal and connective tissue disorders	0	2 (2.2) 2
Product issues	0	1 (1.1) 1

Source: Tables 14.3.1.2.14 and 14.3.1.7.14

Abbreviations: AE = adverse event; E = number of events; EAS = efficacy analysis set; FAS = full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the analysis set; n = number of subjects with events; PT = preferred term; SAE = serious AE; SOC = system organ class

Note: If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count for a given SOC and PT. Adverse events were coded using MedDRA version 19.1.

The most notable difference between AEs reported in the first 2 months versus those reported >2 months after implantation was the percentage of subjects with AEs related to the use of immunosuppressive therapy. A higher percentage of subjects reported hypertension ( $\leq 2$  months: 21 [22.6%] vs >2 months: 7 [7.5%]), hypomagnesemia ( $\leq 2$  months: 15 [16.1%] vs >2 months: 3 [3.2%]), and cytokine release syndrome ( $\leq 2$  months: 18 [19.4%] vs >2 months: 0 [0%]) in the first 2 months as compared to the period >2 months post-transplant. These differences were expected and can be attributed to the use of immunosuppressive medications. Both hypertension and hypomagnesemia are known side effects of CSA while CRS is a known side effect of RATGAM. Of the 20 cytokine release syndrome AEs reported in 18 (19.4%) subjects, all but 1 AE occurred at the time of RATGAM administration. The single event that was not associated with RATGAM administration was reported on Day 43 post-implant and was considered related to IGIV (Subject (b) (6)).

There was also a higher incidence of infections reported in the period >2 months post-implantation. This was likely due to the wider reporting window (2 to 24 months) as compared to <2 months as well as the requirement for subjects to remain in reverse isolation while hospitalized at DUMC, which likely reduced the incidence of infection in the acute post-surgical setting.

An increased reporting of cardiac disorders within the first 2 months (n=17 [18.3%], 21 events) was observed versus the period >2 months after implantation (n=12 [12.9%], 17 events). This was primarily due to a higher frequency of sinus tachycardia within the first 2 months (n=6 [6.5%], 7 events) compared with the period >2 months (n=1 [1.1%], 1 event) after implantation. Two events of sinus tachycardia were assessed as treatment-related in 2 (2.2%) subjects. No events were assessed as serious. One event was of Grade  $\geq 3$ . In all but 2 cases (Subjects (b) (6)) which were ongoing at the time of reporting, the event had recovered/resolved. The higher frequency of cardiac events may be related to the higher frequency of hypertension during the initial 2 months when subjects were receiving CSA.

In contrast, hypothyroidism was more frequent in the period >2 months after (n=16, 17.2%) as compared to the first 2 months following implantation (n=1, 1.1%). Hypothyroidism is a known late-onset AE in subjects with atypical cDGA.

#### **8.4.3.2.2 $\leq 6$ Months versus > 6 Months after Implantation**

The 6-month timeframe was selected as thymic function generally begins to reconstitute and thus, the number of AEs was expected to decline at this time-point. There were 1216 AEs (72%) reported in the first 6 months after RVT-802 implantation (Table 42). All subjects had at least 1 AE during this period. The most notable difference between AEs reported in the first 6 months versus those reported >6 months after implantation was AEs related to the use of immunosuppressive therapy. More subjects reported AEs of hypertension ( $\leq 6$  months: n=25 [26.9%] vs >6 months: n=3 [3.2%]), hypomagnesemia ( $\leq 6$  months: n=17 [18.3%] vs >6 months: n=1 [1.1%]), and cytokine release syndrome ( $\leq 6$  months: n=18 [19.4%] vs >6 months: n=0 [0%]) in the first 6 months as compared to >6 months post-transplant. This was expected since the AEs reported for the first 6 months are also included in the frequency of AEs reported in the first 2 months after implantation.

There were other notable differences between the two time periods as a less intensive monitoring schedule and improvement in subjects' health due to immune reconstitution is expected to decrease the frequency of some AEs. Thus, AEs in the blood and lymphatic

disorders and immune system disorders SOC were much lower in the period >6 months than in the period ≤6 months after implantation. Improvement in immune function resulted in fewer AEs of thrombocytopenia, neutropenia, and anemia. Rash was reported in 27 (29.0%) subjects in the first 6 months but in only 8 (8.6%) subjects >6 months after implantation. This was expected as the frequency of T cell related rashes would decrease with the development of thymic function. Improvements in subjects' general medical condition were reflected in the reduced reporting of AEs such as pyrexia which was reported in 55 (59.1%) subjects in the first 6 months but in only 11 (11.8%) subjects in the period >6 months after implantation.

Similarly, increased serum creatinine was reported in 10 subjects (10.8%) in the first 6 months versus no subjects >6 months after implantation. The reason for this difference is unknown but may be related to the use of immunosuppressive therapies as many of these therapies are nephrotoxic. In addition, it may have been related to the decreased incidence of infection-related AEs as many antibiotics and antiviral therapies are also nephrotoxic. Other AEs associated with the use of immunosuppressive therapy such as hypomagnesemia and hypertension also decreased over time as therapy was discontinued.

**Table 42: AEs Reported ≤ 6 Months vs > 6 Months after Implantation**  
(Applicant's Table)

	Within 6 Months N = 93 n (%) E	After 6 Months N = 93 n (%) E
Number of subjects with AEs	93 (100.0) 1216	68 (73.1) 468
Number of subjects with SAEs	69 (74.2) 259	48 (51.6) 184
System Organ Class		
AE preferred term reported in ≥ 10% of subjects		
Infections and infestations	84 (90.3) 348	57 (61.3) 185
Device-related infection	38 (40.9) 80	20 (21.5) 42
Staphylococcal bacteraemia	12 (12.9) 17	2 (2.2) 2
Clostridium difficile colitis	12 (12.9) 13	3 (3.2) 3
Urinary tract infection enterococcal	11 (11.8) 16	2 (2.2) 2
Viral upper respiratory tract infection	10 (10.8) 11	7 (7.5) 7
General disorders and administration site conditions	58 (62.4) 103	13 (14.0) 17
Pyrexia	55 (59.1) 88	11 (11.8) 13
Skin and subcutaneous tissue disorders	54 (58.1) 82	17 (18.3) 27
Rash	27 (29.0) 37	8 (8.6) 9
Respiratory, thoracic and mediastinal disorders	52 (55.9) 105	22 (23.7) 34
Hypoxia	22 (23.7) 28	5 (5.4) 5
Respiratory failure	11 (11.8) 12	7 (7.5) 8
Investigations	49 (52.7) 127	14 (15.1) 21
Alanine aminotransferase increased	24 (25.8) 27	2 (2.2) 2
Aspartate aminotransferase increased	21 (22.6) 23	1 (1.1) 1
Blood creatinine increased	10 (10.8) 11	0
Gastrointestinal disorders	49 (52.7) 87	22 (23.7) 39
Diarrhoea	19 (20.4) 23	7 (7.5) 8
Vomiting	10 (10.8) 13	5 (5.4) 5
Blood and lymphatic system disorders	45 (48.4) 72	18 (19.4) 25
Anaemia	22 (23.7) 24	2 (2.2) 2
Thrombocytopenia	16 (17.2) 20	6 (6.5) 7
Neutropenia	13 (14.0) 13	3 (3.2) 3
Metabolism and nutrition disorders	45 (48.4) 67	21 (22.6) 28
Hypomagnesaemia	17 (18.3) 17	1 (1.1) 1
Vascular disorders	31 (33.3) 41	3 (3.2) 3
Hypertension	25 (26.9) 26	3 (3.2) 3
Immune system disorders	28 (30.1) 36	5 (5.4) 5
Cytokine release syndrome	13 (13.9) 20	0
Renal and urinary disorders	22 (23.7) 33	8 (8.6) 11
Cardiac disorders	21 (22.6) 30	7 (7.5) 8
Injury, poisoning and procedural complications	18 (19.4) 21	4 (4.3) 4
Hepatobiliary disorders	16 (17.2) 18	8 (8.6) 10
Nervous system disorders	13 (14.0) 24	14 (15.1) 18
Congenital, familial and genetic disorders	7 (7.5) 7	3 (3.2) 3
Eye disorders	4 (4.3) 4	3 (3.2) 4
Endocrine disorders	3 (3.2) 4	16 (17.2) 17
Hypothyroidism	3 (3.2) 3	14 (15.1) 14
Ear and labyrinth disorders	2 (2.2) 2	4 (4.3) 4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.2) 2	2 (2.2) 3
Reproductive system and breast disorders	1 (1.1) 2	0
Product issues	1 (1.1) 1	0
Musculoskeletal and connective tissue disorders	0	2 (2.2) 2

Source: Tables 14.3.1.2.15 and 14.3.1.7.15.1

Abbreviations: AE = adverse event; E = number of events; EAS = efficacy analysis set; FAS = full analysis set;

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the analysis set;

n = number of subjects with events; PT = preferred term; SAE = serious AE; SOC = system organ class

Note: If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count for a given SOC and PT. Adverse events were coded using MedDRA version 19.1.

**8.4.3.2.3 ≤ 12 Months versus > 12 Months after Implantation**

The 12-month timepoint was selected as most subjects were expected to develop thymic function within 1 year after implantation. There were 1684 AEs reported in the FAS; 1462

events (87% of AEs) were reported in the first 12 months after RVT-802 implantation (Table 43). All subjects (n=93 [100.0%]) had at least 1 AE in this time-period. AEs indicative of abnormal immune function (i.e. infections, autoimmune cytopenias, and T cell induced

**Table 43: AEs Reported ≤ 12 Months vs > 12 Months after Implantation**  
(Applicant's Table)

	Within 12 Months N = 93 n (%) E	After 12 Months N = 93 n (%) E
Number of subjects with AEs	93 (100) 1462	52 (55.9) 222
Number of subjects with SAEs	78 (83.9) 348	28 (30.1) 95
<b>System Organ Class</b>		
AE preferred term reported in ≥ 10% of subjects		
<b>Infections and infestations</b>	<b>89 (95.7) 438</b>	<b>35 (37.6) 95</b>
Device-related infection	42 (45.2) 95	12 (12.9) 27
Clostridium difficile colitis	14 (15.1) 15	1 (1.1) 1
Viral upper respiratory tract infection	14 (15.1) 15	3 (3.2) 3
Staphylococcal bacteraemia	12 (12.9) 17	2 (2.2) 2
Urinary tract infection bacterial	11 (11.8) 17	1 (1.1) 1
Urinary tract infection enterococcal	11 (11.8) 16	2 (2.2) 2
Oropharyngeal candidiasis	10 (10.8) 11	2 (2.2) 2
<b>General disorders and administration site conditions</b>	<b>59 (63.4) 112</b>	<b>6 (6.5) 8</b>
Pyrexia	56 (60.2) 94	5 (5.4) 7
<b>Skin and subcutaneous tissue disorders</b>	<b>58 (62.4) 98</b>	<b>7 (7.5) 11</b>
Rash	31 (33.3) 44	2 (2.2) 2
<b>Investigations</b>	<b>55 (59.1) 138</b>	<b>6 (6.5) 10</b>
Alanine aminotransferase increased	24 (25.8) 27	2 (2.2) 2
Aspartate aminotransferase increased	21 (22.6) 23	1 (1.1) 1
Blood creatinine increased	10 (10.8) 11	0
<b>Gastrointestinal disorders</b>	<b>54 (58.1) 108</b>	<b>13 (14.0) 18</b>
Diarhoea	23 (24.7) 28	2 (2.2) 3
Vomiting	13 (14.0) 16	2 (2.2) 2
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>53 (57.0) 121</b>	<b>13 (14.0) 18</b>
Hypoxia	24 (25.8) 30	3 (3.2) 3
Respiratory failure	14 (15.1) 18	2 (2.2) 2
<b>Blood and lymphatic system disorders</b>	<b>51 (54.8) 89</b>	<b>7 (7.5) 8</b>
Thrombocytopenia	22 (23.7) 26	1 (1.1) 1
Anaemia	22 (23.7) 24	2 (2.2) 2
Neutropenia	14 (15.1) 14	2 (2.2) 2
<b>Metabolism and nutrition disorders</b>	<b>50 (53.8) 83</b>	<b>10 (10.8) 12</b>
Hypomagnesaemia	18 (19.4) 18	0
<b>Vascular disorders</b>	<b>33 (35.5) 43</b>	<b>1 (1.1) 1</b>
Hypertension	27 (29.0) 28	1 (1.1) 1
<b>Immune system disorders</b>	<b>29 (31.2) 38</b>	<b>3 (3.2) 3</b>
Cytokine release syndrome	18 (19.4) 20	0
<b>Renal and urinary disorders</b>	<b>25 (26.9) 39</b>	<b>3 (3.2) 5</b>
<b>Nervous system disorders</b>	<b>23 (24.7) 38</b>	<b>4 (4.3) 4</b>
<b>Cardiac disorders</b>	<b>23 (24.7) 34</b>	<b>4 (4.3) 4</b>
<b>Hepatobiliary disorders</b>	<b>23 (24.7) 26</b>	<b>2 (2.2) 2</b>
<b>Injury, poisoning and procedural complications</b>	<b>21 (22.6) 25</b>	<b>0</b>
<b>Congenital, familial and genetic disorders</b>	<b>7 (7.5) 7</b>	<b>3 (3.2) 3</b>
<b>Eye disorders</b>	<b>6 (6.5) 8</b>	<b>0</b>
<hr/>		
<b>Endocrine disorders</b>	<b>5 (5.4) 6</b>	<b>14 (15.1) 15</b>
Hypothyroidism	3 (3.2) 3	14 (15.1) 14
<b>Ear and labyrinth disorders</b>	<b>4 (4.3) 4</b>	<b>2 (2.2) 2</b>
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>3 (3.2) 4</b>	<b>1 (1.1) 1</b>
<b>Reproductive system and breast disorders</b>	<b>1 (1.1) 2</b>	<b>0</b>
<b>Product issues</b>	<b>1 (1.1) 1</b>	<b>0</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>0</b>	<b>2 (2.2) 2</b>

Source: Tables 14.3.1.2.16

Abbreviations: AE = adverse event; E = number of events; EAS = efficacy analysis set; FAS = full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the analysis set; n = number of subjects with events; PT = preferred term; SAE = serious AE; SOC = system organ class

Note: If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count for a given SOC and PT. Adverse events were coded using MedDRA version 19.1.

rashes) was markedly reduced in the period >12 months as compared to <12 months after implantation. In addition, decreased reporting of hypertension, cytokine release syndrome

and hypomagnesemia were due to the reduced use of immunosuppressive medications in the period >12 months after implantation.

The number of subjects who reported new AEs in the infections and infestations SOC decreased from 89 (95.7%) in the first 12 months to 35 (37.6%) in the period >12 months after implantation with a corresponding decrease in the number of AEs from 438 to 95, respectively. This was expected with improvement in thymic function.

Other AEs including cytopenias (reported in the blood and lymphatic system SOC) decreased over time. As expected, the reporting of AEs associated with the use of immunosuppressive medications was minimal in the period >12 months after implantation. AEs of cytokine release syndrome (<12 months: 18 [19.4%] vs >12 months: 0 [0%]) and hypomagnesemia (<12 months: 18 [19.4%] vs >12 months: 0 [0%]) and were not reported after the first year following implantation. All but one event of hypertension (<12 months: 27 [29.0%] vs >12 months: 1 [1.1%]), were reported in the initial 12 months following implantation.

There were relatively few AEs reported in the period >12 months after implantation. The only AEs reported by  $\geq 10\%$  of subjects after 12 months were device-related infection which was reported in 12 (12.9%) subjects and hypothyroidism in 14 (15.1%) subjects. The incidence of hypothyroidism is consistent with data in partial DGA patients where ~20% of adults with partial DGA developed hypothyroidism later in life and was likely reflective of the disease under study.

The only AEs other than hypothyroidism reported to occur in at least 2 subjects and reported more frequently in the period >12 months versus the first 12 months after implantation were ascites (n=2 [2.2%]) and skin exfoliation (2 [2.2%]).

- Ascites: Subject (b) (6) developed Grade 3 ascites on Days 398 to 418 while Subject (b) (6) had Grade 1 ascites on Days 461 to 468. In both cases, the event was not serious, unrelated to study treatment and the subject recovered.
- Skin: Subject (b) (6) had Grade 2 skin exfoliation (verbatim term: red desquamation) on Days 483 to 644 while Subject (b) (6) developed Grade 1 skin exfoliation (verbatim term: skin peeling sides and bottom of feet) on Days 449 to 531. In both cases, the event was not serious, unrelated to study treatment and the subject recovered.

These events do not appear to represent a long-term safety concern of RVT-802. All other AEs that were reported in the period >12 months but not in the first 12 months after implantation were reported in 1 (1.1%) subject each and were not clinically relevant.

These data are consistent with the expectation that, prior to the development of thymic function, the AE profile in study subjects is primarily driven by subjects underlying condition and the interventions required for treatment of these complex and seriously ill subjects.

#### **8.4.4 Treatment Related Adverse Events**

Treatment-related adverse events (TEAE) were considered by the Investigator as any AE related to the RVT-802 implantation procedure or biopsy, RVT-802 itself, protocol required immunosuppression, or supportive care associated with these. There were 223 TEAEs reported within the first 2-year post-implant; the majority was related to the use of protocol prescribed immunosuppression. Autoimmune disorders including autoimmune cytopenias were the most frequent TEAEs that were considered related to RVT-802.

TEAEs reported in the first 2 years after implantation were most frequent in the immune system disorders, blood and lymphatic system disorders, metabolism and nutrition disorders and skin and subcutaneous disorders SOCs (Table 44). TEAEs were also common ( $\geq 10\%$  of subjects) in the vascular disorders, investigations and respiratory, thoracic and mediastinal disorders SOCs. Although AEs in the infections and infestations SOC were common, events in this SOC were assessed as related to treatment in only 7 (7.5%) subjects.

**Table 44: TEAEs within 2 Years of Implantation ( $\geq 5\%$  of Subjects in FAS)**  
(Applicant's Table)

System Organ Class Preferred Term	EAS N = 85		FAS N = 93	
	n (%)	E	n (%)	E
<b>Number of subjects with treatment-related AEs<sup>a</sup></b>	<b>62 (72.9)</b>	<b>180</b>	<b>70 (75.3)</b>	<b>223</b>
<b>Immune system disorders</b>	<b>18 (21.2)</b>	<b>20</b>	<b>23 (24.7)</b>	<b>26</b>
Cytokine release syndrome	18 (21.2)	19	18 (19.4)	19
<b>Blood and lymphatic system disorders</b>	<b>17 (20.0)</b>	<b>24</b>	<b>21 (22.6)</b>	<b>34</b>
Thrombocytopenia	9 (10.6)	12	10 (10.8)	13
Neutropenia	5 (5.9)	5	8 (8.6)	8
<b>Metabolism and nutrition disorders</b>	<b>17 (20.0)</b>	<b>24</b>	<b>20 (21.5)</b>	<b>30</b>
Hypomagnesaemia	14 (16.5)	14	16 (17.2)	16
<b>Skin and subcutaneous tissue disorders</b>	<b>17 (20.0)</b>	<b>19</b>	<b>20 (21.5)</b>	<b>22</b>
Rash	9 (10.6)	9	10 (10.8)	10
<b>Vascular disorders</b>	<b>16 (18.8)</b>	<b>19</b>	<b>19 (20.4)</b>	<b>22</b>
Hypertension	15 (17.6)	16	18 (19.4)	19
<b>Investigations</b>	<b>13 (15.3)</b>	<b>19</b>	<b>15 (16.1)</b>	<b>22</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>11 (12.9)</b>	<b>11</b>	<b>11 (11.8)</b>	<b>11</b>
Hypoxia	5 (5.9)	5	5 (5.4)	5
<b>Renal and urinary disorders</b>	<b>8 (9.4)</b>	<b>12</b>	<b>9 (9.7)</b>	<b>13</b>
Proteinuria	6 (7.1)	6	6 (6.5)	6
<b>General disorders and administration site conditions</b>	<b>5 (5.9)</b>	<b>5</b>	<b>7 (7.5)</b>	<b>8</b>
Pyrexia	4 (4.7)	4	6 (6.5)	7
<b>Infections and infestations</b>	<b>6 (7.1)</b>	<b>6</b>	<b>7 (7.5)</b>	<b>7</b>
<b>Gastrointestinal disorders</b>	<b>3 (3.5)</b>	<b>5</b>	<b>6 (6.5)</b>	<b>8</b>
<b>Injury, poisoning and procedural complications</b>	<b>5 (5.9)</b>	<b>5</b>	<b>6 (6.5)</b>	<b>6</b>
<b>Nervous system disorders</b>	<b>4 (4.7)</b>	<b>4</b>	<b>5 (5.4)</b>	<b>5</b>

Source: Table 14.3.1.8

Abbreviations: AE = adverse event; E = number of events; EAS = efficacy analysis set; FAS = full analysis set; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects included in the analysis set; n = number of subjects with events; PT = preferred term; SOC = system organ class

Note: If a subject had multiple occurrences of an AE, the subject was presented only once in the subject count for a given SOC and PT. Adverse events were coded using MedDRA version 19.1.

a The Investigator considered any AE related to the RVT-802 implantation procedure or biopsy, implantation of RVT-802, protocol required immunosuppression, or supportive care associated with these procedures to be related to study treatment.

The most frequent TEAEs following RVT-802 implantation were related to immuno-suppressive therapy and included cytokine release syndrome (n=18, 19.4%), hypertension (n=18, 19.4%) and hypomagnesemia (n=16, 17.2%). Cytokine release syndrome is a known AE associated with the use of RATGAM which was widely used in these studies while hypertension and hypomagnesemia are known to be associated with the use of calcineurin inhibitors. Treatment-related thrombocytopenia, neutropenia, and anemia were reported in 10

(10.8%), 8 (8.6%) and 2 (2.2%) subjects, respectively. These were expected events prior to the development of thymic function.

Other TEAEs reported in >5% of subjects included rashes (10.8%), proteinuria (6.5%), pyrexia (6.5%) and hypoxia (5.4%). Rashes were generally considered related to RATGAM or an atypical cDGA phenotype. Hypoxia was considered treatment-related in 5 subjects. Two of these events occurred with the initial dose of RATGAM (Subjects (b) (6)). The etiology of the other 3 TEAEs of hypoxia was unknown. Six events of proteinuria were considered related to study treatment. All occurred >140 days post-implantation and were considered possibly related to study treatment as they may have been autoimmune in nature (i.e. autoimmune nephrotic syndrome) or related to the use of calcineurin inhibitor therapy. Four of these 6 TEAEs resolved. Seven events of pyrexia were considered treatment-related including 5 events which occurred within a day of RVT-802 implantation and were likely related to surgery (i.e. post-operative fever) or RATGAM administration. One event of pyrexia was reported 5 days prior to implantation and was considered related to RATGAM. A single event of treatment related pyrexia was reported more than 1 day after implantation. Subject (b) (6) also reported pyrexia 112 days post-implantation following RVT-802 biopsy and Nissen/GT placement that was considered to be post-operative fever.

The paucity of procedure-related AEs was notable. Subjects (b) (6) (Grade 1, onset Day 9), (b) (6) (Grade 1, onset Day 35), (b) (6) (Grade 2, onset Day 14) and (b) (6) (Grade 2, onset Day 197) reported wound dehiscence (n=4, 4.3%). None of these TEAEs were assessed as serious. In Subjects (b) (6), the AEs responded to treatment and resolved. However, wound healing in Subject (b) (6) was poor and was likely due to the administration of steroids. The events in Subjects (b) (6) were ongoing at the last follow-up.

Wound infections such as staphylococcal, stitch abscess and graft hemorrhage were reported in 1 (1.1%) subject each. A Grade 2 methicillin resistant *Staphylococcus aureus* (MRSA) wound infection was reported in Subject (b) (6) (onset Day 6). The event resolved on Day 43. A Grade 1 stitch abscess was reported in Subject (b) (6) (onset Day 13). This involved slight redness at the base of the left thigh incision with slight separation of the incision. An unknown organism was reported. The subject was afebrile, and the event resolved on Day 24 following treatment. A Grade 1 graft hemorrhage was reported on the day of implantation in Subject (b) (6). The event involved bleeding at the implant site and resolved on Day 2 post-implantation. The low frequencies of these TEAEs and their low intensity indicate that the RVT-802 implantation procedure was well tolerated.

TEAEs were assessed as Grade  $\geq 3$  in 46 (49.5%) subjects and were most frequent in the blood and lymphatic system (n=18, 19.4%), immune system (n=10, 10.8%) and respiratory thoracic and mediastinal disorder (n=9, 9.7%) SOCs. The only TEAEs that were assessed as Grade  $\geq 3$  in  $\geq 5\%$  of subjects were thrombocytopenia (n=8, 8.6%), neutropenia (n=8, 8.6%), cytokine release syndrome (n=5, 5.4%) and hypoxia (n=5, 5.4%). These TEAEs were typically associated with the subjects underlying disease, clinical condition and/or treatment with immunosuppressants.

## 8.5 Analysis of Safety

### 8.5.1 Safety Assessment by Dose, Dose Regimen or Duration of Therapy

The Applicant recommend dose of thymic tissue ranged from 2,000 to 20,000 mm<sup>2</sup> per recipient BSA (m<sup>2</sup>) based on their clinical experience during the development program.

While a dose  $>20,000 \text{ mm}^2/\text{m}^2$  BSA was defined as an overdose for this BLA, a maximum tolerated dose was never established during the clinical development program.

Five subjects received  $>20,000 \text{ mm}^2/\text{m}^2$  with a maximal dose of  $23,755 \text{ mm}^2/\text{m}^2$ . The latter was administered to female subject with atypical cDGA (Subject <sup>(b) (6)</sup> in Study 950) on Day 182 of life. The subject received RATGAM, CSA, and steroids. Life-threatening enteritis developed in this Subject on Day 146 post-transplant and a biopsy showed T cell, B cell, and neutrophil infiltration. The enteritis/colitis resolved after 80 days of immunosuppression. It was possible that the enteritis may have been an autoimmune phenomenon related to the relatively high dose of RVT-802. The subject also had Grade 5 SAE (lower respiratory tract fungal infection) 234 days after transplantation. The subject developed respiratory acidosis necessitating intubation but died the same day. An autopsy revealed the cause of death as respiratory failure secondary to sepsis from *Candida tropicalis* and *Candida parapsilosis* but was assessed as unrelated to study treatment.

Four other subjects (Subjects <sup>(b) (6)</sup> received doses  $>20,000 \text{ mm}^2/\text{m}^2$  (range  $20,328$  to  $21,734 \text{ mm}^2/\text{m}^2$  BSA) with no apparent T cell related AEs. All 4 subjects survived at least 2 years post-transplant. Three of the subjects <sup>(b) (6)</sup> developed  $>100$  naïve CD4 T cells which is considered sufficient to fight infection. However, Subject <sup>(b) (6)</sup> had only 83 naïve CD3 and no naïve CD4 T cells reported on 111 days post-transplant despite evidence of thymopoiesis on RVT-802 biopsy (Day 117). Subsequent flow cytometry did not detect naïve T cells within the 2-year follow-up period. However, this subject did go on to develop 67% naïve CD4 T cells after the 2-year follow-up period which is well above the threshold (5% of total T cell population were naïve in phenotype) that defines athymia. Notably, this subject was on prolonged immunosuppression including alemtuzumab and steroids for the treatment of preexisting maternal GVHD through the 2-year follow-up period and this may have impacted naïve T cell development. Thus, doses  $>20,000 \text{ mm}^2/\text{m}^2$  did not appear to impact the ability of these 4 subjects to develop thymic function and survival.

The current RVT-802 clinical data support a wide dose range of <sup>(b) (4)</sup> to  $22,000 \text{ mm}^2/\text{m}^2$  BSA. Given the limited clinical experience at the upper dose range, it is unknown if a higher dose can be tolerated.

### 8.5.2 Safety Assessment-Subgroup Analyses

Adverse event data from the pooled studies were analyzed using the following subgroups:

- RVT-802 and Disease Interaction
  - cDGA phenotype (atypical versus typical);
  - Use of immunosuppression;
  - 22q11.2 hemizyosity;
  - Cytomegalovirus (CMV) infection pre-implantation;
  - Disease etiology, gene mutation (22q11.2, CHARGE/CHD7 mutation, no known mutation/no reported mutation);
  - Renal insufficiency at screening (normal versus elevated serum creatinine);
  - Hepatic function at screening (normal versus elevated AST, ALT)
- Dose (by quartile)
- RVT-802 and Subject Demographic
  - Age at implantation ( $\leq 6$  mos,  $>6$  to  $\leq 12$  mos,  $>12$  to  $\leq 18$  mos,  $>18$  mos);
  - Gender (male, female);

- Race (white, non-white)
- Maximum naïve CD4 count achieved post-implantation (by quartile)
- Manufacture facility (b) (4) versus the (b) (4) facility)

#### 8.5.2.1 Age at implantation

The age categories analyzed were divided into  $\leq 6$  months (N=35),  $>6$  to  $\leq 12$  months (N=29),  $>12$  months to  $\leq 18$  months (N=19) and  $>18$  months (N=10). The AEs were similar in all age categories and consistent with the overall AE profile. In all age groups, the most frequent AEs were device-related infection or pyrexia. The most common AEs in each age category are summarized below:

- Age  $\leq 6$  months: 679 AEs were reported in 35 (100%) subjects. The most frequent AEs were pyrexia (n=20, 57.1%), device-related infection (n=16, 45.7%), rash (n=13, 37.1%), increased ALT (n=12, 34.3%), hypoxia (n=10, 28.6%); increased AST, anemia, and hypertension were reported in 9 (25.7%) subjects each.
- Age  $>6$  to  $\leq 12$  months: 439 AEs were reported in 29 (100.0%) subjects. The most frequent AEs were pyrexia (n=18, 62.1%), device-related infection (n=13, 44.8%), rash (n=11, 37.9%), hypoxia (n=10, 34.5%), hypertension (n=10, 34.5%), and hypomagnesemia (n=8, 27.6%).
- Age  $>12$  months to  $\leq 18$  months: 400 AEs were reported in 19 (100%) subjects. The most frequent AEs were device-related infection (n=15, 78.9%), pyrexia (n=12, 63.2%), diarrhea (n=9, 47.4%), thrombocytopenia (n=8, 42.1%); anemia, increased AST and rash were reported in 6 (31.6%) subjects each.
- Age  $>18$  months: 166 AEs were reported in 10 [100%] subjects. The most frequent were pyrexia (n=6, 60.0%), neutropenia (n=4, 40.0%) and hypertension (n=4, 40.0%).

There was no apparent effect of the subjects age at implantation on the pattern of AEs reported within 2 years of RVT-802 implantation. This was also true for AEs reported at any time after implantation. Similarly, the pattern of SAEs reported was similar in all age groups and consistent with the profile in the overall population. There was no effect of the subjects' age at implant on the pattern of SAEs reported after RVT-802 implantation.

#### 8.5.2.2 Gender

There were 56 male and 37 female subjects in the FAS. The AEs were similar in male and female subjects and were consistent with the overall AE profile. The most frequent AEs were pyrexia (male: n=35 [62.5%] vs female: n=21 [56.8%]), device-related infection (male: n=31 [55.4%] vs female: n=16 [43.2%]), and rash (male: n=18 [32.1%] vs female: n=13 [35.1%]). There were no clinically relevant differences between males and females with respect to the nature of AEs reported within 2 years or at any time post-transplantation.

SAEs within 2 years of implantation were reported in 48 (85.7%) male and 31 (83.8%) female subjects. In general, the number and types of SAEs reported were similar regardless of gender. The most frequent SAEs were device-related infection (males: n=26 [46.4%] vs females: n=15 [40.5%]), hypoxia (males: n=9 [16.1%] vs females: n=4 [10.8%]), and pyrexia (males: n=7 [12.5%] vs females: n=10 [27.0%]). The number of subjects who reported SAEs in the respiratory, thoracic and mediastinal disorders SOC appeared to be higher in males than in females (males: n=27 [48.2%] vs females: n=10 [27.0%]). This was largely due to differences in the frequency of respiratory failure which was reported in 13 (23.2%) males and in only 3 (8.1%) females. Acute respiratory failure was also reported in 2 (3.6%) males and in no females. This may have been related to a higher number of male subjects entering

the study with pre-existing conditions of the respiratory, thoracic, and mediastinal SOC, including hypoxia and a ventilator requirement. These differences are not considered to be clinically relevant. There were no other clinically relevant differences in the SAE frequencies between the two genders.

#### **8.5.2.3 Race**

There were 67 white subjects and 26 non-white subjects. AEs were similar in white and non-white subjects and were consistent with the overall AE profile. In white subjects, the most common AEs were pyrexia (n=41, 61.2%), device-related infection (n=34, 50.7%), and rash (n=26, 38.8%). In non-white subjects, the most common AEs were pyrexia (n=15, 57.7%), device-related infection (n=13, 50.0%), diarrhea (n=8, 30.8%), thrombocytopenia (n=9, 34.6%) and rash (n=5, 19.2%). There were no clinically relevant differences between white and non-white subjects with respect to the nature of AEs reported within 2 years of implantation or at any time after 2 years.

SAEs were reported in 57 (85.1%) white subjects and 22 (84.6%) non-white subjects. The SAE profile was similar in white and non-white subjects and consistent with the SAE profile in the overall population. There was no apparent effect of the subjects' race on the pattern of SAEs reported within 2 years of RVT-802 implantation. This was also true when SAEs reported at any time after implantation were summarized with respect to the subjects' race.

#### **8.5.2.3 cDGA Phenotype**

There were 41 subjects with atypical cDGA and 45 subjects with typical cDGA. The pattern of AEs reported were similar in subjects with atypical and typical cDGA and was consistent with the overall AE profile. In both atypical and typical cDGA, the most common AEs were device-related infection (atypical: n=25 [61.0%] vs typical: n=18 [40.0%]), pyrexia (atypical: n=25 [61.0%] vs typical: n=26 [57.8%]), and rash (atypical: n=14 [34.1%] vs typical: n=17 [37.8%]). The 2 groups differed with respect to the frequencies of AEs that are known to be associated with use of immunosuppressives (hypertension, hypomagnesemia and cytokine release syndrome). These therapies were administered per protocol to subjects with atypical cDGA but were not required in most subjects with typical cDGA. Importantly, symptomatic subjects with atypical cDGA required these agents not only to prevent the rejection of RVT-802, but also to treat the complications associated with the atypical cDGA. Consequently, hypertension (atypical: n=17 [41.5%] vs typical: n=9 [20.0%]), cytokine release syndrome (atypical: n=12 (29.3%) vs typical: n= 4 (8.9%)), and hypomagnesemia (atypical: n=9 [22.0%] vs typical: n=5 [11.1%]) were all reported at higher frequencies in subjects with atypical cDGA. An AE of pancreatitis was more frequent in subjects with atypical cDGA (n=4 [9.8%]) than in subjects with typical cDGA (n=1 [2.2%]). However, as per the discussion of SAEs of pancreatitis below, this difference most likely relates to the per protocol use of CSA in subjects with atypical cDGA.

There were 72 subjects with SAEs within the first 2 years of implantation; 37 of 41 subjects with atypical cDGA (90.2%) and 35 of 45 subjects with typical cDGA (77.8%). Although more subjects with atypical (n=34 [82.9%]) than typical cDGA (n=29 [64.4%]) reported SAEs in the infections and infestations SOC, the profile of events in the 2 groups were similar. In both groups, the most frequent SAEs were device-related infection (atypical: n=23 [56.1%] vs typical: n=14 [31.1%]) and pneumonia (atypical: n=3 [7.3%] vs typical: n=5 [11.1%]). The only other notable difference between the 2 groups were the frequencies of

pancreatitis (atypical: n=3 [7.3%] vs typical: n=0 [0%]), seizure (atypical: n=0 [0%] vs typical: n=3 [6.7%]), and hypothyroidism (atypical: n=0 [0%] vs typical: n=2 [4.4%]).

Pancreatitis was reported as a SAE in 3 subjects with atypical cDGA (Subjects (b) (6)). A medical history of gastrointestinal disorders was reported in all 3 subjects that included gastroesophageal reflux, diarrhea and vomiting. The mother of Subject (b) (6) also confirmed a history of pancreatitis for that subject. Pancreatitis was possibly related to study treatment in Subjects (b) (6) (onset Day 78, Grade 2, ongoing at end of the study) and (b) (6) (Day 266 to Day 363, Grade 3, recovered/resolved) while it was unrelated in Subject (b) (6) (onset Day 64, Grade 4, ongoing at end of the study). This AE may have been related to the use of CSA as acute pancreatitis has been reported with CSA. All 3 subjects who developed pancreatitis were receiving CSA at the time of the AE. Since the majority of typical cDGA subjects did not receive CSA, this difference in AE reporting was expected.

Seizure was reported in Subjects (b) (6) with typical cDGA along with a history of hypocalcemia. Hypoparathyroidism and hypocalcemic seizures were also reported in the latter 2 subjects (subjects (b) (6)). The SAEs were assessed as unrelated to treatment in all 3 subjects. Seizure was not considered related to the cDGA phenotype given the presence of hypocalcemia associated with hypoparathyroidism in cDGA.

Hypothyroidism was reported in Subjects (b) (6) with typical cDGA. Neither subject had a medical history of hypothyroidism. The events were assessed as probably related to treatment in Subject (b) (6) (onset Day 428, Grade 2, ongoing at the end of the study) and possibly related to treatment in Subject (b) (6) (onset Day 590, Grade 2, ongoing at the end of the study). However, hypothyroidism is reported in subjects with partial DGA who have not received RVT-802. In addition, given the small difference (n=2) in number of subjects reporting events of hypothyroidism between the 2 disease phenotypes, this difference was not expected to be related to the cDGA phenotype.

In general, the frequencies of AEs and SAEs were similar in subjects with atypical and typical cDGA. Any difference in reporting was likely due to the presence of comorbidities associated with the atypical phenotype of cDGA (i.e. rash) as well as the increased requirement for immunosuppression among subjects with the atypical phenotype.

#### 8.5.2.4 22q11.2 Hemizygosity

There were 37 subjects with 22q11.2 deletion and 56 subjects without 22q11.2 deletion in the FAS. The pattern of AEs reported were similar in subjects with and without 22q11.2 and was consistent with the overall AE profile. Pyrexia (with: n=20 [54.1%] vs without: n=36 [64.3%]), device-related-infection (with: n=21 [56.8%] vs without: n=26 [46.4%]) and rash (with: n=14 [37.8%] vs without: n=17 [30.4%]) were the most common AEs in the 2 groups.

There were 79 subjects with SAEs; 33 of 37 (89.2%) subjects with 22q11.2 hemizygosity and 46 of 56 (82.1%) subjects without 22q11.2 hemizygosity. The pattern of SAEs reported was similar in subjects with and without 22q11.2 hemizygosity and consistent with the SAE profile of the overall population. Renal failure was reported in 1 (2.7%) subject (Subject (b) (6)) with 22q11.2 hemizygosity and in 4 (7.1%) subjects without 22q11.2 hemizygosity (Subjects (b) (6)). Subject (b) (6) had a medical history of acute kidney injury, hydronephrosis, kidney enlargement, nephrocalcinosis, proteinuria, pyelocaliectasis, renal disorder, and renal impairment. In subjects without 22q11.2 hemizygosity, Subject (b) (6) had a history of hydronephrosis and nephrocalcinosis and Subject (b) (6) had a history of acute kidney injury.

Subjects (b) (6) had no medical history of renal impairment. It is difficult to attribute a causal relationship given the small number of subjects and the subject medical histories.

In summary, there was no effect of 22q11.2 hemizyosity on the pattern of AEs and SAEs reported after RVT-802 implantation in these subjects. This was also true when the AEs and SAEs reported at any time after implantation were analyzed with respect to the presence or absence of 22q11.2 hemizyosity

#### 8.5.2.5 Disease Etiology /Gene Mutation

There were 37 subjects with 22q11.2 deletion, 20 subjects with CHARGE/CHD7 mutation, and 33 subjects with no known/no reported mutation. The AE profile in all groups was similar and consistent with the overall AE profile.

SAEs were reported in 33 (89.2%) of 37 subjects with 22q11.2 mutation, 14 (70.0%) of 20 subjects with CHARGE/CHD7 mutation, and 29 (87.9%) of 33 subjects with no known/ reported mutation. There were no notable differences in the SAE profiles of these groups. This was also true when AEs and SAEs reported at any time after implantation were summarized with respect to subjects' disease etiology/gene mutation.

**Reviewer's comments:** The Applicant is requesting a broad indication for "immune reconstitution of patients with congenital athymia." However, the ISS in this BLA is concentrated on the use of RVT-802 in DGA. There were two subjects (Subjects (b) (6) in the original BLA submission (Dec 2018) who had congenital athymia due to FOXP1 deficiency. Subsequently, a third subject (Subject (b) (6) with FOXP1 deficiency was treated under the 51692 expanded access protocol after a prior cord blood transplantation. Narratives are provided for these 3 subjects since their safety data could not be integrated due to the limited number of subjects.

- **Subject (b) (6)** was a male with FOXP1 deficiency (nude phenotype) who was enrolled as a protocol exception in Protocol 668-2 and received RVT-802 (10,742 mm<sup>2</sup>/m<sup>2</sup>) on Day 266 of life. He was not immunosuppressed due to the very low numbers of T cells at screening (0.74 CD3 cells/mm<sup>3</sup> and 0.63 CD4 cells/mm<sup>3</sup> on Day -9). A biopsy on Day 53 after RVT-802 implantation showed evidence of thymopoiesis. Total T cell counts began to increase around 164 days following implantation with a maximum reported naïve CD4 count of 212 cells/mm<sup>3</sup> 360 days following implantation and a normal response to the mitogen PHA (180,053 cpm).

This subject had 3 SAEs of *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Escherichia coli* infection of his central venous catheter 119 days after implantation, which resolved 6 days later and were considered unrelated to study treatment. This subject also had a non-serious AE of post-operative fever which was related to study treatment; all cultures were negative. This event resolved 3 days later. This subject is alive 12.2 years following implantation with RVT-802.

- **Subject (b) (6)** was a female with FOXP1 deficiency (nude phenotype) who was enrolled as a protocol exception in Protocol 884 and received RVT-802 (12,675 mm<sup>2</sup>/m<sup>2</sup>) on Day 424 of life. The subject's parents were 5th degree cousins. She had oligoclonal T cells prior to implantation (1011 CD3 cells/mm<sup>3</sup> and 473 CD4 cells/mm<sup>3</sup> on Day -6), but very low naïve T cell counts (1 naïve CD4 cell/mm<sup>3</sup>). Given the presence of oligoclonal T cells and an increased T-cell proliferative response (104,246 cpm on Day -6) to PHA the subject was immunosuppressed with CSA (from 7 days prior to 124 days after implant),

daclizumab (on the day of implantation), methylprednisolone (from 6 days prior to the day of implantation, from 4 days to 25 days after implantation, from 80 days to 114 days after implantation, and from 117 days to 123 days after implantation), prednisolone (from 26 days to 79 days after implantation, from 114 days to 116 days after implantation, and on day 120 and day 124 day after implantation), and RATGAM (3 doses from 5 days to 3 days prior to implantation). Thymopoiesis was detected in RVT-802 biopsied on Day 99. Naïve T cells began increasing at ~1 year with 4% naïve CD4 cells reported on Day 348; 35% naïve CD4 cells on Day 726. A naïve CD4 count of 213 cells/mm<sup>3</sup> was reported 4.9 years following implantation. The subject also developed a normal response to PHA of 263,656 CPM on Day 726 post-implantation.

There were 2 SAEs of device-related infection 157 days after implantation. The SAEs included a blood culture positive for *Klebsiella oxytoca* and *Enterococcus faecalis*, which were related to the subject's central line and not to study treatment. The subject was treated with antibiotics and was afebrile within 24 hours. The SAE resolved On Day 179 after implantation. The subject also had a Grade 3 varicella zoster infection acquired at home 231 days after implantation (serious due to caused/prolonged hospitalization) which resolved by Day 252 following implantation. The varicella zoster infection was considered by Investigator to be unrelated to study treatment. The subject remains alive 12.3 years following implantation with RVT-802.

- **Subject** <sup>(b) (6)</sup> was a female with heterozygous FOXN1 deficiency (c.1418 del C, p. Pro473fs) who was treated under Protocol 51692 because she had received a prior cord blood transplantation. The latter was complicated by renal and pulmonary failure and cardiomyopathy. The subject had 42 CD3 cells/mm<sup>3</sup> and 28 CD4 cells/mm<sup>3</sup> 7 days prior to implantation with absolute naïve CD3 and naïve CD4 counts of 3 and 1 cells/mm<sup>3</sup>, respectively. This subject received RVT-802 (total dose of 9,260 mm<sup>2</sup>/m<sup>2</sup>) on Day 1158 of life. Given her prior CBT, the subject was immunosuppressed with a calcineurin inhibitor (from 6 days prior to 241 days after implantation), methylprednisolone (from day 5 to day 1 prior to implantation), and RATGAM (3 doses from day 5 to day 2 prior to implantation). A biopsy of the RVT-802 implant on Day 69 showed evidence of thymopoiesis. Naïve T cell counts began increasing around 6 months after implantation with 59 naïve CD3 cells/mm<sup>3</sup> and 18 naïve CD4 cell/mm<sup>3</sup> reported on Day 187. Absolute naïve T cell counts continued to increase over time with 219 naïve CD3 cells/mm<sup>3</sup> and 188 naïve CD4 cell/mm<sup>3</sup> reported on Day 406. The subject also developed a normal response to PHA (144,193 cpm) on day 343 post implantation. No SAEs or AEs considered by the Investigator to be related to RVT-802 were reported. The subject remains alive 406 days following RVT-802 implantation.

#### 8.5.2.6 *Positive Cytomegalovirus Status Pre-Implantation*

There were 4 subjects with CMV infections and 82 subjects without CMV infection prior to RVT-802 implantation in the FAS (n=93); the CMV infection status was missing for 7 subjects. The 4 subjects with CMV infections were:

- Subject <sup>(b) (6)</sup>: history of cardiac arrest, disseminated intravascular coagulation, respiratory arrest who died of respiratory failure on Day 45.
- Subject <sup>(b) (6)</sup>: history of respiratory failure, ventilator dependent, GVHD who died of hypoxia on Day 82; received cyclosporine, methylprednisolone, cyclophosphamide, prednisolone and RATGAM;

- Subject (b) (6): died due to CMV infection on Day 103; received cyclosporine, MMF, methylprednisolone, prednisolone, RATGAM, and tacrolimus.
- Subject (b) (6): this subject survived but was considered a false positive as there was a single positive CMV urine culture on Day -85 with all other urine cultures and PCRs negative for CMV; received methylprednisolone, cyclosporine and RATGAM.

There were no naïve CD4 or CD8 cells detected in Subjects (b) (6) post-implant.

Subject (b) (6) developed negligible numbers of naïve CD4 cells post-implant (maximum value 3 cells/mm<sup>3</sup> on Day 48 after implantation). These 3 subjects all died before thymic function reconstituted. In contrast, Subject (b) (6) had 858 naïve CD4/mm<sup>3</sup> and 275 naïve CD8/mm<sup>3</sup> on Day 732 after implantation and the subject was alive at 4577 days.

There was an increased risk of death among subjects positive for CMV relative to subjects without CMV prior to transplantation. In the EAS, 3 of 4 subjects (75%) with CMV prior to transplantation died, as compared with 18 of 74 subjects (24%) without CMV infection. The hazard ratio was 7.3 with a 95% CI of [2.21, 24.14] and a p-value = 0.0011. The single surviving subject with pre-existing CMV was considered to have had a false positive test for CMV prior to treatment as all subsequent tests were negative. A similar risk of death was observed in the EAS-cDGA and FAS. However, it should be noted that subjects with CMV infection entered the study with significant morbidities.

The large difference in the number of subjects with and without CMV infections did not permit a meaningful comparison of the reporting frequencies of AEs in the 2 groups. Nonetheless, the profile of AEs reported in the subjects with CMV infection was generally consistent with that in the overall population. Seventy AEs were reported in these subjects. The most common AE was hypoxia (3 [75.0%]). Urinary tract infection enterococcal, device-related infection, enterococcal bacteremia, staphylococcal bacteremia, creatinine increased, occult blood positive, hypertension, hypotension and cytokine release syndrome were reported in 2 (50.0%) subjects each. All other events were reported in only one subject each.

There were 13 SAEs reported in the 4 subjects who were positive for CMV infection prior to RVT-802 implantation. However, only hypoxia (n=2 [50.0%]) and hypotension (n=2 [50.0%]) were reported in more than 1 subject. In subjects without CMV infection, the most frequent SAEs were device-related infection (n=38 [46.3%]), pyrexia (n=17 [20.7%]), and respiratory failure (n=13 [15.9%]). The SAE profile was similar to that of the overall FAS. This was also true when AEs reported at any time after implantation were analyzed with respect to the presence or absence of CMV infection.

There were two subjects who developed CMV infections following RVT-802; Subjects (b) (6) had CMV infections 195 and 158 days post-RVT-802 implantation, respectively. Both subjects recovered from these infections and remain alive 1534 (Subject (b) (6) (Subject (b) (6)) days post-implant. These data support the ability of RVT-802 to fight infection and enable survival.

In conclusion, subjects with pre-existing CMV infections died from their CMV infection prior to the development of thymic function. Immunosuppressive therapy used in 2 of 3 subjects with confirmed CMV may have contributed to the progression of their CMV infection. In the most recent study protocol (Study 25966), subjects requiring immunosuppression were excluded from study participation if they had a preexisting CMV infection

documented by >500 copies/mL in blood by 2 consecutive PCR assays or by 2 positive urine cultures.

#### **8.5.2.7 Use of Immunosuppressive Therapy**

There were 61 subjects who received immunosuppressive therapy and 32 subjects who did not in the FAS. A total of 1143 AEs were reported in the 61 (100%) subjects who received immunosuppression and 541 AEs were reported in the 32 (100%) subjects who did not. In general, a higher percentage of subjects receiving immunosuppression reported AEs which should not be surprising given the toxicities of these therapies. The pattern of AEs reported was generally similar in the two groups and was consistent with the overall AE profile except for AEs considered related to immunosuppressive therapy. The most frequent AEs were pyrexia (with: n=39 [63.9%] vs without: n=17 [53.1%]) and device-related infection (with: n=34 [55.7%] vs without: n=13 [40.6%]). Rash was more frequent in subjects on immunosuppression (n=23 [37.7%]) than in those without (n=8 [25.0%]); this was expected as immunosuppressive therapies were used to control rashes associated with T cells in subjects with atypical cDGA.

There were differences between the 2 groups in the frequency of AEs (cytokine release syndrome, hypertension, and hypomagnesemia) relating to the use of immunosuppressives. Notably, CRS was not reported in subjects who did not receive immunosuppression but was reported in 18 (29.5%) subjects receiving it. This is consistent with the known relationship of CRS to RATGAM, which was widely used during the studies. Hypertension was reported in 24 (39.3%) subjects receiving immunosuppressives and in 4 [12.5%]) subjects who did not. Similarly, hypomagnesemia was reported in 17 (27.9%) subjects receiving and in 1 [3.1%]) subjects who was not receiving immunosuppression. These AEs were expected as they are well known effects of calcineurin inhibitors.

GVHD (3 [4.9%]), GVHD of the gastrointestinal tract (1 [1.6%]), GVHD in skin (1 [1.6%]), and systemic immune activation (1 [1.6%]) were reported in subjects on immunosuppression but not in subjects who were not. This was expected as GVHD required treatment with immunosuppressive therapy. All were assessed as serious.

Renal failure was reported in 6 (9.8%) subjects receiving immunosuppressives and in only 1 (3.1%) subject who was not. This was an expected difference since renal toxicity is a known side effect of calcineurin inhibitors.

There were 79 subjects who developed SAEs; 52 (n=61, 85.2%) subjects receiving immunosuppressives and in 27 (n=32, 84.4%) subjects who did not. The pattern of SAEs reported was similar in both groups and consistent with the profile of the overall population. SAEs were most common in the infections and infestations SOC. In both groups, the most frequent SAE was device-related infection (with: n=29 [47.5%] vs without: n=12 [37.5%]). SAEs were also frequent in the respiratory, thoracic and mediastinal disorders SOC and general disorders and administration site conditions. In these SOCs, respiratory failure (with: n=10 [16.4%] vs without: n=6 [18.8%]), hypoxia (with: n=10 [16.4%] vs without: n=3 [9.4%]), and pyrexia (with: n=12 [19.7%] vs without: n=5 [15.6%]) were frequent SAEs in both groups. Differences in the AE profile of subjects receiving immunosuppressives versus those who did not were also seen in the SAE profile. In the immune system disorders SOC, cytokine release syndrome (n=4 [6.6%]), GVHD (n=3 [4.9%]), GVHD of gastrointestinal tract (n=1 [1.6%]), GVHD in skin (n=1 [1.6%]), and immune system activation (n=1 [1.6%])

were reported in subjects on immunosuppressives and not in subjects who did not. Hypersensitivity was more frequent in subjects not receiving immunosuppressives (n=3 [9.4%]) than in subjects who did (n=1 [1.6%]). Renal failure was reported in 4 (6.6%) subjects receiving immunosuppressives and in only 1 (3.1%) subject who did not.

In summary, a higher percentage of subjects receiving immunosuppressives had AEs and SAEs as compared to those who were not receiving such therapy. These included AEs and SAEs known to be related to the use of immunosuppressive therapy such as hypertension, hypomagnesaemia, cytokine release syndrome, pancreatitis, etc. This was expected as these therapies are associated with a relatively high rate of AEs. Except for AEs and SAEs commonly associated with the use of immunosuppressive therapy, there was no other apparent effect on the use of these medications on the pattern of AEs and SAEs reported within or after 2 years of RVT-802 implantation.

#### **8.5.2.8 Renal Insufficiency at Screening**

Renal and urinary disorder are common in this patient population as deletion at the 22q11.2 locus is reported to play a role in the development of renal anomalies in subjects with partial DGA. Thirty-seven subjects (39.8%) entered RVT-802 clinical studies with a medical history in this SOC. These included pylelocaliectasis (16.1%), hydronephrosis (12.9%), nephrocalcinosis (10.8%), acute kidney injury (6.5%), and renal failure (5.4%). Medical histories of renal anomalies were common including renal aplasia (9.7%), renal dysplasia (2.2%), and renal hypoplasia (2.2%). Interestingly, despite the relatively high incidence of renal anomalies, only 9 subjects had an elevated serum creatinine value at baseline and only 1 subject's serum creatinine remain elevated after implantation. In addition, the reported serum creatinine values were only slightly out of range for most of these subjects.

There were 83 subjects with normal serum creatinine and 9 subjects with elevated values; no creatinine values were available for 1 subject. The pattern of AEs was similar in subjects with and without normal renal function and was consistent with the overall AE profile. In both groups, the most frequent AEs were pyrexia (normal creatinine: n=49 [59.0%] vs elevated creatinine: n=6 [66.7%]), device-related infection (normal creatinine: n=41 [49.4%] vs elevated creatinine: n=5 [55.6%]), and rash (normal creatinine: n=28 [33.7%] vs elevated creatinine: n=3 [33.3%]). The percentage of AEs reported in the renal disorders SOC was greater in subjects with elevated creatinine (n=4 [44.4%]) versus subjects with normal creatinine (n=22 [26.5%]), but the limited number of events prevents a definitive conclusion.

SAEs were reported in 69 (n=83, 83.1%) subjects with normal serum creatinine and in 9 (n=9, 100%) subjects with elevated serum creatinine. SAEs were also reported in one subject with a missing serum creatinine value. While the small number of subjects with elevated serum creatinine limits the ability to compare the frequencies of SAEs across the subgroups, the pattern of SAEs reported was similar in both groups and consistent with the profile in the overall population. SAEs were most frequent in the infections and infestations SOC.

Renal failure was reported as a SAE in 3 (3.6%) subjects (Subjects (b) (6) ) with normal baseline creatinine and in 2 (22.2%) subjects (Subjects (b) (6) ) with an elevated baseline creatinine. A medical history of renal impairment was reported in the latter two subjects (Subjects (b) (6) ) as well as in Subject (b) (6) . Subjects (b) (6) had no history of renal impairment but were both seriously ill and hospitalized at the time of the SAE. This marked difference in the frequency of the SAE likely reflects the large disparity in

the number of subjects in the two groups. In addition, all subjects had received immunosuppressive therapy.

An increased risk of death was observed among subjects with an elevated serum creatinine prior to implantation relative to subjects with a normal serum creatinine. In the EAS, 5 of 9 subjects (56%) with an elevated serum creatinine died as compared with 18 of 75 subjects (24%) with a normal serum creatinine prior to RVT-802. The hazard ratio was 3.14 with a 95% CI of [1.18, 8.33] and a p-value of 0.0215. An increased risk of death for subjects with an elevated serum creatinine was also observed in the EAS-cDGA and FAS.

The clinical significance of this analysis is unclear as only 9 subjects had an elevated serum creatinine value, and this analysis was based on a single laboratory assessment of serum creatinine which may not have been reflective of the subjects' overall renal function. The increase in creatinine persisted in only 1 of the 9 subjects (Subject <sup>(b) (6)</sup>) post-transplant. Furthermore, the reported serum creatinine values were only slightly out of range for most of these subjects. Nonetheless, impaired renal function is not expected to impact RVT-802, as RVT-802 is a human tissue product and is not renally cleared.

#### **8.5.2.9 Hepatic Insufficiency at Screening**

There were no differences in the nature and frequency of AEs or SAEs reported in subjects with normal AST at screening (n=67) when compared with subjects with elevated AST (n=26) at screening. Similarly, there were no meaningful differences in the nature and frequency of AEs or SAEs reported in subjects with normal ALT (n=57) at screening when compared with subjects with elevated ALT (n=36) at screening. This was also true for AEs or SAEs reported at any time after implantation were analyzed with respect to subjects' baseline hepatic function. This was not unexpected given that RVT-802 is a human tissue product and is not hepatically metabolized. Furthermore, hepatic dysfunction is not anticipated to impact RVT-802 survival or immune reconstitution.

#### **8.5.2.10 Maximal Naïve CD4 Count Achieved Post-Implantation (by Quartile)**

The maximal naïve CD4 count that was achieved following RVT-802 transplantation was divided into the following quartiles (Q) for this analysis:

- Q1 = 0.0 to 16.0 naïve CD4 cells/mm<sup>3</sup>;
- Q2 = >16.0 to 232.0 naïve CD4 cells/mm<sup>3</sup>;
- Q3 = >232.0 to 393.0 naïve CD4 cells/mm<sup>3</sup>;
- Q4 = >393.0 to 1836.1 naïve CD4 cells/mm<sup>3</sup>.

There was a trend towards a decrease in AEs of the blood and lymphatic system disorders SOC with increasing naïve CD4 count. Thrombocytopenia and neutropenia decreased in frequency with increasing CD4 cell count. Thrombocytopenia decreased from 10 subjects (47.6%) in Q1 to 3 (15.0%) in Q4. Neutropenia decreased from 8 (38.1%) in Q1 to 0 (0.0%) in Q4. This result is consistent with an increase in immune function after RVT-802 implantation, as expressed by an increase in naïve CD4 cell count.

Similarly, there was a trend towards a decrease in SAE reporting with an increase in maximal naïve CD4 cell count. This was most apparent in the infections and infestations and the respiratory and mediastinal disorders SOCs and particularly with respect to device-related infection, lower respiratory tract infection bacterial, hypoxia, and respiratory failure. However, these observations should be viewed with caution given the small number of subjects in each group and the absence of further information relating to the time of reporting

of the SAEs, particularly since the frequency of events decreased over time after implantation. Nonetheless, a decrease in the frequency of events such as infections and respiratory complications is consistent with the expected improvement of immune function.

#### **8.5.2.11 Manufacturing Facility**

Six subjects (Subjects (b) (6) ) received RVT-802 manufactured at the (b) (4) manufacturing facility while 87 subjects received RVT-802 manufactured in (b) (4) . The difference in the number of subjects does not permit a meaningful comparison of the reporting frequencies of AEs or SAEs. Nonetheless, the AE profile in the two groups appeared to be consistent with that in the overall FAS population. These observations were also true when AEs or SAEs reported at any time after implantation were summarized with respect to the manufacturing site.

#### **8.5.3 Adverse Events of Special Interest**

Adverse events of special interest (AESI) defined in the study protocols included infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas.

- Infection-related AEs were of interest as the ability to respond and control infections is indicative of the development of thymic function.
- Autoimmune diseases, GVHD, and granulomas were potential AEs that may have been related to RVT-802 given its' ability to reconstitute the immune system. Granulomas were of interest as they may have been indicative of the development of sarcoidosis. If granulomas were found, assessment of angiotensin converting enzyme (ACE) and eye examinations were performed.
- Rashes were of interest as these may have been indicative of new development or flare of pre-existing rashes associated with atypical cDGA. Rashes persisting more than 2 weeks were biopsied to assess the etiology of the rash.
- Cancer: subjects were followed for the development of cancers given the risk of malignancy in subjects with poor T cell function.

##### **8.5.3.1 Infection-related Adverse Events**

Infection-related AEs were of interest as the ability to respond to and control infections are indicative of thymic reconstitution. Infection-related AEs were compared by the time of onset with a Wilcoxon signed-rank test that compared the number of infections with an onset <6 months after implantation before normal T cell function had developed versus those reported between >6 to ≤12 months post-implantation. This analysis was also conducted to compare the number of infection-related AEs with onset ≤12 months versus >12 to ≤24 months after implantation.

There were more infection-related AEs with an onset ≤6 months vs onset >6 to ≤12 following implantation (median difference = 2.0,  $p < 0.001$ ). Similarly, the Wilcoxon signed-rank test on the difference between the number of infection-related AEs with an onset ≤12 months versus >12 to ≤24 months after implantation was also statistically significant (median difference = 3.0,  $p < 0.001$ ) with fewer infection related AEs at the later timepoints. These data support the claim that the incidence of infection-related AEs decreased over time with the development of immune function.

Infection-related AEs in most subjects ( $n=72$  [77.4%]) were of Grade  $\geq 3$ , were assessed as serious in 67 (72.0%) subjects, and as related to study treatment in 7 (7.5%) subjects. The pathogens that were reported in  $\geq 10\%$  of subjects included:

- Viral upper respiratory tract infection: RSV (9 subjects), rhinovirus (7 subjects), rhinovirus/enterovirus (2 subjects), coronavirus (1 subject), human metapneumovirus (1 subject), unknown (1 subject)
- Clostridium difficile colitis: (16 subjects, 19 events)
- Staphylococcal bacteremia: (15 subjects)
- Urinary tract infection, bacterial: Enterobacter cloacae (5 subjects), Enterobacter (3 subjects), Citrobacter freundii (2 subjects), Serratia marcescens (1 subject), Enterobacter cloacae/asburiae (1 subject), Burkholderia cepacian (1 subject), Proteus mirabilis (1 subject), unknown (1 subject)
- Oropharyngeal candidiasis: (13 subjects)
- Lower respiratory tract infection, bacterial: Stenotrophomonas (5 subjects), Serratia Marcescens (2 subjects), Unknown (2 subjects), Neisseria (1 subject), Citrobacter (1 subject), Delftia acidovorans (1 subject), mixed gram negative rods (1 subject), Enterococcus Faecalis (1 subject), Enterococcus (1 subject), Proteus (1 subject), Sphingobacterium (1 subject), Acinetobacter (1 subject), Flavobacterium meningosepticum (1 subject), and Nocardia (1 subject).

There were 7 subjects (7.5%) with infection-related AEs that were assessed as related to study treatment. These included CMV infection (n=2 [2.2%]), device-related infection (n=1 [1.1%]), staphylococcal skin infection (n=1 [1.1%]), stitch abscess (n=1 [1.1%]), varicella-zoster virus infection (n=1 [1.1%]), and staphylococcal wound infection (n=1 [1.1%]). There were 3 treatment-related infectious SAEs including 2 SAEs of CMV infection and 1 SAE of device-related infection. These events are described below:

- **Subject** <sup>(b) (6)</sup>: This subject developed a Grade 5 CMV infection which was first detected 77 days prior to implantation (serious due to death) that was considered related to the use of RATGAM.
- **Subject** <sup>(b) (6)</sup>: This subject developed a Grade 5 CMV infection 38 days after implantation (serious due to life-threatening and death) with symptoms of fever and increased respiratory rate. This SAE was possibly related to RVT-802 as both the donor and recipient tested positive for CMV post-implantation although the donor had tested negative prior to thymic donation.
- **Subject** <sup>(b) (6)</sup>: This subject reported a Grade 2 device-related infection 4 days prior to RVT-802 implantation which was considered related to study treatment (serious due to other medically important event). The subject developed a coagulase negative *Staphylococcus* infection following insertion of a central line infection for RATGAM administration. This SAE was not considered related to RVT-802.

### 8.5.3.2 Autoimmune Disease

Autoimmune diseases have been commonly reported in subjects with partial DGA and were expected events in this study given the ability of RVT-802 to reconstitute the immune system. The autoimmune AESIs evaluated includes cytopenias (such as thrombocytopenia, neutropenia and anemia), hypothyroidism, alopecia, autoimmune hepatitis, and transverse myelitis.

#### 8.5.3.2.1 Autoimmune Cytopenia

The most common cytopenia involved the platelet lineage with 22 subjects (23.7%) developing thrombocytopenia. The thrombocytopenia was assessed as treatment-related in 10 (10.8%) subjects, serious in 6 (6.5%), and as serious and treatment-related in 5 (5.4%)

subjects. Most of the cases were reported in the first 12 months following RVT-802 implantation, prior to full immune reconstitution.

Neutropenia was the second most common cytopenia and was reported in 16 (17.2%) subjects and occurred  $\leq 12$  months after implantation in 14 subjects. While some events of neutropenia were associated with infection or other unrelated events, 8 subjects (8.6%) reported events of neutropenia considered related to study treatment. All 5 (5.4%) neutropenic events that were assessed as SAEs were also assessed as related to treatment. Finally, 1 subject (1.1%) developed febrile neutropenia but was considered not autoimmune in nature or related to treatment.

Autoimmune hemolytic anemia was reported as SAEs in 2 (2.2%) subjects and both events occurred  $\leq 12$  months after implantation. The 2 SAEs were of Grade  $\geq 3$  and related to treatment.

In general, autoimmune cytopenias occurred in the first-year post-implant prior to the development of a normal T cell repertoire. It is likely that the absence of T cells contributed to the development of autoimmune cytopenias since autoreactive B cells are left unchecked. One hypothesis is that the T cell repertoire had not fully developed resulting in the absence of regulatory FOXP3<sup>+</sup> CD4 T cells as well as total CD4<sup>+</sup> T cells. CD4 T cells and FOXP3<sup>+</sup> T regulatory cells do not populate the various TCRBV families equivalently in the first year. For instance, some TCRBV families have high levels of CD4 T cells but no FOXP3<sup>+</sup> T regulatory cells and vice versa. Thus, in the first year after RVT-802, there are no/insufficient regulatory T cells to control autoreactive B lymphocytes.

#### **8.5.3.2.2 Autoimmune Thyroid Disease**

Autoimmune thyroid disease manifesting as hypo- or hyperthyroidism was reported. The former was the most common presentation and developed in 17 (18.3%) subjects in the FAS. It was assessed as related to study treatment in only 2 (2.2%) subjects and none were  $\geq$  Grade 3. The first 2 subjects who developed hypothyroidism was considered as related to study treatment as these were the first two cases developing this condition post-RVT-802 implant. However, all subsequent cases of hypothyroidism were not considered treatment-related, as hypothyroidism is common in patients with partial DGA (20%) who do not receive RVT-802. In addition, 11 (11.8%) subjects had a medical history of hypothyroidism at baseline.

One subject (Subject <sup>(b) (6)</sup>) reported two events of hyperthyroidism including 1 event of hyperthyroidism and 1 event of Basedow's Disease (Graves' Disease). Both events were considered possibly related to study treatment. These events were expected as hyperthyroidism including Graves' disease has been reported following HSCT to treat other primary immunodeficiencies and following treatment with alemtuzumab. It is hypothesized that Graves' disease may be related to immunoregulatory disturbances that occurs following immune reconstitution.

#### **8.5.3.2.3 Autoimmune Hepatitis**

Autoimmune hepatitis was reported in 1 (1.1%) subject within 1 year of implantation. Subject <sup>(b) (6)</sup> developed Grade 3 SAE of autoimmune hepatitis 245 days after implantation (serious because "other medically important event"). On Day 245, the subject was diagnosed with autoimmune hemolytic anemia, which was treated with blood transfusion, steroids, and rituximab. The subject developed elevated liver enzymes approximately 2 months later. The subject was negative for the following antibodies: anti-mitochondrial, anti-LKM (liver,

kidney, microsomal), anti-smooth muscle, anti-reticulin, anti-gastric parietal cells, and anti-ribosome. The maximal value for AST was 606 U/L, and ALT was 861 U/L. The subject underwent a liver biopsy, which showed lymphocytic infiltrate consistent with autoimmune hepatitis. The subject was treated with steroids with liver enzyme levels decreasing by Day 385 after (AST was 70 U/L, and ALT was 103 U/L). The subject was in remission on Day 3156 and the SAE was considered resolved on Day 3202 after implantation.

A second case of autoimmune hepatitis was reported in Subject (b) (6), >2 years after RVT-802. This subject developed Grade 3 autoimmune hepatitis 949 days after implantation with liver enzymes (ALT and AST) up to 20 times normal values. Otherwise, the subject was clinically well. Treatment with immunosuppressives was given with liver enzymes returning into the normal range on Day 1116.

#### 8.5.3.2.4 Autoimmune Myelitis

Subject (b) (6) reported an event of transverse myelitis 283 days post-implant. While the etiology of the transverse myelitis is unknown, it was potentially autoimmune in nature. The subject also had a C77G polymorphism in the protein tyrosine phosphatase, receptor type, C (PTPRC) gene, or CD45 gene. This mutation has been reported to be associated with multiple sclerosis, autoimmunity and infectious diseases. The contribution of this gene mutation to this subject's disease process is unknown. The event of transverse myelitis was ongoing at the time of last follow-up (1992 days post-implantation).

#### 8.5.3.3 Skin Conditions

Skin rashes were an AESI, especially those persisting more than 2 weeks as they may be related to T cell infiltration of the skin. T cells are commonly found in skin biopsies of subjects with atypical cDGA and is an expected AE in these subjects. Rashes may also be related to maternal engraftment prior to the development of thymic function. Thus, subjects were closely monitored for rashes post-implant and were biopsied when possible.

Rash was reported in 31 (33.3%) subjects within the first 2 years after implantation with all 31 subjects reporting it within 12 months of treatment. Only 2 (2.2%) subjects reported rashes >12 months after implantation. The event was  $\geq$  Grade 3 in 5 (5.4%) subjects and were assessed as related to treatment in 10 (10.8%) subjects. Of the latter, 9 were considered related to RATGAM (Subjects (b) (6) inadequate immunosuppression in subjects with atypical cDGA (Subjects (b) (6)), infection (Subject (b) (6)), or of unknown etiology (Subjects (b) (6)).

There was one (1.1%) subject who developed a rash that was assessed as an SAE and treatment-related. Subject (b) (6) with atypical cDGA developed a Grade 4 rash resembling GVHD on Day 218 after RVT-802 implantation. A biopsy of the rash showed dyskeratotic cells and focal interface dermatitis, which is a rash of atypical cDGA. The subject was also diagnosed with Grade 4 hypoxia (oxygen saturation of 89%) secondary to GVHD. Oxygen was administered via nasal cannula, but the subject was subsequently intubated for respiratory failure. Steroids (15 mg/kg IV every 12 h for a total of 4 doses) and tacrolimus were also administered. The rash improved with therapy but did not resolve and was ongoing, as was hypoxia, at the time of the subject's death due to respiratory failure secondary to sepsis from *C. tropicalis* and *C. parapsilosis*, 234 days after implantation.

Skin conditions that were potentially autoimmune in nature included urticaria (see Section 8.5.3.5), alopecia, eczema, atopic dermatitis. Alopecia is an autoimmune condition which can

occur at any time after implantation and may have been related to the atypical phenotype. Alopecia was reported in 5 (5.4%) subjects and occurred  $\leq$  12 months after implantation in 3 (3.2%) subjects. The AE was assessed as treatment-related in 1 (1.1%) subject (Subject (b) (6) who also had hypothyroidism. The latter is known to be associated with hair loss. Other skin conditions that are common in young children including atopic dermatitis was reported in 2 (2.2%) subjects and eczema in 3 (3.2%) subjects. They were not related to RVT-802.

There were several other rashes, but most were rashes expected in childhood and were unrelated to study treatment.

- Subject (b) (6) had a rash associated with vancomycin (PT: drug eruption) that was unrelated to study treatment.
- Subject (b) (6) developed a macular-papular rash, assessed as  $\geq$ Grade 3 that was likely related to an adenovirus infection and not related to study treatment.
- Skin exfoliation was reported in 2 (2.2%) subjects (b) (6) (verbatim term: skin peeling sides and bottom of feet) and (b) (6) (verbatim term: red/desquamation). Neither event was  $\geq$ Grade 3, and neither were serious or related to treatment.
- Subject (b) (6) developed a pruritic diaper rash that was unrelated to study treatment.
- Subject (b) (6) developed a vesicular rash that was assessed as Grade  $\geq$  3, and unrelated to treatment.

#### 8.5.3.4 *Graft versus Host Disease*

GVHD is a potentially serious complication following the transplantation of thymic tissue into an unmatched recipient. GVHD results when an immunocompetent donor's T cells recognize the recipient as foreign and mount an immune response against the recipient's tissues. This results in significant morbidity most commonly impacting the skin, liver and gastrointestinal tract. Symptoms may include rash, nausea/vomiting, diarrhea, elevated bilirubin and liver enzymes, and can be fatal in severe cases. Subjects were also at risk for the development of maternal engraftment and associated GVHD given the significant T cell immunodeficiency present at birth. In addition to the risks of externally mediated GVHD, subjects with the atypical cDGA may develop autologous GVHD (Omenn syndrome) which is associated with oligoclonal "host" T cells that are autoreactive. This condition may have occurred prior to or just after treatment with RVT-802 and prior to the development of thymic function. For the purposes of data summarization, events of autologous GVHD were coded to Omenn syndrome. When possible, chimerism testing was performed to determine the etiology of GVHD events.

Three subjects had a history of pre-existing GVHD at enrollment.

- Subject (b) (6) had mild GVHD related to a prior CBT
- Subject (b) (6) had GVHD due to maternal T cells and was treated with a calcineurin inhibitor prior to enrollment
- Subject (b) (6) had autologous GVHD (Omenn syndrome) and was treated with equine ATG, dexamethasone, and calcineurin inhibitors prior to enrollment.

Five subjects developed GVHD following treatment with RVT-802; GVHD in 3 (3.2%) subjects (Subjects (b) (6) GVHD of the gastrointestinal tract in 2 (2.2%) subjects (Subjects (b) (6) and GVHD of skin in 1 (1.1%) subject (Subject (b) (6)). Two of the subjects had SCID, 2 subjects had cDGA, and 1 subject was considered to have partial DGA as of the time of treatment but is now considered to have atypical cDGA.

There were 4 subjects with Omenn syndrome; 1 subject (Subject (b) (6)) with a prior history at study entry and 3 subjects (Subjects (b) (6)) who developed it  $\leq 12$  months post-RVT-802 implantation. Subject (b) (6) developed a flare of Omenn syndrome that was confirmed via a gut biopsy on Day 150 post-implantation. The other 3 events were related to atypical cDGA. None of the events were assessed as related to study treatment but were assessed as SAEs in 2 (2.2%) subjects.

#### **8.5.3.5 Cytokine Release Syndrome/Hypersensitivity/Urticaria**

Cytokine release syndrome, an expected effect of RATGAM administration, was reported as an AE in 18 (19.4%) subjects (20 events). Of these 20 events, 15 were moderate in intensity and 5 were severe and  $\geq$  Grade 3 with 19 events assessed as related to treatment. All of the latter were reported at the time of RATGAM administration. Four events in 4 (4.3%) subjects were assessed as SAEs including 3 events related to RATGAM administration and 1 event reported 43 days post-implantation that was unrelated to study treatment and likely related to IVIG administration (Subject (b) (6)). In all 3 subjects in which the event was assessed as serious and related to treatment with RATGAM, the SAE resolved after the completion of RATGAM administration.

Hypersensitivity was reported in 11 (11.8%) subjects and occurred  $\leq 12$  months after implantation in 9 (9.7%). These AEs were assessed as treatment-related in only 1 (1.1%) subject (Subject (b) (6)) but was related to a blood transfusion and not RVT-802. It was considered related to treatment because the blood transfusion was required for anemia secondary to study mandated phlebotomy. Hypersensitivity was assessed as an SAE in 4 (4.3%) subjects but were not related to study treatment. The significance of these hypersensitivity reaction is unknown since they are common and expected events in immunocompromised subjects.

Urticaria was reported in 8 (8.6%) subjects and were possibly related to study treatment in 4 (4.3%) subjects (5 events). Subject (b) (6) reported one event related to cyclosporine and one event related to basilizimab. The other 3 events were related to the anti-coagulant lovenox (enoxaparin sodium, Subject (b) (6)), a food allergy (Subject (b) (6)) and an unknown cause (Subject (b) (6)). The significance of the urticaria AEs is unknown since the thymus is not known to play a role in the etiology of this event.

#### **8.5.3.6 Malignancy**

Malignancies were considered AESIs since poor T cell function leads to the loss of immune surveillance. Cancers have been reported in patients with partial DGA. Furthermore, subjects were considered at risk for the development of lymphoproliferative disorders associated with EBV or CMV. Five neoplasms were reported as AEs in 4 (4.3%) subjects within 2 years of RVT-802 implantation. These included Grade 1 benign hepatic neoplasm and Grade 1 benign splenic tumor (Subject (b) (6)), Grade 3 myelodysplastic syndrome (Subject (b) (6)) and Grade 2 squamous cell carcinoma (Subject (b) (6)). They were not related to treatment. In Subject (b) (6) the benign growths were hemangiomas. Subject (b) (6) had 3 episodes of EBV lymphoma prior to implantation that were treated with chemotherapy. Notably, Subject (b) (6) EBV lymphoma entered remission post-treatment with RVT-802. The event of squamous cell carcinoma also resolved. This subject remains alive and in remission 1057 days post-implantation.

A SAE of Grade 5 EBV associated lymphoma was reported in Subject (b) (6) and was assessed as related to treatment. This subject had pre-existing EBV lymphoma prior to implantation

and the lymphoma progressed post-implantation. The Investigator concluded it was possible the RVT-802 implantation protocol (specifically the use of fludarabine and dexamethasone) may have contributed to the progression of lymphoma; however, no mechanism by which the study treatment could have hastened the progression of the lymphoma was identified. The lymphoma would have likely progressed and led to the subject's death irrespective of the subject's participation in this study.

Subject <sup>(b) (6)</sup> reported a Grade 1 nodule over the site of thymus implantation (preferred term: skin mass) 2031 days post-implantation. This event was considered possibly related to RVT-802 and resolved 594 days after onset. The clinical significance of this finding is unknown.

## **8.6 Clinical Laboratory**

Clinical laboratory assessments included the following:

- Hematology: hemoglobin, hematocrit, platelet count, white blood cell count (WBC), neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils, atypical lymphocytes, and other myelocytes.
- Chemistry: sodium, potassium, chloride, CO<sub>2</sub> (bicarbonate), glucose, blood urea nitrogen (BUN), and creatinine.
- Liver function tests: AST, ALT, alkaline phosphatase (ALP), bilirubin, lactate dehydrogenase (LDH), lipase, amylase, albumin, total protein, gamma-glutamyl transpeptidase (GGT), and triglycerides.
- Endocrine: calcium, ionized calcium, magnesium, phosphorus, urine calcium, urine creatinine, ratio, thyroxine (T<sub>4</sub>), free T<sub>4</sub>, thyroid stimulating hormone (TSH), intact parathyroid hormone (iPTH), anti-TGB (anti-thyroglobulin), and anti-TPO (anti-thyroperoxidase).

### **8.6.1 Hematology**

There were no clinically meaningful changes from baseline through Year 2 in the hematocrit, hemoglobin, leukocytes, lymphocytes, monocytes, neutrophils band forms, neutrophils, eosinophils, and platelet counts in the RVT-802 studies.

### **8.6.2 Biochemistry**

There were no clinically meaningful changes over the course of the clinical program in the following parameters: sodium, potassium, chloride, CO<sub>2</sub> (bicarbonate), glucose, BUN, and creatinine.

### **8.6.3 Liver Function Studies**

There were no clinically meaningful changes over the course of the clinical program in the following parameters: AST, ALT, AP, bilirubin, LDH, lipase, amylase, albumin, total protein, GGT, and triglycerides.

### **8.6.4 Endocrine Studies**

In general, there were no clinically meaningful changes over the course of the clinical program in the following parameters: calcium, ionized calcium, urine calcium/creatinine ratio, magnesium, phosphorus, T<sub>4</sub>, free T<sub>4</sub>, TSH, iPTH, anti-TGB, and anti-TPO. However, the wide variation in the number of subjects assessed at each time point did not permit a meaningful conclusion as to the effect of RVT-802 implantation on these parameters.

### 8.6.5 Immunogenicity

An analysis by the Principal Investigators and her colleagues found no correlation between HLA-matching on immune outcomes in 30 subjects treated with RVT-802 at 1-year post-implantation. Therefore, HLA matching was not required for RVT-802 implantation.

### 8.7 Safety Conclusion

In the clinical development program, 93 subjects received RVT-802 including 87 subjects with cDGA, 2 subjects with FOXP1 deficiency, 2 subjects with SCID, 1 subject with athymia of unknown origin, and 1 subject with partial DGA at the time of implantation but who is now considered to have atypical cDGA. The subject's medical histories and baseline conditions were consistent with that expected in congenital athymia. The most common medical conditions were related to the underlying disease including congenital cardiac or cardiothoracic vascular anomalies, hypoparathyroidism, hypocalcemia, deafness/ear pinnae anomalies, GERD, developmental delays, pyrexia (likely associated with infections with no identified organism), and diarrhea/vomiting. Most subjects (>50%) entered the studies with pre-existing central venous catheters and G tubes, with over a third of subjects requiring parenteral nutrition. A quarter of subjects had pre-existing oxygen requirements, including a medical history of mechanical ventilation. These findings confirm the medical complexity and serious clinical condition of study subjects consistent with the disease under study.

The median dose of RVT-802 implanted in the FAS, was 13,098 mm<sup>2</sup>/m<sup>2</sup> (range: 4,523 to 23,755 mm<sup>2</sup>/m<sup>2</sup>) using a median of 30 slices (range: 10 to 108). At the time of implantation, subjects' ages ranged from 33 days to 16.9 years in the FAS. The oldest subject was (Subject (b) (6)) was implanted in adolescence after the development of EBV lymphoma following a prior CBT. Subjects included in the EAS (all subjects with cDGA or FOXP1 deficiency and who had not received a prior HSCT) ranged in age at the time of implantation from 33 days to 1.8 years.

Twenty-seven subjects (29%) died following RVT-802 implantation; 21 subjects died within the first year after implantation, prior to the development of thymic function. Most of these deaths were due to infections, complications associated with infection or respiratory failure/hypoxia and were therefore consistent with the disease under study. These data highlight the importance of implanting RVT-802 as early as possible after diagnosis of congenital athymia and prior to the development of severe and life-threatening infections.

All 93 subjects who received RVT-802 had at least one AE with a total of 1684 AEs reported within the first 2 years and a total of 2003 AEs reported at any time following RVT-802 implantation. The most common (>25% of subjects) AEs at any time were pyrexia (64.5%), device-related infection (52.7%), rash (35.5%), diarrhea (30.1%), hypertension (30.1%), increased alanine aminotransferase (29.0%), hypoxia (26.9%), thrombocytopenia (26.9%), anemia (26.9%), and increased aspartate aminotransferase (25.8%). These AEs were consistent with the subject's reported medical histories, use of immunosuppression, and disease under study.

When evaluated by SOC, the most frequent AEs at any time post-implant were in the infections and infestations SOC with 89 (95.7%) subjects reporting a total of 681 infection-related events. The most common (>15% of subjects) infections included device-related infection (52.7%), viral upper respiratory tract infection (21.5%), *Clostridium difficile* colitis (17.2%), staphylococcal bacteremia (16.1%), pneumonia (15.1%), urinary tract infection

enterococcal (15.1%), and ear infection (15.1%). The high incidence of infection-related AEs was expected given the immunocompromised population under study.

The AE profile was generally found to be consistent across the subgroups analyzed. There were no clinically relevant effects of age at implantation, gender, race, 22q11.2 hemizygoty, disease etiology/gene mutation, hepatic insufficiency prior to implantation, renal insufficiency prior to implantation, maximum naïve CD4 cell count post implantation, dose, or manufacturing facility on the AE profile. Overall, the AE profile in these subgroups was consistent with that of the overall subject population, supporting a consistent safety profile of RVT-802 in these subgroups. However, there were 3 subgroups where the AE profile was different: cDGA phenotype (atypical versus typical), use of immunosuppression, and pre-existing CMV infection.

Differences in the AE profile among subjects with typical and atypical cDGA were expected and can be attributed to differences in the use of immunosuppressive medications. The latter medications were administered per protocol in subjects with atypical cDGA but were only required in a small subset of those with typical cDGA who had an elevated immune response at baseline. In contrast, the former subjects required immunosuppressive therapy not only to prevent the rejection of RVT-802 but also to treat the complications associated with pre-existing oligoclonal T cell proliferations associated with atypical cDGA. Consequently, hypertension (atypical cDGA: 17 [41.5%] vs typical cDGA: 9 [20.0%]), hypomagnesemia (atypical cDGA: 9 [22.0%] vs typical cDGA: 5 [11.1%]) and cytokine release syndrome (atypical cDGA: 12 (29.3%) vs typical cDGA: 4 (8.9%)) were all reported at higher frequencies in subjects with atypical cDGA. Similar differences in AEs were observed between the subgroups of subjects who were or were not receiving immunosuppressant medications.

The AE profile was notable in subjects with confirmed pre-existing CMV infections because all 3 subjects died after receiving RVT-802 and prior to the development of thymic function. The use of immunosuppression in 2 of these subjects may have contributed to the progression of CMV infection. Despite the limited number of subjects, treatment with RVT-802 in subjects with pre-existing CMV should be carefully considered, especially in subjects requiring immunosuppression as they may not survive long enough to develop thymic function and the use of such therapy may contribute to the progression of the CMV infection.

The studies considered any AE associated with the RVT-802 implantation procedure or biopsy, supportive care associated with these procedures including protocol required immunosuppression, or RVT-802 as related to study treatment. This approach resulted in a relatively high number of treatment-related AEs relative to a traditional approach in which only AEs associated with study drug would be considered treatment-related. There were 72 subjects (77.4%) reporting 237 events (11.8% of all reported AEs) considered treatment-related. Most of these events were considered likely related to the use of immunosuppression (e.g. cytokine release syndrome, hypomagnesemia, and hypertension), and the incidence of these events decreased over time as thymic function developed and immunosuppressive therapies were weaned. With a more stringent criterion defined by relatedness to either the implantation procedure or the implanted RVT-802 drug product (and not to concomitant immunosuppressive medications or other procedures), the number of AEs at any time after RVT-802 implantation decreased from 2003 to only 77 events (3.8% of all reported AEs).

AEs related to RVT-802 were generally classified into 3 main categories: autoimmune diseases, complications associated with the implantation procedure, and T cell related events. The most common category of reported events was autoimmune disorders which typically occurred within the first year following RVT-802 implantation prior to the development of thymic function. Autoimmune cytopenias were the most common events considered related to RVT-802 in the first year after implantation. These events typically resolved with the development of thymic function. In addition to cytopenias, other reported autoimmune disorders including hypothyroidism, proteinuria, abnormal lymphocytes, and autoimmune hepatitis. A direct attribution of these AEs to RVT-802 is difficult since autoimmune disorders are common in patients with partial DGA who have not received RVT-802 and as such were expected events. Nonetheless, given the ability of RVT-802 to reconstitute the immune system, a role for RVT-802 in the development of autoimmune diseases cannot be excluded.

AEs associated with the implantation procedure included post-operative fever (5 events), wound/stitch infections at the site of implantation (7 events), or other complications at the site of implantation (1 event of graft site hemorrhage, 1 event of hematoma at the implantation site, and 1 event of skin mass [nodule] at the implantation site); these events were generally mild to moderate in intensity and typically resolved within a few days. The low frequencies of wound related infections and their low intensity indicate that the RVT-802 implantation procedure was well tolerated.

Finally, T cells related events included 4 events of GVHD (2 with SCID, 1 with cDGA and prior HSCT, and 1 with atypical cDGA [previously thought to be partial DGA]), rashes considered possibly related to T cells, and gastrointestinal disorders including diarrhea (2 events) and enteritis (1 event). In subjects in the EAS, these events typically resolved with the development of thymic function. The incidence of GVHD in subjects with congenital athymia was surprising low. All 4 events of GVHD were considered possibly related to RVT-802 but none could be directly attributed to donor T cells originating from RVT-802. The GVHD resolved as expected with the development of thymic function in the 2 subjects with cDGA. However, the outcome was different for the 2 subjects with SCID who developed GVHD, as both subjects had ongoing GVHD at the time of study withdrawal. The immunologic basis for the different outcomes in these 4 subjects has not been definitively established. The Investigator hypothesized that SCID subjects may also have defective APCs, resulting in a failure of the SCID subjects' APCs to present self (subject) MHC to the developing thymocytes. The inability of these APCs to induce self-tolerance may have resulted in the development of GVHD. Unlike SCID, subjects with congenital athymia have functional APCs that can present self (subject) MHC to the developing thymocytes. This process enables the development of T cells that are tolerant of both donor and recipient tissues.

The clinical laboratory and vital signs data from these studies did not raise any safety concerns for RVT-802 when administered to subjects with congenital athymia.

In conclusion, the safety data support the use of RVT-802 in subjects with congenital athymia. There were 2003 AEs reported post-implantation but only 11.8% of all reported AEs were considered related to study treatment (RVT-802 implantation or biopsy procedures, RVT-802, immunosuppressive therapy, or supportive care associated with these procedures). There were even fewer AEs (77; 3.8% of all reported AEs) related to the

implantation procedure for RVT-802 or RVT-802 itself, suggesting the procedure and treatment are well tolerated. The majority of deaths (21 of 27 deaths) were within the first-year post-implantation, prior to the development of thymic function.

## 9. CLINICAL UPDATE - 120 DAYS

### 9.1 Subject Database

The Applicant provided a 120-day safety update in July 2019 that was based upon updated data from the 7 core, single-site, open-label, non-randomized clinical studies under IND 9836 (Studies 668-1, 668-2, 884/884.1, 931, 932, 950/950.1 and 25966), 2 additional IND protocols (Studies (b) (6) and 51692), and 1 non-IND single subject protocol (735).

There were 7 new subjects who have been treated under the following protocols since the original clinical BLA submission in Dec 2018.

- Study 25966 – 2 subjects (Subjects (b) (6))
- Study 51692 - 5 subjects (Subjects (b) (6))

The following new data were included in the 120 days update report:

- Updated safety, efficacy, and vital status data from the ongoing 25966 and 51692 studies including data from the 7 new enrolled subjects.
- Updated vital status data (as available) for all historically treated subjects from studies 668-1, 668-2, 884, 931, 932, and 950.

### 9.2 Demographics and Disease Characteristics

Five of the 7 new subjects had a diagnosis of cDGA including 4 with typical cDGA (Subjects (b) (6)) and 1 with atypical cDGA (Subject (b) (6)). One subject (Subject (b) (6)) was diagnosed with athymia associated with FOXP1 deficiency while the remaining subject (Subject (b) (6)) had athymia associated with a TBX1 mutation.

The demographics and baseline characteristics of the updated FAS (uFAS) remained essentially unchanged from the Dec 2018 submission except for a longer waiting time to receive RVT-802. The 7 new subjects were slightly older than the initial BLA population with a median age at the time of implantation of 686 days (1.9 years; range: 280 to 1814 days) versus 245 days (0.67 years; range: 33 to 4741 days. This was because the (b) (4) facility was closed to clinical production for much of 2018 so as to address manufacturing changes for commercialization. Thus, no subjects were treated with RVT-802 between January 2018 and February 2019. As a result, the most recently treated subjects were older when compared to the median treatment age in the original Dec 2018 submission.

Most subjects (n=92, 92%) in the uFAS had a diagnosis of cDGA with a similar number of subjects with the typical (49 subjects) and atypical (42 subjects) phenotypes. A wide range of phenotypic features associated with athymia were observed. All subjects had a diminished T cell count for their age and most subjects reported a congenital cardiothoracic vascular anomaly (87%), hypocalcemia (85%), growth/mental retardation (52%), deafness or ear pinnae anomalies (51%). These findings were consistent with the disease under study and with data reported in the initial CSS.

The median dose of RVT-802 implanted in the FAS was 12,736 mm<sup>2</sup>/m<sup>2</sup> (range: 4,523 to 23,755 mm<sup>2</sup>/m<sup>2</sup>) using a median of 30 slices (range: 10 to 108 slices).

### 9.3 Subject Disposition

The updated full analysis set (uFAS) consisting of all subjects (n=100) treated with RVT-802 was used for all analyses of safety. The efficacy analysis set (uEAS; n=90) included all subjects with congenital athymia associated with cDGA or FOYN1 deficiency, who had no prior HSCT and were treated with RVT-802. The updated EAScDGA (uEAScDGA) included all 88 subjects in the uEAS except those with FOYN1 deficiency.

There were 10 subjects who were excluded from the uEAS.

- Subject (b) (6) (Study 884) diagnosed with cDGA but had undergone 2 fetal thymus transplants prior to receipt of RVT-802.
- Subject (b) (6) (Study 950.1) had an unknown form of athymia and had received 2 prior HCTs.
- Subject (b) (6) (Study (b) (6)) diagnosed with cDGA but had received a prior sibling peripheral blood mononuclear cell transplant.
- Subject (b) (6) (Study 51692) had a heterozygous FOYN1 mutation and received 2 prior cord blood transplants (CBT).
- Subject (b) (6) (Study 51692) had received a prior CBT.
- Subject (b) (6) (Study 51692) had received a prior CBT.
- Subject (b) (6) (Study 51692) had an unknown form of athymia associated with a TBX1 mutation.
- Subject (b) (6) (Study 668-2) had a diagnosis of SCID.
- Subject (b) (6) (Study 932) was initially thought to have cDGA but was later confirmed to have a diagnosis of SCID post-implantation.
- Subject (b) (6) (Study 735) diagnosed with partial DGA at the time of enrollment but is now believed to have cDGA with autologous GVH (Omenn Syndrome).

Two subjects were included in the uEAS but not included in the uEAS-cDGA. Both subjects had a homozygous FOYN1 deficiency:

- Subject (b) (6) (Study 668-2);
- Subject (b) (6) (Study 884).

Subject (b) (6) had a heterozygous FOYN1 mutation but was excluded from the uEAS and uEAS-cDGA due to a prior CBT.

### 9.4 Efficacy

#### 9.4.1 Primary Efficacy Endpoint

The median follow-up time for all subjects in the uEAS was 2735 days (7.5 years) and ranged from 0 to 9301 days (25.5 years) after RVT-802 implantation. The Overall survival was 72% in the uEAS. The median survival time for the 25 subjects (28%) who died was 137 days (range: 0 to 3116 days [8.5 years]) after RVT 802 implantation. Survival rates were similar across analysis populations. The Kaplan-Meier estimated survival rates at Year 1 and Year 2 post-implant in the uEAS were 76% (95% CI 0.658, 0.838) and 75% (95% CI 0.646, 0.828), respectively.

Survival > 50% at Year 1 and Year 2 post-implant was tested using the binomial exact test. In the uEAS, with 2 subjects censored, 67 of 90 subjects (76.1%) were alive at Year 1 post implantation. The binomial exact test with null hypothesis that no greater than 50% of subjects would survive at Year 1 gave a 95% CI of [0.66, 0.85] with a p-value < 0.0001. At

Year 2 post implantation, with 63 of 90 subjects (74.1%) alive and 5 subjects censored, the exact binomial test gave a 95% CI of [0.63, 0.83] with a p-value < 0.0001.

For the 7 newly treated subjects, only 4 (Subjects (b) (6) ) have been followed for more than one year post-implant. The remaining 3 subjects (Subjects (b) (6) ) were transplanted within the past 6 months and thus have limited or no data to establish thymic function, which is expected to develop 6 to 12 months post-implant. Nonetheless, these 3 subjects are alive with evidence of thymic function in Subject (b) (6) . Among the 4 subjects treated for more than 1 year, 3 remain alive with the latest follow-up reported on Day 497 (Subject (b) (6) ), Day 406 (Subject (b) (6) ), and Day 490 (Subject (b) (6) ). One subject (Subject (b) (6) ) died 339 days following RVT-802 implantation due to methicillin resistant *Staphylococcus aureus* which was considered unrelated to study treatment.

#### **9.4.2 Secondary Efficacy Endpoints**

Flow cytometry results were consistent with those reported in the initial CSE. Naïve T cell counts generally increased from levels considered athymic (< 50 cells/mm<sup>3</sup> or < 5% of the total T cell count being naïve in phenotype) to levels considered sufficient to fight infection and enable survival within approximately 1-year post-implantation. In the uEAS, median naïve CD4 cell counts (cells/mm<sup>3</sup>) were 1.0 (n = 60) at baseline, 21 at Month 6 (n= 64), 215 at Year 1 (n = 41), and 246 at Year 2 (n = 26).

The T cell proliferative response data to mitogen/antigens including PHA, concanavalin A, soluble CD3, immobilized CD3, *Candida*, and tetanus toxoid were consistent with those reported in the initial BLA.

### **9.5 Safety**

#### **9.5.1 Deaths**

Seventy-one (71%) of the 100 subjects who received RVT-802 (FAS) were alive at their most recent follow-up, 26 (26%) were dead, and 3 (3%) had withdrawn from the study (2 of whom died after study withdrawal). There was one additional death since the initial December 2018 data cut for the clinical BLA. Subject (b) (6) died due to Methicillin resistant *Staphylococcus aureus* bacteremia 339 days post-implantation. Thus, a total of 28 subjects died after RVT-802 implantation; 22 within the first years, 2 within the second year and 4 deaths after 2 years. The causes of deaths in the first-year post-implantation were expected for the disease under study and included infection/sepsis/complication due to infection (n = 13), respiratory failure/hypoxia (n = 5), hemorrhage related events (n = 3), and cardio-respiratory arrest (n = 1). The 2 subjects who died between 1- and 2-years post-implant were due to an unrelated intracranial hemorrhage at 480 days post-implant and after study withdrawal (375 days post-implant). Four subjects died more than 2 years post-implantation including 3 subjects who died during study follow-up due to respiratory failure (n=2 on Days 2769 and 3116) and cardiopulmonary arrest (Day 1617) and 1 subject who died 950 days post-implantation after withdrawing from the study.

#### **9.5.2 Serious Adverse Effects**

There were 488 SAEs reported in 82 (82%) subjects in the FAS during the 2 years following RVT-802 implantation. The most frequent SAEs were in the infections and infestations SOC (70%) but only device-related infection (44%), pneumonia (8%), *Staphylococcal* bacteremia (5%), lower respiratory tract infection bacterial (5%) and viral upper respiratory tract infection (5%) were reported in ≥5% of subjects. SAEs were also frequently reported in the

respiratory and mediastinal disorders SOC (39%); the most frequent were respiratory failure (17%), hypoxia (15%) and respiratory distress (6%). Pyrexia was also common (18%). The pattern of SAEs reported in the first 2 years after RVT-802 implantation was consistent with subjects' underlying conditions and medical histories. There were no differences in the trends of the SAEs since the initial Dec 2018 BLA submission.

There were 42 SAEs reported in 2 of the 7 newly treated subjects; only 2 of the SAEs were reported in more than 1 subject. Device related infection and hypoxia were each reported by 2 subjects. Neither of these events were considered related to RVT-802. The majority of the SAEs (26 events) were infections and were expected given the disease under study. The SAEs reported in the 7 recently treated subjects were consistent with and similar to those previously reported in the original BLA submission.

#### **9.5.2.1 Treatment Related Serious Adverse Effects**

SAEs were classified as treatment-related if the Applicant/Investigator considered them related to the RVT-802 implantation procedure or biopsy, RVT-802, supportive care associated with these procedures, or protocol mandated immunosuppression. In the 2 years following implantation, 61 SAEs were reported in 31 (31%) subjects in the FAS. The most frequent were in the blood and lymphatic system disorders SOC where 22 SAEs in 13 (13%) subjects were related to treatment. However, the only SAEs assessed as treatment-related in  $\geq 5\%$  of subjects in any SOC were thrombocytopenia and neutropenia, each of which were reported in 5 subjects (5%). The only other SAE that was assessed as treatment-related in more than 2 subjects was CRS which was reported in 3 (3%) subjects; this SAE was considered related to the use of RATGAM in all 3 subjects. The majority of the SAEs reported as treatment-related were either autoimmune in nature or likely related to the immunosuppressive therapy administered prior to, concomitantly, and/or after RVT-802 implantation.

There has been one additional RVT-802 related SAE reported since the initial BLA submission. Subject (b) (6) reported a SAE of ovarian failure which was considered to be possibly related to RVT-802.

#### **9.5.3 Adverse Effects**

Ninety-nine subjects (99%) had at least one AE in the first 2 years after RVT-802 implantation. There were no AEs reported for Subject (b) (6) as the last follow-up was only 13 days post-implant. There were 1790 AEs reported in the 99 of 100 subjects included in the uFAS (106 new AEs since the Dec 2018 submission). Most subjects (87 [87%]) had events that were  $\geq$  Grade 3 and included 23 (23%) subjects who died within the first 2 years after implantation. Nearly all subjects (93 [93%]) reported at least one infection-related AE including 12 (12%) subjects with life-threatening and 11 (11%) subjects with fatal infections. Nearly all subjects (82 [82%]) had at least 1 SAE. An additional 329 events (10 new AEs since the Dec 2018 submission) were reported more than 2 years after implantation through the reporting period of 04 June 2019, resulting in a total of 2119 AEs at the time of this 120-day update.

The most frequent AEs reported within the first 2 years post-implant were in the infections and infestations SOC where 93 (93%) subjects reported at least one AE. This was consistent with the immunocompromised nature of the clinical population under study. AEs were also commonly reported ( $\geq 50\%$  of subjects) in the general disorders and administration site

conditions (63%), gastrointestinal disorders (63%), skin and subcutaneous tissue disorders (62%), respiratory, thoracic and mediastinal disorders (60%), investigations (58%), blood and lymphatic system disorders (58%), and metabolism and nutrition disorders (55%) SOCs.

The most frequently reported AEs (> 20% of subjects) by PT were pyrexia (59%), device-related infection (50%), rash (33%), hypertension (29%), ALT increased (25%), hypoxia (27%), diarrhea (27%), anemia (23%), thrombocytopenia (23%), and AST increased (22%). These events were consistent with the reported medical histories, concomitant use of immunosuppression, and disease under study.

The AEs reported among the most recently treated subjects were similar to those reported in the original BLA submission. There was potentially a higher incidence of acute kidney injury among the 7 new subjects with 2 of 7 (29%) reporting this event as compared to 2 of 93 (2%) subjects in the original BLA submission. However, these events were not considered to be related to RVT-802 and were likely due to the use of nephrotoxic medications including calcineurin inhibitor therapy as well as some anti-viral and antibiotic therapies. Other AEs were generally similar across the treatment groups.

There was only one AE considered related to RVT-802 among the 7 most recently treated subjects. Subject <sup>(b) (6)</sup> reported a non-serious Grade 1 AE of edema considered to be related to RVT-802. The subject developed post-operative swelling on the day of implantation at the site of RVT-802 implantation (right thigh) that resolved 13 days following implantation. This subject had a preexisting condition of poor venous drainage that worsened with RVT-802 implantation.

#### **9.5.3.1 Adverse Events $\geq$ Grade 3**

Of the 1790 AEs reported in the uFAS within 2 years of implantation, 725 events in 87 (87%) subjects were  $\geq$  Grade 3 in severity. These were most frequent in the infections and infestations SOC (74 [74%]); however, only device-related infection (44 [44%]) and pneumonia (10 [10%]) were reported in  $\geq$  10% of subjects in the FAS. Other  $\geq$  Grade 3 AEs that were reported in  $\geq$  10% of subjects were hypoxia (21%), anemia (19%), neutropenia (17%), respiratory failure (17%), pyrexia (14%), AST increased (13%), ALT increased (12%), thrombocytopenia (11%), and diarrhea (11%). This profile of events was consistent with the overall AE profile and with the clinical population under study.

#### **9.5.3.2 Treatment Emergent Adverse Events**

The Applicant/Investigator considered any AE related to the RVT-802 implantation procedure or biopsy, RVT-802 itself, protocol-required immunosuppression, or supportive care associated with these procedures to be related to study treatment.

The most frequent TEAEs (by SOCs) in the first 2 years after implantation were blood and lymphatic system disorders (22%), immune system disorders (22%), metabolism and nutrition disorders (21%), skin and subcutaneous disorders (21%), and vascular disorders (20%). TEAEs were also commonly reported ( $\geq$  10% of subjects) in the investigations (15%), renal and urinary disorders (11%), and respiratory, thoracic and mediastinal disorders (11%) SOCs. Although TEAEs in the infections and infestations SOC were commonly reported, only 8% (8 subjects) in this SOC were assessed as related to treatment.

The most frequent TEAEs following RVT-802 implantation were related to immunosuppressive therapy and included CRS (18 [18%]), hypertension (19 [19%]) and

hypomagnesemia (17 [17%]). Cytokine release syndrome is a known AE associated with RATGAM which was widely used in the studies while hypertension and hypomagnesemia are well known AEs associated with calcineurin inhibitors.

Other treatment-related AEs reported in  $\geq 5\%$  of subjects included: thrombocytopenia (10%), neutropenia (8%), rashes (11%), proteinuria (7%), pyrexia (6%) and hypoxia (5%). No notable differences in trends in treatment related AEs were observed since the initial clinical BLA submission.

#### **9.5.3.2.1 TEAEs Related to RVT-802 or the Implantation Procedure**

AEs that were considered related to either the RVT-802 drug product and to the implantation procedure but not to concomitant immunosuppressive medications or other study procedures were assessed. There were 42 (42%) subjects who reported 82 TEAEs that were possibly related to RVT-802 in the uFAS. This accounted for 3.9% of all reported AEs (82 of 2119 reported AEs). The RVT-802 TEAEs could be categorized into 3 main categories: autoimmune diseases, complications associated with the implantation procedure, and events related to T cells.

Since the initial Dec 2018 BLA submission, there were 5 additional TEAEs in 4 subjects that were considered possibly related to RVT-802. These TEAEs include Grade 3 Coombs positive hemolytic anemia, Grade 1 peripheral edema, Grade 2 psoriasis, Grade 3 psoriatic arthropathy, and Grade 3 ovarian failure.

#### **9.5.3.3 Adverse Events of Special Interest**

AESIs after RVT-802 implantation included infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas. There were 218 non-infection-related AESIs reported in 81 (81%) subjects within 2 years and 40 additional non-infection-related AESIs reported more than 2 years after implantation. This included 17 new non-infection-related AESIs reported at any time post-implantation since the initial clinical BLA submission. The 17 new AESIs were reported in the following SOCs: skin and subcutaneous disorders (7 new events), blood and lymphatic system disorders (6 new events), immune system disorders (1 event), endocrine disorders (1 new event), musculoskeletal and connective tissue disorders (1 event) and reproductive system and breast disorders (1 event). In addition, 1 previously reported AESI of serum sickness which was included in the immune system disorder SOC was removed upon further review. The Applicant/Investigator considered the event of serum sickness previously reported in Subject (b) (6) to be due to the reactivation of a *Varicella zoster* infection following treatment with RATGAM and not due to the development of serum sickness. The new AESIs in the skin and subcutaneous disorders SOC (rash and eczema) were not considered by the PI to be related to RVT-802. A new event of autologous GVHD in the gastrointestinal tract (also referred to as Omenn syndrome) was not considered by the PI to be related to RVT-802. The remaining newly reported AESIs in the other SOCs were generally considered to be possibly autoimmune in nature and as such possibly related to RVT-802.

#### **9.5.3.4 Adverse Events by RVT-802 Manufacturing Site**

There were 13 subjects implanted with RVT-802 that was manufactured at the (b) (4) manufacturing facility. No new subjects were treated with RVT-802 manufactured in (b) (4) maintaining the total number of subjects treated

there at 87. The difference in group size between the (b) (4) treated subjects did not permit a meaningful comparison of the reporting frequencies of AEs or SAEs. Nonetheless, the profile of reported AEs in the 2 groups within 2 years of implantation appeared to be consistent with that in the overall FAS population.

#### **9.6 Clinical Laboratory**

There were no clinically meaningful changes in clinical laboratory data (hematology, fluids, electrolytes, liver function, endocrine, and immunoglobulins) since the initial Dec 2019 clinical BLA submission.

#### **9.7 Conclusion**

The 120-day updated clinical efficacy safety data from 100 subjects who were treated with RVT-802 continue to support the conclusions presented in the CSE (Section 7) and CSS (Section 8) of this review. RVT-802 is safe and effective for the treatment of subjects with congenital athymia.

### **10. ADDITIONAL CLINICAL ISSUES**

#### **10.1 Special Populations**

DiGeorge Anomaly and *FOXNI* deficiency are ultra-rare congenital diseases, with the latter even rarer than the former. The prevalence of the disease is too small for subdividing into subpopulations.

##### ***10.1.1 Human Reproduction and Pregnancy Data***

This section is not applicable since DiGeorge Anomaly and *FOXNI* deficiency are congenital diseases where the children die prematurely before reaching reproductive age.

##### ***10.1.2 Use During Lactation***

This section is not applicable since DiGeorge Anomaly and *FOXNI* deficiency are congenital diseases where the children die prematurely before reaching reproductive age.

##### ***10.1.3 Pediatric Use and PREA Considerations***

DiGeorge Anomaly and *FOXNI* deficiency are congenital diseases that manifest at birth. Therefore, the clinical development program was conducted in infants and newborns and RVT-802 is indicated for use in the pediatric population.

##### ***10.1.4 Immunocompromised Subjects***

DiGeorge Anomaly and *FOXNI* deficiency manifest as a severe combined T-cell and B-cell immunodeficiency due to the absence of a thymus. Therefore, the clinical development program was conducted in infants and newborns who were severely immunocompromised.

##### ***10.1.5 Geriatric Use***

There are no data on the use of RVT-802 in the geriatric population since the afflicted individuals generally do not survive beyond the age of 2 years.

### **11. CONCLUSION**

Enzyvant has submitted a BLA that assesses the efficacy and safety of RVT-802 when used for immune reconstitution of patients with congenital athymia. The most common disease associated with congenital athymia is DiGeorge anomaly with the thymus completely absent in ~1-2% of patients. Both T cell numbers and function are highly abnormal with peripheral blood CD3 T cells that are <3 standard deviations below the normal age adjusted range (T

cell count  $<50/\text{mm}^3$ ). Afflicted infants must be placed in protective isolation, maintained on IGIV and antibiotic prophylaxis for pneumocystis. Their prognosis is poor with death within one to two years of birth.

An even rarer condition is FOXN1 deficiency (also known as nude severe combined immunodeficiency) with only ~10 cases reported in the literature as of November 2018. It is caused by homozygous autosomal recessive loss-of-function mutations in the *FOXN1* gene which encodes a transcription factor essential for development of the thymus. Clinical manifestations include athymia, alopecia, and dysplastic nails. The lack of T cell development as in cDGA renders afflicted individuals susceptible to infection and these children die from infection in the first few years of life.

RVT-802 is an investigational therapy being developed for immune reconstitution in patients with congenital athymia. It is an allogeneic cultured postnatal thymus tissue manufactured from tissue obtained from unrelated donors under the age of 9 months. After a 12 to 21-day culturing and manufacturing process to create the RVT-802 drug product, it is implanted into the recipient's quadriceps muscles by means of an open surgical procedure. RVT-802 reconstitutes the immune system in which the recipient bone marrow stem cells migrate to the thymus allograft and develop into immunocompetent T cells that are tolerant of both donor and recipient tissues.

The RVT-802 development program has been conducted at an academic center (DUMC) during the past 25 years under the guidance of Dr Louise Markert. The primary clinical data included in this Application are derived from 7, single-site, non-randomized, open-label, clinical studies in subjects with congenital athymia (Studies 668-1, 668-2, 884 [includes 884-1], 931, 932, 950 [includes 950-1], and 25966) and three supporting single-subject/ expanded access studies (Studies 735, (b) (6), and 51692). These studies cumulatively treated 93 subjects with RVT-802 and constitute the FAS with 85 and 83 subjects, respectively, in the EAS and EAS-cDGA.

The EAS included all subjects with congenital athymia associated with cDGA ( $n=83$ ) or FOXN1 deficiency ( $n=2$ ). In the former condition, 43 subjects had typical cDGA and 39 subjects had the atypical cDGA phenotype. Eight additional subjects were included in the FAS and provide supportive efficacy data. These subjects included 2 subjects with SCID ( $N=2$ ), 3 subjects with cDGA who had received prior HSCT, 1 cDGA subject who had 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.

RVT-802 prolonged survival in a disease that is universally fatal by the age of 2 years. There were only 27 (29%) deaths following RVT-802 implantation; 21 within the first year. Approximately three-quarters of the subjects were alive at 1-year (76%; 95% CI: 0.659, 0.841) and 2-year (75%; 95% CI: 0.646, 0.831) post-transplant in the EAS. The survival rate was essentially unchanged thereafter; 75% to 70% from Year 2 to Year 9 with no deaths after Year 9. Most deaths were within the first year after transplantation before immune reconstitution. The longest surviving subject was up to 24 years post-implantation. The survival rates were similar across analysis populations at all time points.

The survival benefit of RVT-802 transplantation was supported by several secondary endpoints that were consistent with immune reconstitution. These included a decrease in the

incidence of infections accompanied by evidence of thymopoiesis on RVT-802 biopsy within 2 to 3 months of implantation. There is an increase in naïve CD3, CD4, and CD8 T cells beginning at ~6 months post-implant, T cell proliferation in response to antigen and mitogen, and emergence of a diverse TCRV $\beta$  repertoire.

There were many AEs (2003 AEs) reported in these studies with 1684 AEs reported within the first 2 years. However, the number of AEs related to either the implantation procedure or the implanted RVT-802 drug product at any time after RVT-802 implantation was only 77 events (3.8% of all reported AEs). The AEs related to RVT-802 could be classified into 3 main categories: autoimmune diseases (cytopenia, hypothyroidism, hepatitis, etc) complications associated with the implantation procedure, and T cell related events. Most of these AE occurred within the first year of implantation and resolved with the development of thymic function.

All 93 subjects who received RVT-802 had at least one AE. The most common (>25% of subjects) AEs at any time were pyrexia (64.5%), device-related infection (52.7%), rash (35.5%), diarrhea (30.1%), hypertension (30.1%), increased alanine aminotransferase (29.0%), hypoxia (26.9%), thrombo-cytopenia (26.9%), anemia (26.9%), and increased aspartate aminotransferase (25.8%). These AEs were consistent with the subject's reported medical histories, concomitant use of immunosuppression, and disease under study.

The safety and efficacy data from the RVT-802 development program support the use of RVT-802 in subjects with congenital athymia. RVT-802 reconstituted a functional immunocompetent T cell population that resulted in a reduction in infections that enabled long-term survival in a population with an otherwise fatal disease. In conclusion, RVT-802 implantation in subjects with congenital athymia has a favorable risk-benefit profile. Given the poor medical prognosis of these pediatric, immunodeficient, athymic subjects, treatment with RVT-802 was associated with an acceptable tolerability and safety profile with a low rate of treatment related AEs.

## **12. RISK-BENEEFIT CONSIDERATIONS AND RECOMMENDATIONS**

### **12.1 Risk Benefit Considerations**

Congenital athymia is a fatal disease where afflicted individuals do not survive beyond the age of 2 years. The Applicant has clearly demonstrated that RVT-802 prolongs life with ~75% of the subjects alive at 1-year and 2-year post-implant. The longest surviving subject has lived for more than 24 years since receiving the therapy. Most of the deaths occurred within the first year after transplantation before the thymic transplant has fully reconstituted the immune system. The survival benefit of RVT-802 transplantation was supported by a decreased incidence of infections. The proposed mechanism of action was supported by the presence of thymopoiesis on RVT-802 biopsy at 2 to 3 months, an increase in naïve CD3, CD4, and CD8 T cells beginning at ~6 months, T cell proliferation in response to antigen and mitogen, and the emergence of a diverse TCRV $\beta$  repertoire.

The risk associated with the use of RVT-802 was not minimal as there was an average of 21.5 AEs and 5.6 SAEs reported for each subject. Furthermore, 79 of the 93 subjects (84.9%) in the FAS had an SAE with some of the SAEs such as GVHD being potentially fatal. However, the number of AEs related to either the implantation procedure or the implanted RVT-802 drug product was only 77 events (3.8% of all reported AEs). In general, the AEs reported for RVT-802 were consistent with the subject's reported medical histories,

concomitant use of immunosuppression, and disease under study. The 120-day updated clinical efficacy and safety data included 7 new subjects who were treated after the original clinical BLA submission in Dec 2018. The updated data from the new total of 100 subjects continue to support the conclusion that RVT-802 is safe and effective for the reconstitution of the immune system in subjects with congenital athymia.

In summary, the risk associated with the use of RVT-802 was not trivial but can be viewed as favorable in the context of the ability of RVT-802 to prolong survival in a universally fatal disease. These issues are further described in Table 46.

**Table 46: Risk Benefit Assessment**

<b>Decision Factor</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• Congenital athymia is a rare pediatric condition in which children suffer recurrent, severe infections and usually die by 2 years of age from an infection.</li> <li>• Congenital athymia most commonly is due to cDGA, but can occur with FOYN1 deficiency.</li> </ul>	<ul style="list-style-type: none"> <li>• Congenital athymia is a serious disease that is associated with severe infections and is generally fatal in the first 2 years of life.</li> </ul>
<b>Unmet Medical Need</b>	<ul style="list-style-type: none"> <li>• There are no approved therapies that treat congenital athymia.</li> <li>• With infection control measures and immunoglobulin therapy, patients' lifespans is generally under 2 years of age.</li> <li>• Experimental HSCT has a 2 year survival of only about 33%.</li> </ul>	<ul style="list-style-type: none"> <li>• There is a substantial unmet medical need.</li> </ul>
<b>Clinical Benefit</b>	<ul style="list-style-type: none"> <li>• 3 single-patient and 7 single-center, open label, single-arm studies treated 85 evaluable children under 2 years of age with congenital athymia from cDGA or FOYN1 deficiency.</li> <li>• Mortality data, number of infections and biochemical immunologic data was provided for 85 evaluable children. All subjects were followed for at least 1 year, with the maximum follow-up duration of 24 years.</li> <li>• There are no control subjects; natural history data is based on the medical literature for cDGA.</li> </ul>	<ul style="list-style-type: none"> <li>• There is a major survival benefit, as without treatment, cDGA is fatal in nearly all children by 2 years of age, and 75% of children treated with RVT-802 were alive at 2 years of age.</li> <li>• Children had fewer infections after 6 and 12 months following RVT-902 treatment.</li> <li>• Most treated subjects had an increase in naïve CD3, CD4, and CD8 cell counts and T cell proliferative response to antigen and mitogen by 12 months after RVT-802.</li> </ul>
<b>Risk</b>	<ul style="list-style-type: none"> <li>• Most common adverse reactions were autoimmune diseases, implantation procedure complication, and T cell related.</li> <li>• AE and SAEs were common due to underlying congenital athymia and immunosuppressant medications.</li> <li>• Following RVT-802, engraftment may take 12 months, and subjects are at risk of SAE from infectious prior to engraftment.</li> </ul>	<ul style="list-style-type: none"> <li>• Most AEs are due to underlying medical condition and</li> <li>• Patients can be monitored for most likely potential complications including autoimmune disorders and malignancy</li> </ul>
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>• No REMS.</li> </ul>	<ul style="list-style-type: none"> <li>• Warnings and Precautions to include information about potential for acquiring transmissible infectious disease, autoimmune disorders, malignancy and GVHD, and that pre-existing CMV is associated with mortality.</li> </ul>

From a clinical perspective, this Reviewer recommends the approval of this Application since the benefit of implanting RVT-802 for the treatment of subjects with congenital athymia is favorable relative to the adverse effect profile.

**12.2 Recommendations on Regulatory Actions**

**12.3 Labeling Review and Recommendations**

**12.3.1 Indication**

The Applicant is requesting a broad indication of “immune reconstitution of patients with congenital athymia” due to the lack of consistent terminology regarding the individual conditions associated with athymia. For example, patients with athymia associated with CHARGE syndrome would be classified as cDGA under the RVT-802 clinical study protocols while institutions outside of Duke University Medical Center may describe these patients as having athymia associated with CHARGE syndrome without mentioning cDGA.

The number of conditions resulting in congenital athymia are limited and are listed in Table 47. The two most prevalent conditions are 22q11.2DS and CHARGE syndrome. The next most prevalent condition is FOXP1 deficiency with a total of 10 cases described in the literature. Diabetic embryopathy

**Table 47: Conditions Associated with Congenital Athymia**

(Applicant’s Table)

Disease/Condition/Mutation	Disease Manifestation	Incidence
22q11.2 deletion syndrome (22q11.2 DS)	<ul style="list-style-type: none"> <li>• Congenital heart disease</li> <li>• Palate defects, facial abnormalities</li> <li>• T-cell immunodeficiency</li> <li>• Hypocalcemia and hypoparathyroidism</li> <li>• Hearing loss or kidney abnormalities</li> </ul>	1.0-2.5/10,000 births
CHARGE Syndrome (Chromodomain helicase DNA binding protein 7 [CHD7] mutation)	<ul style="list-style-type: none"> <li>• Coloboma of the eye and CNS abnormalities</li> <li>• Heart defects</li> <li>• Choanal atresia</li> <li>• Growth and developmental deficiencies, low muscle tone</li> <li>• Genital hypoplasia</li> <li>• Ear anomalies and associated hearing loss</li> </ul>	0.65-1.5/10,000 births
SEMAPHORIN 3E (SEMA3E)	<ul style="list-style-type: none"> <li>• Similar to CHARGE</li> </ul>	Only 2 patients
T-box transcription factor 1 (TBX1) haplosufficiency	<ul style="list-style-type: none"> <li>• Congenital cardiac defects</li> <li>• Thymus hypoplasia/aplasia</li> <li>• Hypocalcemia</li> </ul>	Unknown
T-box transcription factor 2 (TBX2) mutation	<ul style="list-style-type: none"> <li>• Congenital cardiac defects</li> <li>• Skeletal malformations</li> <li>• Craniofacial dysmorphism</li> <li>• Developmental impairments</li> <li>• T-cell immunodeficiency</li> <li>• Endocrine abnormalities</li> </ul>	Unknown
Paired box 1 (PAX1) deficiency	<ul style="list-style-type: none"> <li>• T-cell immunodeficiency</li> <li>• Otofaciocervical syndrome</li> <li>• Ear anomalies and associated hearing loss</li> </ul>	Only 1 patient
10p deletions	<ul style="list-style-type: none"> <li>• Congenital heart disease</li> <li>• Palate defects, facial abnormalities</li> <li>• T-cell immunodeficiency</li> <li>• Hypocalcemia and hypoparathyroidism</li> </ul>	Only 1 patient
FOXP1 deficiency	<ul style="list-style-type: none"> <li>• T-cell immunodeficiency</li> <li>• Congenital alopecia</li> <li>• Nail dystrophy</li> </ul>	Only 10 patients

Subjects enrolled in the RVT-802 studies were required to have athymia based on flow cytometry (<50 naïve T cells/mm<sup>3</sup> or <5% of naïve T cells in peripheral blood). In addition to athymia, subjects were required to have a diagnosis of complete DiGeorge anomaly (cDGA), which was defined as athymia in addition to at least one of the following criteria (criteria were similar across studies) to distinguish patients with athymia from those with severe combined immunodeficiency (SCID):

- Congenital heart defect
- Hypoparathyroidism (or hypocalcemia requiring replacement)
- 22q11.2 hemizyosity or 10p13 hemizyosity
- Coloboma, heart defect, choanal atresia, growth and development retardation, genital hypoplasia, ear defects including deafness (CHARGE) association or CHD7 mutation.

Additional genetic mutations related to the development of conotruncal heart disorders and congenital athymia have been identified since the initial clinical studies. These include mutations in T-box transcription factor 1 (TBX1), T-box transcription factor 2 (TBX2), paired

box 1 (*PAX1*), and *SEMAPHORIN 3E (SEMA3E)*. To date, no patients with *PAX1* deficiency, 10p deletions, *TBX2* or *SEMA3E* mutations have been treated with RVT-802.

In support of their request for a broad indication, the Applicant provided an analysis by disease etiology following the 120-day safety update. One-hundred subjects have been treated with RVT-802; 92 were diagnosed with cDGA and 8 subjects had another diagnosis. In the latter group, 3 were diagnosed with FOXN1 deficiency (2 subjects with a homozygous mutation and 1 subject with a heterozygous mutation), 2 with SCID who were not athymic (one of whom also had 22q11.2DS), 2 with an unknown form of congenital athymia, (including one subject who had a unique presentation with a *TBX1* mutation) and 1 subject with partial DiGeorge syndrome at the time of treatment who is now thought to have atypical cDGA.

The safety and efficacy of RVT-802 following implantation in the two groups were compared; 92 subjects with cDGA and 5 subjects with athymia associated with diseases other than cDGA. There were 3 subjects excluded from the latter group:

- Subject (b) (6) was diagnosed with SCID and did not have athymia
- Subject (b) (6) was diagnosed with SCID and did not have athymia
- Subject (b) (6) was thought to have partial DiGeorge syndrome at the time of treatment but is now thought to have cDGA.

Subjects with cDGA had a younger median age at the time of implantation of 250.5 days (range 33 to 6163) as compared to subjects in the non-cDGA group (1050.0 days [range 266 to 1814]). Consistent with this, subjects in the non-cDGA group were generally diagnosed with athymia later in life (median age at diagnosis of 365 days) as compared to subjects with cDGA (median age at diagnosis of 25 days). Non-cDGA subjects also generally lacked the phenotypic features commonly associated with cDGA including congenital heart anomalies (0 of 5 subjects) and hypocalcemia (2 of 5 subjects). Given the limited sample size of the non-cDGA group, the other baseline demographics were generally similar regardless of disease etiology.

The Kaplan-Meier estimated survival rates at Year 1 in the FAS were 76% (95% CI: 0.653, 0.832) and 100% (95% CI: 1.000, 1.000) for subjects diagnosed with cDGA and non-cDGA, respectively. No subjects in the non-cDGA group have died following treatment with RVT-802. The median naïve CD4 T cell counts were above 100 cells/mm<sup>3</sup> at Year 1 and Year 2 post-implantation regardless of disease etiology although the data were limited (Table 48). This threshold is considered sufficient to fight infection and supports the use of RVT-802 in patients regardless of their disease etiology.

**Table 48: Naïve CD4 Cell Count by Disease Etiology**  
(Applicant’s Table)

Subgroup		Baseline		Year 1		Year 2	
		n	Median	n	Median	n	Median
Disease Etiology	cDGA (N = 92)	63	1.000	40	266.475	26	246.160
	Non-cDGA (N = 5)	4	1.000	3	188.000	1	377.910

Similar to the flow cytometry data, subjects had normal responses to mitogens/antigens at Year 1 and Year 2 regardless of disease etiology. Evidence of thymopoiesis was also noted

on RVT-802 biopsy regardless of disease etiology. Notably, all 4 of the non-cDGA subjects who were biopsied demonstrated evidence of thymopoiesis. In general, given the differences in sample sizes between the two populations, there were no differences in AEs by disease etiology.

**Reviewer's comments:** These data support the granting of a broad label for congenital athymia. Due to the decision to issue a CR, there is no agreed upon labeling for this product.

#### **12.4 Recommendations on Postmarketing Actions**

Due to the issuing of a CR, post-marketing requirements or commitments are not relevant.