Enzyvant Therapeutics GmbH

STATISTICAL ANALYSIS PLAN

Program: RVT-802

Treatment: Allogeneic cultured post-natal thymus tissue for transplantation; RVT-802

Safety and Efficacy of Cultured, allogenic thymic tissue for transplantation as therapy for primary immune deficiency resulting from congenital athymia associated with complete DiGeorge Anomaly (cDGA) or forkhead box protein N1 (FOXN1) deficiency

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The Lead Statistician is signing below to confirm they have authored/reviewed and approved the Statistical Analysis Plan in accordance with the study protocol and CRF.

Approval Signature Print Name Date (dd mmm yyyy)	[redacted]

The Project Manager is signing below to confirm they have reviewed and approved the Statistical Analysis Plan in accordance with the study protocol and CRF.

Approval Signature Print Name Date (dd mmm yyyy)	[redacted]

☐ **Not applicable – No [redacted] PM assigned**

The Independent Statistician is signing below to confirm they have reviewed and approved the Statistical Analysis Plan in accordance with the study protocol and CRF.

Approval Signature Print Name Date (dd mmm yyyy)	[redacted]

The Sponsor Representative is signing below to confirm they have reviewed and approved the Statistical Analysis Plan in accordance with the study protocol, CRF, and any other study requirements.

Approval Signature Print Name Job Title Date (dd mmm yyyy)	[redacted]

[redacted]

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Contents

1 Abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BLA	Biologics License Application
BMTCTN	Blood and Marrow Transplant Clinical Trials Network
BP	Blood Pressure
BSA	Body Surface Area
cDGA	Complete DiGeorge Anomaly
CMV	Cytomegalovirus
CPM	Counts Per Minute
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DKL	Kullback-Leibler Divergence
EAS	Efficacy Analysis Set
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEN	Fractional Excretion of Sodium
GVHD	Graft Versus Host Disease
HCT	Hematopoietic Cell Transplant
HLA	Human Leukocyte Antigen
IND	Investigational New Drug
IV	Intravenous
kg	Kilogram
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	Minimum
ml	millilitre
MMF	Mycophenolate Mofetil
PHA	Phytohemagglutinin
PTH	Parathyroid Hormone

RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SCID	Severe Combined Immunodeficiency
SD	Standard Deviation
TCR	T Cell Receptor
TREC	T Cell Receptor Excision Circles
TREG	Regulatory T Cells
WBC	White Blood Cell Count

2 Introduction

This document presents the statistical analysis plan (SAP) for Enzyvant Therapeutics GmbH, RVT-802 Program: Safety and Efficacy of Thymus Transplantation in Complete DiGeorge Anomaly. Table 2.1 includes a summary of the core studies which will be used to support the BLA. Individual clinical study reports including available efficacy and safety data will be written for each protocol described in this table.

Table 2.1 Summary of Protocols to Support the BLA

Study	Primary Use	Total Transplanted	cDGA, no prior HCT	Non-cDGA or prior HCT cDGA	Analysis Population		Reporting
	A. CORE IND 9836 PROTOCOLS FOR BLA				**EAS**	**FAS**	
668-1[a]	Support BLA	14	14	0	14	14	CSR
668-2[a]	Support BLA	12	10	2	11	12	CSR
884[b]	Support BLA	12	10	2	11	12	CSR
931	Support BLA	5	5	0	5	5	CSR
932	Support BLA	7	6	1	6	7	CSR
950[c]	Support BLA	14	14	0	14	15	CSR
25966	Support BLA	24	24	0	24	24	CSR
	B. ADDITIONAL IND 9836 PROTOCOLS						
33170	Single patient protocol	1	0	1	0	1	Synoptic report, safety listing
51692	Non cDGA expanded access	2	0	2	0	2	Ongoing; interim synoptic report, safety listing
	C. Non-IND PROTOCOL						
735	Single patient protocol	1	0	1	0	1	Synoptic report, safety listing
	Total Transplanted	**93**	**83**	**10**			
	Total Efficacy Analysis Set				**85**		
	Total Full Analysis Set					**93**	

[a] Protocols 668-1 and 668-2 will be combined into a single CSR.
[b] Data from the single subject 884.1 study will be included in the overall 884 CSR.
[c] Data from the single subject 950.1 study will be included in the overall 950 CSR.

Study 668: Phase II Study of Thymus Transplantation in Complete DiGeorge Syndrome

This was a Phase II, single site, open, nonrandomized clinical protocol conducted at Duke University Medical Center. The principal investigator/sponsor was [redacted] All subjects were diagnosed as having complete DiGeorge syndrome, characterized by very low T cell

numbers (<50/cumm) or less than 50/cumm naive T cells (CD3+CD45RA+CD62L+) and a very low proliferative T cell function (<20 fold response to phytohemagglutinin (PHA) or less than 5,000 counts per minute (CPM), whichever was higher). Due to the constraints of available thymus tissue and other practical issues (such as small muscle size), subjects were not assigned to dose categories.

668-1: Enrollment was initiated in 1993 and ended in 2001. Study 668-1 was a descriptive study without specified endpoints.

668-2: Enrollment occurred between 2001-2005. Two primary efficacy endpoints included survival at one year post-transplant and T cell function at one year as measured by the T cell proliferative response to tetanus toxoid. Secondary efficacy parameters included the incidence of infections, autoimmune disease, and hospitalizations. Secondary laboratory efficacy parameters included numbers of CD3, CD4 and CD8 T cells, numbers of naive CD4 and naive CD8 T cells, proliferative T cell responses to mitogens and CD3, and TCR repertoire variability.

Both studies were combined in a single closeout report. Two subjects (SCD002 and DIG037) did not have cDGA (1 severe combined immunodeficiency [SCID] and 1 FoxN1) but were transplanted as enrollment exceptions and were not included in the primary endpoint evaluation. As per agreement with the FDA, the FoxN1 patient will be included in both the efficacy analysis set (EAS) and the full analysis set (FAS) whereas the SCID patient will only be included only in the full analysis set (FAS).

Study 884: Thymus Transplantation with Immunosuppression

This was a Phase I, single site, open, nonrandomized clinical protocol conducted at Duke University Medical Center. The principal investigator/sponsor was [redacted] Twelve patients were planned for treatment with thymus transplantation. There were two groups of patients with DiGeorge syndrome whose immune evaluations suggest that they would reject a thymus transplant if they were not given immunosuppression. 1) Atypical complete DiGeorge patients who have rash, lymphadenopathy and oligoclonal T cell proliferations and 2) Typical complete DiGeorge syndrome patients who have > 20 fold response to PHA.

The primary efficacy endpoint was survival at one year post-transplant. Secondary clinical efficacy parameters included numbers of CD3, CD4 and CD8 T cells, numbers of naive CD4 and naive CD8 T cells, proliferative T cell responses to mitogens, and TCR repertoire variability.

Study 931: Thymus and Parathyroid Transplantation for Complete DiGeorge Syndrome

This was a Phase I, single site, open, nonrandomized clinical protocol conducted at Duke University Medical Center. The principal investigator/sponsor was [redacted] This study was designed to evaluate parathyroid function after parathyroid allotransplantation into infants with complete DiGeorge syndrome. All subjects also underwent thymus transplantation with immunosuppression. Twelve total patients were planned for treatment with thymus

transplantation and immunosuppression with or without a parathyroid transplant. All patients had a diagnosis of typical or atypical complete DiGeorge syndrome, characterized by very low T cell numbers (<50/cumm) or less than 50/cumm naive T cells (CD3+CD45RA+CD62L+). Patients were also required to have hypoparathyroidism, which was defined as a requirement for calcium supplementation to maintain ionized calcium levels greater than 1.0 mmol/L. Typical complete DiGeorge syndrome patients did not have rash and lymphadenopathy associated with circulating oligoclonal T cells. Atypical complete DiGeorge syndrome patients were those who developed rash and lymphadenopathy associated with circulating oligoclonal T cells that include less than 50/cumm naive T cells or less than 5% of the total T cells being naive in phenotype, whichever is higher.

Both typical and atypical complete DiGeorge syndrome patients were enrolled and were treated with one of two different immunosuppression regimens depending on T cell phenotype and function. The two treatment groups consisted of:

1. The immunosuppression consisted of 3 doses of 2 mg/kg/day Thymoglobulin prior to transplantation. This was usually given on days -5, -4, and -3 followed by two days of rest and then the transplant. No post transplantation immunosuppression was used.

Or

2. Immunosuppression including 3 doses of 2 mg/kg/day Thymoglobulin prior to transplantation as described above. Cyclosporine was also started pretransplantation with trough levels of approximately 150-220 ng/ml. This was continued until the T cell count dropped below 100/cumm or until naive T cells were greater than 5% of total T cells or PHA responses increased to 3 fold over baseline (baseline was the mean of 2 consecutive studies). At this point the cyclosporine was weaned over 8 weeks.

The primary efficacy endpoint among subjects receiving a parathyroid transplant was whether or not calcium or calcitriol supplementation was required at 1 year post-transplant. Secondary efficacy analyses included survival at one year post transplant, ionized calcium values, numbers of CD3, CD4 and CD8 T cells, numbers of naive CD4 and naive CD8 T cells, proliferative T cell responses to mitogens and antigens, and TCR repertoire variability.

Study 932: Dose Study of Thymus Transplantation in DiGeorge Anomaly

This was a Phase II, single site, open, nonrandomized clinical protocol conducted at Duke University Medical Center. The principal investigator/sponsor was [redacted] This study was designed to correlate the dose of thymus tissue to immunologic parameters after thymus transplantation and to evaluate the efficacy of thymus transplantation via overall survival and T cell phenotypic and functional parameters. Up to 24 subjects were planned for thymus transplantation with no immunosuppression prior to transplantation. The subjects were entered into one of two arms, subjects would receive thymus only or would receive thymus plus parathyroid tissue. All subjects with profoundly low parathyroid function (parathyroid hormone

(PTH) <5 pg/ml when the ionized calcium is less than or equal to 1.1 mmol/L) were offered parental parathyroid transplantation; however, no subjects received a parathyroid transplant during this study. All subjects were diagnosed as having complete DiGeorge anomaly, characterized by very low T cell numbers (<50/cumm) or less than 50/cumm naive T cells (CD3+CD45RA+CD62L+) or naïve T cells being less than 5% of total T cells (whichever was higher) and very low proliferative T cell function (<20 fold response to phytohemagglutinin, PHA, or less than 5,000 counts per minute (CPM) (whichever was higher). Due to the constraints of available thymus tissue and other practical issues (such as small muscle size), subjects were not assigned to dose categories.

The primary endpoints for the evaluation of dose effect were PHA response, number of naïve T cells, and TCR repertoire variability at one year post transplant. Overall survival at one year post-transplant was also assessed. Applicable secondary efficacy analyses also included the total CD4 T cell number at 1 year, total naive CD4 cells at 1 year (regarding HLA-DR matching), total CD8 T cells, and total naive CD8 T cells at 1 year (for HLA class I matching).

Study 950: Phase I/II Trial of Thymus Transplantation with Immunosuppression

This was a Phase I/II, single site, open, nonrandomized clinical protocol conducted at Duke University Medical Center. The principal investigator/sponsor was [redacted]. Subjects were able to receive a thymus transplant or thymus/parathyroid transplant with immunosuppression prior to transplantation under this study protocol; however, no subjects received a parathyroid transplant. Subjects were enrolled into one of three treatment groups including the following:

1. Treatment group # 1: included subjects with typical complete DiGeorge anomaly who had a proliferative response to PHA of less than 50,000 cpm but over 5,000 cpm and over 20 fold over background. These subjects were given 3 doses of rabbit anti-thymocyte globulin IV of 2 mg/kg/day followed by thymus transplantation.
2. Treatment group # 2: included subjects with typical complete DiGeorge anomaly who had a proliferative response to PHA of over 50,000 cpm. It was also used for subjects with atypical complete DiGeorge anomaly who had a PHA response of less than 75,000 cpm (when not on immunosuppression) or a PHA response of less than 40,000 cpm when on immunosuppression. The subjects received three doses of rabbit antithymocyte globulin IV as above plus pre and post cyclosporine administration. Cyclosporine was started as soon as it is determined that the subject had athymia with rash and very low naive T cells. The cyclosporine was started at least seven days before transplantation. Pretransplantation steroid therapy was added if the T cell count was over 4,000/cumm.
3. Treatment group # 3 was used for subjects with atypical complete DiGeorge anomaly who had a proliferative response to PHA of over 75,000 when not on immunosuppression or PHA response of over 40,000 cpm despite pre-transplant treatment with immunosuppression. The subjects received 3 doses of 2 mg/kg rabbit antithymocyte

globulin IV, pre and post transplantation cyclosporine, and pre and post transplantation steroids. Daclizumab and mycophenolate mofetil MMF were added if subjects met T cell number and phenotype criteria after finishing rabbit anti-thymocyte globulin as descried in the study protocol.

All subjects were diagnosed as having complete DiGeorge anomaly, characterized by very low T cell numbers (<50/cumm) or less than 50/cumm naive T cells (CD3+CD45RA+CD62L+) or naïve T cells being less than 5% of total T cells.

The primary efficacy analysis was survival at one year post-transplant. Secondary efficacy parameters included numbers of CD3, CD4, CD8, naive CD4, and naive CD8 cells as well as proliferative T cell responses (cpm) to mitogens/antigens, and TCR repertoire variability by spectratyping reported as the Kullback-Leibler divergence (DKL score) at one year post transplant. An evaluation of thymus graft biopies for thymopoiesis, defined as the presence of lacy keratin with some thymocytes with a cortical phenotype (CD1a+ or Ki-67+) was also performed.

Study 25966: Safety and Efficacy of Thymus Transplantation in Complete DiGeorge Anomaly

This is an ongoing Phase I/II, single site, open, nonrandomized clinical protocol conducted at Duke University Medical Center. The principal investigator/sponsor is [redacted] Subjects will receive a postnatal cultured allogeneic thymus transplant with or without immunosuppression prior to transplantation. Subjects will be enrolled in one of four Groups. All subjects will have been diagnosed as having complete DiGeorge anomaly, characterized by very low T cell numbers (<50/mm^3) or less than 50/mm^3 naive T cells (CD3+CD45RA+CD62L+) or naïve T cells being less than 5% of total T cells.

The primary efficacy endpoint for this study will be survival at one year post-transplant. Additional efficacy endpoints will include naïve CD4 T cell counts at 12 months post-transplant and the following variables assessed at 6 and 12 months post-transplant: total CD3, total CD3+CD4+, total CD3+ CD8+, total naive CD3+ CD4+, total naive CD3+ CD8+, total TCR$\alpha\beta$ and TCR$\gamma\delta$ T cells, total B and NK cells. Proliferative T cell responses in counts per minute (cpm) to phytohemagglutinin and tetanus toxoid (if done) and TCR repertoire variability by flow cytometry of CD3+ CD4+ cells will also be assessed at one year post-transplant. If an allograft biopsy is performed, the following will be assessed at the time of biopsy: presence of thymopoiesis, presence of Hassall bodies, and presence of graft rejection.

Studies 735, 33170, and 51692:

Non-core IND 9836 protocols for BLA were also conducted and will contribute subjects to the FAS (Table 2.1). Synoptic study reports including available demographic, survival, and safety information (adverse events and serious adverse events) will be developed. All available data will be listed.

3 Objectives

The objectives of all studies was to investigate the safety and efficacy of thymus transplantation in complete DiGeorge Anomaly patients. Each study had slightly different objectives, but in general, the goal was to examine survival and immune system response at 1 year post transplantation. The studies all followed subjects through two years post-transplant, thus objectives will also be summarized at 2 years post-transplant.

3.1 Protocol Defined Endpoints

Each protocol defined its own primary and secondary endpoints. In general, the protocols overlapped significantly and are summarized in the table below.

Table 3.1.1 Summary of Protocol Defined Endpoints

	668	884	931	932	950	25966
Primary Endpoints						
Survival at year 1	x	x		x	x	x[a]
T cell proliferative response to tetanus toxoid at year 1	x					
Calcium or calcitriol supplement needed at year 1			x			
PHA response at year 1				x		
naïve CD4 T cells at year 1				x		
naïve CD8 T cells at year 1				x		
TCR repertoire variability at year 1				x		
Secondary Endpoints (at year 1 unless otherwise specified)						
T cell proliferative response to tetanus toxoid at year 1		x		x		x
Survival at year 1			x			
Anti-tetanus toxoid antibody				x		
Incidence of infections	x				x	
Incidence of autoimmune disease	x					
Incidence of hospitalization	x					
CD3 T cells	x	x	x		x	6 and 12 months
CD4 T cells	x	x	x	x	x	
CD8 T cells	x	x	x	x	x	

	668	884	931	932	950	25966
naïve CD4 T cells	x	x	x		x	x
naïve CD8 T cells	x	x	x		x	
Total TCRαβ T cells						6 and 12 months
Total TCRγδ T cells						6 and 12 months
Total B cells						6 and 12 months
Total NK cells						6 and 12 months
Proliferative T cell responses to mitogens	x	x	x		x	
Proliferative T cell responses to CD3 T cells	x					
Proliferative T cell responses to antigens		x	x		x	
Proliferative T cell responses to phytohemagglutinin						x
TCR repertoire variability	x	x	x		x	x
Calcium or calcitriol supplement needed			Parathyroid Recipients	Parathyroid Recipients	Parathyroid Recipients	
Biopsy Results					x	x
Grade 3 and 4 AEs					x	
Grade 3 and 4 toxicities of surgery or immunosuppressive medications					x	
Use of immunosuppression as part of transplant					x	
PHA response at year 1					x	
TREC		x	x	x	x	x

[a] Survival at year 1 will be calculated for all subjects, for all cDGA subjects with CMV infection, and all subjects without CMV infection.

See the individual IND protocols for greater detail and explanation of the endpoints measured.

3.2 Efficacy Endpoints to be Analyzed

In order to aid in cross study comparisons and total project analyses, the consistency of the endpoints has been highlighted and will be analyzed across studies. The list of endpoints included for analysis in this SAP are given in the table below.

Table 3.2.1 Summary of Efficacy Endpoints Analyzed

	668	884	931	932	950	25966
Primary Endpoints						
Survival at year 1	x	x	x	x	x	x
Survival at year 2	x	x	x	x	x	x
Secondary Endpoints (at year 1 unless otherwise specified)						
CD3 T cells	x	x	x	x	x	6 and 12 months
CD4 T cells	x	x	x	x	x	6 and 12 months
CD8 T cells	x	x	x	x	x	6 and 12 months
naïve CD4 T cells	x	x	x	x	x	6 and 12 months
naïve CD8 T cells	x	x	x	x	x	6 and 12 months
Total TCRαβ T cells						6 and 12 months
Total TCRγδ T cells						6 and 12 months
Total B cells						6 and 12 months
Total NK cells						6 and 12 months
Calcium or calcitriol supplement needed at one year			x	*	*	
Proliferative T cell responses to phytohemagglutinin (PHA)				x	x	x
Proliferative T cell responses to mitogens. These include PHA, ConA, Sol CD3, Insol CD3, TT, and Candida.	x	x	x		x	
Anti-tetanus toxoid antibody				x		
TCR repertoire variability	x	x	x	x	x	x
TREC/TREG#		x	x	x	x	x
Biopsy of Transplanted Thymus	x	x	x	x	x	x

*No patients received parathyroid transplantation in this study, hence the calcium or calcitriol supplements will not be summarized.

#Summaries of TREC/TREG will only be done for studies where data is present in the database.

The above table is a guideline for endpoints to be analyzed. If any of the above endpoints have data for a particular study, then it will be summarized and listed.

The endpoints from Section 2.1 about use of immunosuppression will be summarized separately and are discussed in Section 3.4, which deals with concomitant medications.

The endpoints from Section 2.1 related to grade 3 or 4 adverse events or toxicities will be summarized as part of the safety analysis.

3.3 Primary Hypotheses

Each study had a different primary hypothesis or hypotheses (or none). These are summarized in the table below, along with the pre-specified analysis model.

For simplicity and consistency, the only hypotheses that will be tested is if survival at year 1 and if survival at year 2 is > 50% using the binomial exact test. For Protocol 931, the binomial exact test will examine whether < 30% of survivors at year 1 required calcium or calcitriol supplementation (for subjects receiving parathyroid transplant). Additional hypotheses will be tested at the project level and discussed in the Integrated Summary of Safety or Integrated Summary of Effectiveness, as appropriate.

Table 3.3.1 Summary of Protocol Defined Hypotheses

Primary Alternative Hypothesis	668	884	931	932	950	25966
Survival at year 1 is > 50%	Fisher Exact					Fisher Exact
> 60% of survivors at year 1 have a proliferative response to tetanus toxoid of > 10 fold	Fisher Exact					
< 30% of survivors at year 1 require calcium or calcitriol supplements (for subjects receiving parathyroid transplant)			Fisher Exact			
To determine if there is an effect of dose on immune outcome at year 1.				Regression		
> 50% of subjects have >100 naïve CD4 T cells at year 1						Fisher Exact

3.4 Safety Endpoints

Safety assessments including adverse events (AEs), serious adverse events (SAEs), clinical laboratories, physical examinations, and vital signs were performed for at least two years in all studies. A summary of planned safety endpoints for analysis by study is included in Table 3.4.1 below.

Table 3.4.1 Overall Summary of Safety Assessments

Safety Endpoints	668	884	931	932	950	25966	735	33170	51692
Vital Signs	X	X	X	X	X	X			
Adverse Events / Serious Adverse Events	X	X	X	X	X	X	X	X	X
Infection-Related Adverse Events	X	X	X	X	X	X	X	X	X
Adverse Events of Special Interest (Protocol Defined)	X	X	X	X	X	X	X	X	X
Medical History	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X			
Liver Function Studies	X	X	X	X	X	X			
Thyroid Studies	X	X	X	X	X	X			
Hematology	X	X	X	X	X	X			
FEN	X	X	X	X	X	X			

Non-infection-related AEs and SAEs were graded (Grades 1-5) according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). CTCAE version 3.0 was used for studies 668-1/2, 884/884.1, 931, 932, 950/950.1, 25966, 735, and 33170. CTCAE version 4.0 was used for Study 51692. The severity all AEs will be used as collected, thus for the analysis of AEs of Grade ≥ 3 will be based on the CTCAE version used in the respective protocol. Additionally, a table of AEs related to study treatment with Grade ≥ 3 will also be generated.

Infection-related AEs were evaluated using criteria defined in the Blood and Marrow Transplant Clinical Trials Network (BMTCTN) definitions of infection severity. Infection-related AEs with BMTCTN severity $\geq$ severe will be included in the analysis of AEs of Grade ≥ 3.

Expected AEs were defined in each study protocol and included rash, cytopenia, autoimmune disease, GVHD, pulmonary inflammation (early after transplantation), hypocalcemia, fever, infection, cancer, granuloma, wound dehiscence, infection, and inflammation.

Clinical laboratory assessments included hematology, clinical chemistry, and liver function assessments. In particular, hematology assessments included hemoglobulin, hematocrit, white blood cell count (WBC), red blood cell count (RBC), platelets, and differentials. Clinical chemistries included the measurement of sodium, potassium, chloride, bicarbonate, glucose, BUN, and creatinine. Liver function studies included AST and ALT. Additional safety laboratories were performed as clinically indicated.

Full clinical study reports will be written for studies 668-1/2 (the 2 subparts of this study will be combined into a single CSR), 884/884.1, 931, 932, 950/950.1, and 25966. These reports will include listings of all available safety data and summary tables of all available safety data through 2-years post-transplant. Synoptic study reports will be written for Studies 735, 33170, and 51692. These synoptic reports will include available patient disposition/vital status data as well as all reported AEs, SAEs, infection-related AEs, and hospitalizations.

Additional study specific safety analyses are described by study below, as applicable.

Study 931: Thymus and Parathyroid Transplantation for Complete DiGeorge Syndrome
Study 931 was the only study during which subjects received both a thymus and a parathyroid transplant. Safety analyses from this study will include those described in Table 3.4.1 as well as the following:

- Summary of ionized calcium levels through 2 years post-transplant (Endocrine Panel)
- Summary of parathyroid hormone (PTH) levels through 2 years post-transplant (Endocrine Panel)
- Number subjects requiring calcium supplementation at one-year post-transplant

Study 950: Phase I/II Trial of Thymus Transplantation with Immunosuppression
Study 950 included the safety assessments described in Table 3.4.1.

Since no subjects received a parathyroid transplant under the 950 protocol, the number of subjects requiring calcium supplementation at one-year post-transplant will not be reported.

4 Study Design

4.1 Discussion of Study Design

Refer to Section 1: Introduction for a description of the core IND 9836 study designs.

4.2 Study Treatment

The study treatment is thymus transplantation using allogeneic cultured postnatal tissue from unrelated donors under the age of 9 months (RVT-802). The tissue is sectioned upon harvest. Tissue slices are held in a tissue culture incubator with daily feeding for 12 to 21 days. After 2 to 3 weeks, the slices are brought to the operating room and inserted into the recipient's quadriceps muscles. Usually both quadriceps are used.

As specified in the individual study protocols, the dose planned for transplantation was the number of grams of transplanted tissue divided by the weight of the infant in kilograms or per square meter of BSA of the infant. In 2015, the IND was updated to define a dose range using the surface area of thymus tissue transplanted per recipient body surface area (IND 009836 Amendment Serial Number 209). Based on the 2015 IND amendment, to ensure consistency across study protocols, dosing will be reported in mm^2/m^2 for all studies.

Over the course of the clinical development program, there have been two thymus tissue manufacturing sites: Dr. Markert's Laboratory (DML) and the Good Manufacturing Process (GMP) Manufacturing Facility. Subjects transplanted under Protocols 668-1, 668-2, 884,

884.1, 931, 932, 950, 950.1, 735, and 33170 received RVT-802 manufactured by DML. Subjects transplanted under Protocols 25966 or 51692 could have received RVT-802 manufactured by either DML or GMP depending on the timing of transplantation.

For RVT-802 manufactured by DML, 4-6 thymus tissue slices were cultured on each plate. For each slice the millimeter dimensions were provided. The length (mm) by width (mm) surface area was calculated for each slice. If all of the thymus slices on a plate were not transplanted, e.g., 3 of 4 slices were used, then the dose received from that plate would be 75% of the plate dose. If it was unknown how many slices on a plate were transplanted, 50% of the plate dose was used. The total dose transplanted (mm^2/m^2) was the sum of the thymus tissue surface area (mm^2) divided by the recipient BSA (m^2) for each thymus slice transplanted.

For RVT-802 manufactured by GMP, the millimeter dimensions for each slice were not provided; only the number of slices transplanted and the total dose transplanted (mm2/m2) was supplied.

4.3 Study Schedule

Visit schedules vary among the seven core IND 9836 studies. Refer to the individual protocols for schematics of visit schedule.

4.4 Concomitant Medication

Immunosuppressive therapies and calcium/calcitriol (parathyroid recipients ONLY – Study 931) required per protocol will be summarized. Refer to the study protocols for specific details regarding protocol prescribed immunosuppressive therapy.

4.5 Study Analysis Populations

There are three analysis populations defined for these studies: the efficacy analysis set (EAS), modified efficacy analysis set (EAS-cDGA), and the full analysis set (FAS). Definitions for these populations are provided below.

4.5.1 Efficacy analysis set (EAS)

The efficacy analysis set includes all subjects with athymia associated with complete DiGeorge anomaly or FoxN1 deficiency, who had no prior hematopoietic cell transplant (HCT) and were treated with RVT-802 allogeneic, cultured postnatal thymus tissue administered once by transplantation. Across the seven IND 9836 protocols, a total of 85 subjects are included in the EAS.

4.5.2 Modified efficacy analysis set (EAS-cDGA)

The modified efficacy analysis set includes all subjects in the EAS but excludes subjects without complete DiGeorge anomaly. Across the seven IND 9836 protocols, a total of 83 subjects are included in the EAS-cDGA.

4.5.3 Full analysis set (FAS)

The full analysis set is comprised of all patients receiving a thymus transplant in one of the IND 9836 protocols. Specifically, this is all subjects in the EAS plus infants with primary immunodeficiency associated with severe combined immunodeficiency (SCID) [n= 2], infants with cDGA that had received prior HCT [n= 4], and one patient that had received a prior fetal thymus transplant. Across the seven core IND 9836 protocols and three additional IND 9836 protocols (two single patient protocols and one expanded access protocol) a total of 93 subjects are included in the FAS.

4.6 Withdrawn Subjects

Handling of prematurely withdrawn subjects was not pre-specified in any of the protocols covered in this SAP.

4.7 Randomisation

Not applicable. All studies were open label, uncontrolled, non-randomized studies.

4.8 Blinding

None of the protocols covered in this SAP were blinded: all subjects received the investigational medicinal product. Accordingly, the Investigator, study site personnel, representatives of the Sponsor and CRO were unblinded to study treatment.

4.9 Sample Size

Refer to Appendix 1 for individual study sample sizes.

5 Statistical Methodology

5.1 Planned Analyses

There are three analysis populations defined for these studies: the efficacy analysis set (EAS), modified efficacy analysis set (EAS-cDGA), and the full analysis set (FAS), which are defined in Section 3.5. Efficacy analyses will be carried out using the EAS and EAS-cDGA. The demographic and safety analysis will be carried out on the FAS.

Summary statistics will be presented for continuous variables, by way of n, mean, standard deviation (SD), median, quartiles, and ranges and by way of frequencies and percentages for categorical variables.

Survival will be evaluated one year and two years post-transplant.

All statistical analyses will be performed in SAS version 9.4 or later running on a validated platform.

5.2 Interim Analysis

Two protocols covered in this SAP are ongoing: protocols 25966 and 51692. An interim analysis of available data from subjects transplanted as of 15-JUL-2017 will be performed. As all studies are unblinded, this interim analysis poses no risk to the integrity of the ongoing protocol.

5.3 Visit Windows

Only data through two years post-transplant will be collected in the database, except survival, adverse events, and immunizations which were collected longer than two years. All CSR summaries will only go out until the two-year time point; the integrated summary of efficacy will explore long term survival (more than two years).

5.3.1 Efficacy Analysis Visit Windows

The efficacy endpoints in Section 2.2 were generally specified at year 1. In summary tables, both the year 1 and year 2 time points will be summarized, as applicable, and all data collected will be listed. Non-survival related efficacy data will be assigned visits using the rules assigned in the table below. In the case that there are multiple visits within the analysis window, then the visit closest to the target date will be used for analysis; if two visits are equidistant from the target date, then the later visit will be used.

In efficacy tables, if a subject has not yet reached the Year 1 or Year 2 visit, then that subject will not be included in the table summaries.

Table 5.3.1.1 Efficacy Analysis Windows

Visit Name	Target Day Post-Transplant	Window
Month 6	182	[137, 227]
Year 1	365	[305, 425]
Year 2	731	[671, 791]

5.3.2 Safety Analysis Visit Windows

The safety endpoints in Section 2.4 were generally collected while at the hospital following transplantation. Further safety assessments were scheduled at months 3, 6, 9, 12, 18, and 24. Table summaries will only include the time points in the table below, and all data collected in the database will be listed. Data will be assigned visits using the rules assigned in the table below, where Day 0 is the day of transplant. In the case that there are multiple visits within the analysis window, then the visit closest to the target date will be used for analysis; if two visits are equidistant from the target date, then the later visit will be used.

Table 5.3.2.1 Safety Analysis Windows

Visit Name	Target Day Post-Transplant	Window
Pre-Transplant	n/a	[- ∞, -1]
Week 1	7	[1, 10]
Week 2	14	[11, 17]
Week 3	21	[18, 24]
Week 4	28	[25, 31]
Week 8	56	[49, 63]
Month 3	90	[65, 120]
Month 6	182	[152, 212]
Month 9	273	[243, 303]
Month 12	365	[335, 395]

Month 18	548	[488, 608]
Month 24	731	[671, 791]

5.4 Disposition of Subjects

The number of subjects receiving study treatment, in each analysis population, status (ongoing, died, withdrew) and the reasons for any premature discontinuation from the study (most commonly death) will be summarized and listed. Premature discontinuation from the study was defined as study discontinuation within two years after transplantation.

5.5 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarised for each protocol. This will include age on day of transplantation (in days), sex, race, ethnicity, height, weight, BSA, and relevant medical history. Baseline is defined as the last value obtained prior to thymus transplantation. For subjects who received RATGAM prior to the transplantation, baseline for flow cytometry, proliferation, and PHA values will be defined as the last value obtained prior to the initiation of the first dose of RATGAM. If multiple values are recorded on the same day, the average of all measurements taken on that day will be used as the baseline value.

Notes:

- BSA will be calculated using Haycock's formula:
  - BSA (m^2) = 0.024265 x (weight[kg])$^{0.5378}$ x (height[cm])$^{0.3964}$
- Medical history will be coded according to MedDRA version 19.1.
- Relevant medical histories are all medical histories recorded in the CRF.
- Any duration [days] = end day – onset day + 1

5.6 Concomitant Medication

Medically needed therapies to treat the subject are allowed; however, per protocol this information will not be databased or summarized. Protocol required immunosuppressive therapies and calcium/calcitriol supplementation (parathyroid transplant recipients only) will be summarized and listed.

5.7 Efficacy / Primary and Secondary Analysis

5.7.1 Method of analysis for primary endpoints

Because the profound immune deficiency of athymia leads to death from infection usually before the age of 2 years, survival was the primary endpoint of the clinical studies. The Kaplan-Meier

estimates of survival at Year 1 and Year 2 will be presented with number at risk, number with events, and estimated survival probability. The Kaplan-Meier survival tables (Table 14.2.1.2.1 and Table 14.2.1.2.14) and the associated figures (Figure 14.2.1.2.1 and Figure 14.2.1.2.14) will be limited to a five-year duration.

5.7.2 Methods of analysis for secondary outcomes

Immune outcomes and dose effect are assessed after thymus transplantation by examining biopsies of the allografts by immunohistochemistry; flow cytometry; assessing variability of the T cell receptor beta gene variable (TCRβV) region; assessing T cell proliferative responses and measuring B cell antibody responses to antigens. Descriptive summaries will be provided at Year 1, and if available at Year 2.

5.8 Safety Analysis

Safety assessments were gathered for at least two years in all studies. Summaries of safety events will include events happening within two years of transplantation. All reported events, regardless of time of onset, will be included in the listings.

5.8.1 Adverse events

Adverse events and serious adverse events will be summarised 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 and preferred term, having each individual event and the severity, relationship and outcome of each event. Number of events is also presented. Missing severity, relationship or outcome will be classed as unknown.

A subject with more than one occurrence of the same adverse event in a particular system organ class will be counted only once in the total of those experiencing adverse events in that particular system organ class. If a subject experiences the same adverse event 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 will be given precedence. Any missing severity, causality, or outcome will not be imputed and classed as unknown.

Summaries classifying both events according to severity and relationship will be presented.

Related events are defined as events that are 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 Common Terminology Criteria for Adverse Events (CTCAE). CTCAE version 3.0 was used for studies 668-1/2, 884/884.1, 931, 932, 950/950.1, 25966, 735, and 33170. CTCAE version 4.0 was used for Study 51692. The severity AEs will be used as collected, thus for the analysis of AEs of Grade ≥ 3 will be based on the CTCAE version used in the respective protocol.

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 ≥ severe will be included in the analysis of AEs of Grade ≥ 3. For the purposes of summarization, all AEs including infection related AEs will be included in AE summary tables unless otherwise specified.

5.8.1.1 Subsets

- Adverse events will be presented by system organ class and preferred term
- Serious adverse events will be presented by system organ class and preferred term
  - Related serious adverse events will be presented by system organ class and preferred term.
- Deaths will be listed

All other information collected (e.g., action taken) will be listed as appropriate.

All adverse events will be included in the adverse and serious adverse event summaries.

Notes:

- Tables presented will contain both counts of subjects and events. Subjects who have multiple events in the same system organ class and preferred term will be counted only once in the subject counts.
- AEs coded using MedDRA version 19.1.

5.8.1.2 Adverse events of special interest

Adverse events of special interest (AESI) will be summarized by system organ class and preferred term, and will include infection-related AEs, cancers, autoimmune diseases, GVHD, rashes, and granulomas.

5.8.2 Safety and Efficacy Laboratory findings

Results from the following laboratory parameters (5.8.2.1 and 5.8.2.2) will be summarised using the value at each visit and change from baseline at each visit.

Categorical and numeric variables will be presented separately.

Clinically significant treatment-emergent laboratory findings will be summarised as adverse events.

Notes:

- All results outside predefined normal ranges will be flagged in the data listings.

- Repeat laboratory results within a visit will not be used in any summary calculations. Unscheduled (those obtained outside of the safety analysis windows defined in Section 4.3.2) and repeat results will be listed only.
- Any other laboratory results will be listed only.

5.8.2.1 Clinical Safety Laboratories

Hematology:

Hemoglobin, Hematocrit, Platelet Count, RBC, WBC, Neutrophils, Bands, Lymphocytes, Monocytes, Eosinophils, Basophils, Atypical Lymphocytes, and other Myelocytes.

Endocrine:

Calcium, Ionized Calcium, Magnesium, Phosphorus, Urine Calcium, Urine Creatinine, Ratio, T4, Free T4, TSH, iPTH, Anti-TGB, and Anti-TPO.

FEN:

Sodium, Potassium, Chloride, CO_2 (Bicarbonate), Glucose, BUN, and Creatinine.

Liver Function:

AST, ALT, Alkaline Phosphatase, Bilirubin, LDH, Lipase, Amylase, Albumin, Total Protein, GGT, and Triglycerides.

5.8.2.2 Clinical Efficacy Laboratories

Serum Immunoglobulins and Isohemagglutinins:

IgG, IgA, IgM, IgG, Anti-A, and Anti-B.

Flow Cytometry:

Percentage of ALC, CD3, CD4, CD8, DB Neg, TCRαβ, TCRγδ, B, NK, Naïve CD3, Naïve CD4, and Naïve CD8 cells.

Number of ALC, CD3, CD4, CD8, DB Neg, TCRαβ, TCRγδ, B, NK, Naïve CD3, Naïve CD4, and Naïve CD8 cells.

TCR Flow:

VB1, VB2, VB3, VB4, VB5.1, VB5.2, VB5.3, VB7.1, VB7.2, VB7, VB8, Vb8.1/8.2, Vb9, VB11, VB12, VB13.1, VB13.2, VB13.6, VB14, VB16, VB17, VB18, Vb20, VB21.3, VB22, and VB23.

Proliferation Assay:

PT CONA, PT CONA BKG, CONTROL CONA, CONTROL CONA BKG, PT SOL CD3, PT SOL CD3 BKG, PT INSOL CD3 PT INSOL BKG, PT IMMOB CD3, PT IMMOB CD3 BKG, CONTROL SOL CD3, CONTROL SOL CD3 BKG CONTROL IMMOB CD3, CONTROL

IMMOB CD3 BKG, PT TT, PT TT BKG (PT AG BKG), CONTROL TT, CONTROL TT BKG (CTRL AG BKG), PT CANDIDA, PT CANDIDA BKG, CONTROL CANDIDA, and CONTROL CANDIDA BKG.

5.8.3 Vital signs

A summary of vital signs for observed value and change from baseline over time will be produced using the safety analysis windows given in Table 5.3.2.1. All data will be listed.

5.9 Adjustment for Covariates

No covariates will be included in the analyses.

5.10 Missing Values – Missing Visits

No imputation of missing data will be done.

5.11 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 ...varn;
    BY byvar; (optional)
    OUTPUT OUT=outname
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that present the binomial proportion test:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1 / BINOMIAL (P=0.XX);
    EXACT BINOMIAL;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that present Fisher's Exact or CMH:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
```

*TABLES var1*var2 / CMH score=MODRIDIT EXACT;*
OUTPUT OUT=outname CMH EXACT;
RUN;

- **Tables that need number of events/censored and probabilities of failure/survival at cut off times:**

PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM INTERVALS=12, 24;
*TIME duration*censor (0 or 1);*
ID subject;
STRATA treatment;
RUN;

6 Tables and Listings

6.1 Table Format

All output will be produced using SAS version 9.4 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number*, programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left. The *database lock date or data snapshot date* will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and listings is proposed using *Times New Roman* font. A maximum SAS line size=141 and page size=44 for *8-point* font size will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number and/or visit name) must be presented at the beginning of that page.

6.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted group, subject and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

6.3 Tables

Not all tables will be created for all studies. The list below will be adapted based on what is available and required in each study. For example, the calcium or calcitrol use at year 1 was only collected and required in study 931.

6.3.1 Section 14.1: Disposition, Exposure, and Demographics

The tables below will be created using the EAS-cDGA, EAS, and FAS.

Table 14.1.2	Subject Disposition
Table 14.1.3	Analysis Populations
Table 14.1.4.1	Demographics and Selected Baseline Characteristics
Table 14.1.4.2	Disease History
Table 14.1.5	Thymus Transplant and Dose Information
Table 14.1.6.1	Medical History
Table 14.1.6.2	Pre-Transplant Infection History
Table 14.1.7.1	Immunosuppressive Medications

6.3.2 Section 14.2: Efficacy

The tables below will be created using the EAS-cDGA, EAS, and FAS.

Table 14.2.1.1.1	Summary of Kaplan-Meier Survival
Table 14.2.1.1.14	Summary of Kaplan-Meier Survival (Day of Life)
Table 14.2.1.2.1	Kaplan-Meier Survival by Year
Table 14.2.1.2.14	Kaplan-Meier Survival by Year (Day of Life)
Table 14.2.1.3.1	Binomial Exact Test of Survival at Year 1 Post-Transplantation
Table 14.2.1.3.2	Binomial Exact Test of Calcium Use at Year 1 Post-Transplantation*
Table 14.2.1.3.14	Binomial Exact Test of Survival at Year 2 Post-Transplantation
Table 14.2.2.1.1	T Cell Count - Flow Cytometry
Table 14.2.2.2.1	Biopsy
Table 14.2.2.3.1	T Cell Proliferation
Table 14.2.2.4.1	Immunoglobulins
Table 14.2.2.5.1	B Cell Function Elevation
Table 14.2.2.6.1	TRECs
Table 14.2.2.7.1	TREGs
Table 14.2.2.8.1	T Cell Receptor Diversity (Immunoscope / Spectratyping)
Table 14.2.2.9.1	Subject Infection
Table 14.2.2.10.1	T Cell Receptor Diversity (TCR Flow)

*only applies to Study 931.

6.3.3 Section 14.3: Safety

The tables below will be created using the EAS-cDGA, EAS, and FAS.

6.3.3.1 Adverse events

Table 14.3.1.1	Summary of Adverse Events (within 2 Years of Transplantation)
Table 14.3.1.2.1	Adverse Events by System Organ Class and Preferred Term (within 2 Years of Transplantation)
Table 14.3.1.3.1	Adverse Events by Preferred Term in Decreasing Order of Frequency (within 2 Years of Transplantation)
Table 14.3.1.4.1	Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (within 2 Years of Transplantation)
Table 14.3.1.4.2	Adverse Events by System Organ Class, Preferred Term, and Severity (within 2 Years of Transplantation)
Table 14.3.1.5	Grade $\geq$ 3 AEs using either CTCAE or BMTCTN by System Organ Class and Preferred Term (within 2 Years of Transplantation)
Table 14.3.1.6	Treatment Related Grade $\geq$ 3 AEs using either CTCAE or BMTCTN by System Organ Class and Preferred Term (within 2 Years of Transplantation)
Table 14.3.1.7.1	Serious Adverse Events by System Organ Class and Preferred Term (within 2 Years of Transplantation)

Table 14.3.1.8	Adverse Events Related to Treatment by System Organ Class and Preferred Term (within 2 Years of Transplantation)
Table 14.3.1.9	Infection Related Adverse Events by System Organ Class and Preferred Term (within 2 Years of Transplantation)
Table 14.3.1.9.2	Infection Related Adverse Events by System Organ Class and Preferred Term (within 1 Year of Transplantation)
Table 14.3.1.10	Other Adverse Events of Special Interest by System Organ Class and Preferred Term (within 2 Years of Transplantation)
Table 14.3.1.10.2	Other Adverse Events of Special Interest by System Organ Class and Preferred Term by Protocol(Within 1 Year of Transplantation)
Table 14.3.1.12	Serious Adverse Events Related to Treatment by System Organ Class and Preferred Term (within 2 Years of Transplantation)

6.3.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 14.3.2.1	Listing of Deaths
Table 14.3.2.2	Listing of Serious AEs (within 2 Years of Transplantation)
Table 14.3.2.3	Listing of Treatment Related Serious AEs (within 2 Years of Transplantation)

6.3.3.3 Vital Signs

Table 14.3.3.1	Vital Signs Over Time

6.3.3.4 Laboratory results

The tables below will be created using the EAS-cDGA, EAS, and FAS.

Table 14.3.5.1	Summary of Hematology
Table 14.3.5.2	Summary of Endocrinology
Table 14.3.5.3	Summary of FEN
Table 14.3.5.4	Summary of Liver Function Studies

6.4 Listings

Listing 16.2.1	Patient Disposition
Listing 16.2.1.4	Patient Eligibility
Listing 16.2.4.1	Demographics
Listing 16.2.4.2	Medical History
Listing 16.2.4.3	Disease History
Listing 16.2.4.4	Pre-Transplant Infection History
Listing 16.2.5.1	Parathyroid Donor Information and Lab Data *
Listing 16.2.5.2	Transplant and Dose Information
Listing 16.2.5.3	Summary of Transplant and Dose Information
Listing 16.2.6.1	Vital Status

Listing 16.2.7.1	Adverse events, including reported and coded terms
Listing 16.2.7.2	Infection related adverse events
Listing 16.2.8.1	Immunoscope/Spectratyping
Listing 16.2.8.2	TRECs
Listing 16.2.8.3	TREGs
Listing 16.2.8.4	Hematology
Listing 16.2.8.5	Flow Cytometry
Listing 16.2.8.6	PHA
Listing 16.2.8.7	Proliferation
Listing 16.2.8.8	Chimerism (Genetics)
Listing 16.2.8.9	Serum Immunoglobulins and Isohemagglutinins
Listing 16.2.8.10	Antigens/Titers
Listing 16.2.8.11	TCR Flow
Listing 16.2.8.12	Endocrinology
Listing 16.2.8.13	Fluids, Electrolytes, Nutrition (FEN)
Listing 16.2.8.14	Liver Function Studies
Listing 16.2.8.15	HLA Typing/Antibodies
Listing 16.2.8.16	Thymus Biopsy
Listing 16.2.8.17	CMV Testing
Listing 16.2.8.18	EBV Testing
Listing 16.2.8.19	Skin Biopsy
Listing 16.2.9.1	Vital Signs
Listing 16.2.9.3	Immunizations
Listing 16.2.10.1	Immunosuppressive Medications
Listing 16.2.10.2	Calcium Use *
Listing 16.2.11.1	Deaths

*only applies to Study 931.

6.5 Figures

Figure 14.2.1.2.1	Kaplan-Meier Survival by Year
Figure 14.2.1.2.14	Kaplan-Meier Survival by Year (Day of Life)

6.6 Appendices

Appendix 1	RVT-802 Program

6.7 References

Markert ML, Devlin BH, McCarthy EA. Thymus Transplantation. Clin Immunol. 135:236-246, 2010.

7 Appendix 1: List of Protocols Planned for Inclusion in BLA Submission

Study	Primary Objective	Subjects
668-1	To assess combination of thymus tissue plus either BM or cord blood derived stem cell transplant	Typical cDGA (3 atypical cDGA received immune suppression under treatment plans)
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 immune suppression; however, 2 atypical cDGA received immunosuppression under treatment plans
884	To assess safety, tolerability, and efficacy of thymus transplant with immunosuppression	Typical cDGA with but elevated T cell function (PHA responses 20-fold over background) and atypical cDGA with immune suppression
884.1	To assess the safety of thymus transplantation administered with a modified immunosuppressive regimen in a single subject with pre-existing GVHD and CMV	Atypical cDGA subject with pre-existing GVHD and CMV
931	To assess thymus tissue and parental parathyroid transplantation	Typical and atypical cDGA with hypoparathyroidism
932	To evaluate correlations between dose of thymus tissue transplanted and immunological outcomes after transplant	Typical and atypical with immune suppression
950	Thymus transplantation with immune-suppression tailored to patient immune status	3 groups of typical or atypical cDGA with varying PHA responses pre-transplantation
950.1	Single patient protocol to determine if naïve T cells develop in non-cDGA patient who had 2 previous HCT	non-cDGA
25966	Thymus transplantation with immunosuppression regimens tailored to patient immune status as in 932 and 950	4 groups based on immune status and peri-transplantation immune suppression regimen
735	Thymic transplantation in partial DiGeorge syndrome	Partial DiGeorge syndrome
33170	Rescue thymus transplant in single cDGA subject who received sibling PBMC and had EBV-lymphoma	EBV lymphoma and cDGA
51692	Expanded access use in other conditions (hematologic malignancy, immunodeficiency, severe autoimmune disease related to poor thymic function; prior HCT)	Varied