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Summary Basis for Regulatory Action

Date:	**October 8, 2021**
From:	Tom Finn, PhD, Review Committee Chair, Office of Tissues and Advanced Therapies, Division of Cellular and Gene Therapies
BLA STN:	**125685/0**
Applicant:	**Enzyvant Therapeutics GmbH**
Submission Receipt Date:	**Original submission: April 5, 2019** **Resubmission: April 9, 2021**
PDUFA* **Action Due Date:**	**October 8, 2021**
Proper Name:	**allogeneic processed thymus tissue-agdc**
Proprietary Name:	**RETHYMIC**
Indication:	**For immune reconstitution in pediatric patients with congenital athymia**

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Tissues and Advanced Therapies

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Tom Finn, PhD (OTAT/DCGT) Irina Tiper, PhD (OTAT/DCGT) Alyssa Kitchel, PhD (OTAT/DCGT) Sukhanya Jayachandra, PhD (OTAT/DCGT) Safa Karandish, PhD (OTAT/DHT) Ekaterina Allen, PhD (OCBQ/DMPQ) Lily Koo, PhD (OCBQ/DMPQ) Randa Melhem, PhD (OCBQ/DMPQ) Marie Anderson, PhD (OCBQ/DBSQC) Simleen Kaur (OCBQ/DBSQC)
Clinical • Clinical (Product Office) • Postmarketing safety epidemiological review (OBE/DE) • BIMO (OCBQ/DIS/BIMO)	Gumei Liu, MD, PhD (OTAT/DCEPT) Winson Tang, MD (OTAT/DCEPT) Melanie Blank, MD (OTAT/DCEPT) Alisha Thomas, MD, MPH OBE/DE Malcolm Nasirah, PharmD, (OCBQ/DIS/BIMO)
Statistical • Clinical data (OBE/DB)	Jiang Hu, PhD (OBE/DB)
Non-clinical/Pharmacology/Toxicology • Pharmacology and Toxicology (OTAT)	Wei Liang, PhD; OTAT
Clinical Pharmacology	Not applicable
Labeling • Promotional (OCBQ/DCM APLB) • Labeling review • Carton and Container review	Michael Brony, PharmD, (OCBQ/DCM/APLB)
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	
Advisory Committee Summary	No advisory committee meeting was held

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1. Introduction

Enzyvant Therapeutics GmbH submitted a Biologics License Application (BLA), STN 125685, for licensure of allogeneic processed thymus tissue-agdc for immune reconstitution in pediatric patients with congenital athymia. The proprietary name is RETHYMIC. RETHYMIC is composed of yellow to brown slices of processed and cultured thymus tissue supplied adhered to filter membranes. The slices are teased away from the filters prior to surgical implantation into thigh muscle. Patients born with congenital athymia have severely reduced numbers of naïve functional T cells, making them highly susceptible to infection. Based on natural history data, the vast majority of

patients die by 2 years of age, and congenital athymia is considered universally fatal by 3 years of age due to infectious disease. RETHYMIC is a one-time treatment.

RETHYMIC is manufactured from allogeneic-unrelated donor thymus tissue that is collected from donors <9 months of age who are undergoing heart surgery. The product is manufactured on demand, and although a product lot is intended for a specific patient, HLA-matching of donor and recipient is not performed, and the product lot can be targeted to a different patient if needed as long as the dosage is consistent with the body surface area of a different patient. The thymus tissue slices are collected for transplantation after 12 to 21 days of culture. The primary purpose of the manufacturing process is to greatly reduce viable allogeneic thymocyte levels within the tissue slices for safety reasons, while maintaining similar overall tissue organization, viability, and retention of important cell types believed to be important for product function. RETHYMIC is intended to function as if it is a normal endogenous thymus. Its thymic endothelial cells recruit immature host T cells (thymocytes) into the slices where they undergo further maturation and positive and negative selection, releasing into circulation immunocompetent naive T-cells that are capable of providing protection from infection.

This document summarizes the basis for approval of RETHYMIC. Primary evidence of safety and effectiveness was based on accumulated data from multiple clinical trials conducted over a period of 28 years. These studies showed a substantial survival benefit. The most common adverse reactions were hypertension, cytokine release syndrome (CRS), rash, hypomagnesemia, renal impairment/failure, thrombocytopenia and Graft versus Host Disease (GVHD). Most of these conditions were due to immunosuppression and could be managed medically. Besides GVHD, other serious risks included development of autoimmune disorders and potential transmission of infectious diseases and development of lymphoproliferative disorder. Given the substantial survival benefit of RETHYMIC in an otherwise invariably fatal condition, there is a favorable benefit-risk profile for RETHYMIC in pediatric patients with congenital athymia.

A complete response letter was issued for the original BLA submission due to pre-license facility observations that were not adequately addressed, and Chemistry, Manufacturing, and Controls (CMC) concerns, including the histology-based potency test method, timing of testing, product stability, manufacturing consistency, and final container closure. A Type A meeting was held on March 19, 2020 with Enzyvant to discuss their approach to resolving the deficiencies. In response to FDA concerns, Enzyvant instituted substantial changes to the manufacturing and testing procedures, Quality System, and manufacturing facility. New validation studies were conducted. All complete response letter (CRL) items were satisfactorily addressed.

Substantial evidence of effectiveness for RETHYMIC for this rare disease with an unmet medical need is based on adequate and well controlled investigations with confirmatory evidence. Specifically, we consider the integrated data from subjects with congenital athymia treated in the 7 open-label studies and 3 single-patient studies compared to a historical control to comprise a single adequate and well controlled investigation. Based on the objective endpoint, mortality, and large treatment effect size, comparison to an external control is adequate to provide substantial evidence of effectiveness, consistent with the regulatory requirements of section 351 of the Public Health Act. The survival

benefit of RETHYMIC was supported by clinically meaningful improvements in infection and additional biochemical and T-cell functional testing data to indicate immune reconstitution. Thus, these laboratory data combined with the biologic plausibility that the allogeneic thymus tissue-based product would induce immune reconstitution serve as confirmatory evidence.

2. Background

Congenital athymia (CA) is a rare inherited condition in which the thymus does not develop at birth, resulting in a low number of T cells with impaired function, leading to life-threatening, recurrent serious infections. Congenital athymia is usually fatal by two years of age. The diagnosis of congenital athymia is based on documentation of a low number of naïve T cells by flow cytometry. Congenital athymia most commonly occurs as part of Complete DiGeorge Anomaly (cDGA), either typical or atypical. Complete DGA is characterized by T-cell immuno-deficiency, congenital heart disease, and hypocalcemia from hypoparathyroidism; the atypical phenotype is characterized by oligoclonal T-cells, lymphadenopathy and rash. Congenital athymia can also occur in infants with diabetic embryopathy and fetal exposure to retinoic acid. The known genetic mutations associated with CA include 22q11.2 deletion, and mutations in chromodomain helicase DNA binding protein 7 (CHD7), Forkhead Box Protein N1 (FOXN1), T Box transcription factor 1 and 2 (TBX1), (TBX2) and Paired Box 1 (PAX1). Approximately, 20 children are born with congenital athymia annually in the United States.

Currently, there is no disease-modifying treatment available for congenital athymia. Investigational hematopoietic cell transplantation (HSCT) is of limited benefit. Management of congenital athymia consists of taking precautions to avoid infection, such as good hygiene procedures and social distancing, intravenous immune globulin (IVIG), antibiotic prophylaxis, and prompt treatment of infections.

RETHYMIC is an allogeneic, processed, partially T cell-depleted thymus tissue-based product developed to provide immune reconstitution in patients with congenital athymia. RETHYMIC slices are implanted into the quadriceps of patients with congenital athymia in a single surgical session. The proposed mechanism of action is migration of the recipient's bone marrow-derived T cell progenitors 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.

Normal thymus is composed of lobules of tissue representing repeating subregions of tissue, with each lobule containing cortical and medullary areas. These regions have specific functions in T cell maturation and education. Immature T cells derived from bone marrow are recruited to the thymus via chemokines. Once in the thymus, the immature $CD4^-CD8^-$ T cells move from a cortical-medullary junction into cortical regions. Within cortical regions, they interact with cortical thymic epithelial cells that act as antigen-presenting cells. After undergoing maturation into $CD4^+CD8^+$ T cells, the T cells undergo positive selection; T cells that do not recognize antigen in the context of MHC are eliminated through apoptosis. The T cells then move to medullary regions where they undergo negative selection to remove self-reactive T cells. The medullary region is also important in Treg production. T cell movement within the thymus is partially directed

through chemokines. T cells that survive both selection processes leave the thymus as either $CD4^+$ or $CD8^+$ T cells. These T cells are functional naive T cells that express $CD62L^+CD45RA^+$ cell surface markers. The presence of increased numbers of naïve T cells in peripheral blood is one measure of RETHYMIC function in recipients. Negative selection by RETHYMIC in transplanted patients must also include tolerance to donor antigens present in the transplanted thymus slices.

Table 1. Regulatory History -

Regulatory Events / Milestones	Date
1. IND submission	May 28, 2001
2. Fast Track designation granted (if applicable)	N/A
3. Orphan Drug designation granted	August 15, 2003
4. Breakthrough Therapy designation granted	April 13, 2017
5. Regenerative Medicine Advanced Therapy designation granted	April 13, 2017
6. Pre-BLA meeting	November 8, 2017
7. Rare Pediatric Disease designation granted	April 5, 2019
8. BLA 125685/0 submission	April 5, 2019
9. BLA filed	June 4, 2019
10. Mid-Cycle communication	July 8, 2019
11. Late-Cycle meeting	September 27, 2019
12. Complete Response	December 4, 2019
13. Type A meeting	March 19, 2020
14. Re-submission after Complete Response	April 9, 2021
15. Action Due Date	October 8, 2021

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Manufacturing summary

The entire tissue slice of RETHYMIC is considered the active ingredient, (b) (4)

A “slice” is

defined as the total amount of material partially covering the filter. A slice can be of variable size, shape, and thickness, and a slice can be comprised of more than one tissue slice on the same filter. (b) (4) medium is applied (b) (4) to feed the slices and (b) (4) . This process is repeated up to Day 21. The final product is harvested in a window between 12 and 21 days. The final container closure is the same culture dish used for manufacturing, using the same culture medium as excipient, with each dish holding up to 4 slices.

Coordination of product manufacturing with patient treatment

The product is made on-demand, and once the cultures are harvested, is provided fresh with a (b) (4) manufacturing dating period (shelf life). Careful coordination of product manufacturing with preparation of a potential patient to receive the product must occur. The availability of source material depends on whether pediatric heart surgery is being performed at the same treatment hospital, whether thymus tissue is removed during surgery, whether sufficient tissue mass is provided to begin processing, and whether donor consent is provided. Product availability is also limited by donor qualification, including infectious agent donor eligibility in accordance with 21 CFR 1271 Subpart C requirements, which is typically not known until (b) (4) into the manufacturing process. Sterility and mycoplasma testing is performed (b) (4) lot. Most patients receiving RETHYMIC require immunosuppression to prevent rejection of the product and GVHD; immunosuppression is associated with additional risks. To provide assurance the product lot will likely meet final product testing, in-process (b) (4) testing are conducted. If all in-process testing completed up to that time is acceptable, then the intended recipient is preconditioned with immunosuppressants and a target date for surgery is planned. A manufacturing window of 12 to 21 days in culture allows adjustment of product harvesting with the surgery date, including delays due to the condition of the patient and surgical team availability. Final product testing is conducted for sterility, mycoplasma, endotoxin, dose, and histology-based potency and overall quality, with final histology, dose, and endotoxin results available at the time of patient treatment. Formulation and transfer of the product to the final container closure occurs just before the planned surgical time, and the product is placed back into the incubator until the surgical team notifies the manufacturer the patient is ready to receive the product. The product is then packaged for transfer to the hospital, and manufacturing personnel hand-carry the product to the operating suite where they inspect the product containers prior to making a final determination on the disposition of the product. If the product lot is deemed acceptable for final release, the manufacturing personnel hand each product dish to the surgical team and record the number of slices used for implantation.

Manufacturing controls

A product lot is composed of up to (b) (4) slices of tissue dependent on the amount of donor thymus tissue available for processing, with (b) (4) slices used for product testing. RETHYMIC quality is assessed by histology performed on (b) (4) tissue sections. The overall architecture is evaluated on (b) (4) . The presence of viable TEC and the degree of nonviable allogeneic $CD3^+$ thymocytes remaining are assessed, and the presence, arrangement, and distribution of TEC by (b) (4) is evaluated. Histological evaluation, including for potency, by histology is reasonable for a tissue-based product, though is limited by

sensitivity and variabilities inherent in the method. Safety testing includes in-process (b) (4) . The product dose is based on the total surface area of all cultured thymus slices measured a day before harvest, and the body surface area of the recipient. One product lot is made from thymus tissue from one donor. All slices produced for a product lot are used to treat a single patient, and slices not implanted are transferred back to the manufacturing facility where unused product is discarded as medical waste.
No Phase 3 study of safety and efficacy was conducted from which manufacturing data could be evaluated. The Applicant chose to use all clinical data from all subjects dating back to 1993; however, prior to 2001, not all manufacturing data were collected. Over the course of 28 years, manufacturing changes were introduced, test methods were changed, specifications were modified (and in some cases acceptance criteria widened during development), product sampling points were broadened, the manufacturing facility was changed, and for the commercial process, additional manufacturing flexibility was proposed. The Applicant also proposed to change the (b) (4) to something with (b) (4) , but would result in a (b) (4) , but for which there were no clinical data available. Further, very little histology testing data were provided on product lots used to treat subjects who received the product. Together, these issues made evaluation of manufacturing consistency challenging, and determining appropriate manufacturing controls were in place difficult. A complete response letter (CRL) was issued based on insufficient evidence to support that manufacturing controls were acceptable.

To address FDA concerns, Enzyvant made changes to the manufacturing facility, made substantial changes to manufacturing and testing procedures, and conducted new validation studies. Critically, Enzyvant also provided additional product histology data from clinical lots used in the study, and converted the histology-based assay from a (b) (4) assay. A retrospective study was conducted on product lots for (b) (4) treated subjects who had slower than normal elevation of peripheral blood naïve T cells compared with all other treated subjects, and no significant difference was found in the product properties of these lots. All facility and CMC CRL items have been addressed. The intended commercial manufacturing process is best represented by product manufacturing that has occurred since 2016. A subset analysis of subjects treated with lots produced since that time show similar levels of safety and efficacy relative to those produced earlier.

Manufacturing changes during BLA review
Several changes were made to the proposed commercial manufacturing and testing process during the review of this BLA:

- The maximum number of slices manufactured has been (b) (4) from 42 (b) (4) to accommodate an (b) (4) but the maximum dose transplanted (b) (4)
- To be consistent with instructions for the surgeon to transplant as many slices as feasible from a product lot, the manufacturing process has been adjusted for manufacturing personnel to generate as many slices as can be obtained from the single donor thymus provided.

- A source material holding time of (b) (4) at room temperature prior to processing, (b) (4) , has been established and is consistent with product lots used during clinical development.
- Most patients will be preconditioned with immunosuppressive agents, which represents an additional risk for this patient population. For patients who will receive immunosuppressants, additional in-process testing for (b) (4) is conducted (b) (4)
- The timing of product sampling for final product histology testing for release has been adjusted from (b) (4) in culture regardless of the total time in culture up to (b) (4) from the final harvest, with a target in most cases to within 3 days of final harvest and release. This is more consistent with regulations and how testing was conducted for most lots produced under IND.
- The assessment of histological features for determining potency and overall product quality has been converted from a (b) (4) assay to a (b) (4) assay based on a rating scale established through assay validation. The (b) (4) results are now captured in the batch record.
- The final container closure was changed from the proposed (b) (4) container to the (b) (4) culture dish container used for nearly all lots produced since 1993.
- The final container medium volume has been reduced from (b) (4) to 5 mls to reduce the chance for a product leak during transport to the hospital.
- The manufacturing dating period (shelf life) has been reduced from (b) (4) . The (b) (4) shelf life is supported by stability data and clinical experience.
- Manufacturing personnel who transport the product to, and handle the product in, the surgical suite now inspect the primary containers as part of final product disposition just prior to surgical implantation.

CMC post-marketing commitments (PMC)
The CMC team recommends two post-marketing commitments. The rationale for the commitments is described below, and the PMC agreements are detailed in Section 11c of this document:

1. The commercial manufacturing process is supported by clinical results of safety and efficacy due to the fact that key elements of manufacturing and testing are similar to that used in clinical studies, including histology-based testing. The change to a (b) (4) histology assay represents an improvement to the assay in terms of precision and reproducibility. It is limited in sensitivity, which may make future assessments of manufacturing consistency and comparability difficult to determine.

The commercial final container closure (b) (4) culture dish) is the same container that has been in use for this therapy for 28 years and has been suitable for the intended purpose. No safety-related issues were associated with this container. The effective container closure system relies on the secondary container to provide greater integrity and protection that the primary container cannot provide.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the RETHYMIC drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that each RETHYMIC lot is used to treat a single patient. Failure of a single lot will have a minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved and the activities performed in the manufacture of allogeneic processed thymus tissue are listed in the table below and are further described in the paragraphs that follow.

Manufacturing Facilities Table for RETHYMIC

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
(b) (4) (b) (4) -Drug Substance (DS) and Drug Product (DP) Manufacturing -Primary and Secondary Packaging -DP Release Testing	(b) (4)	(b) (4)	Pre-License Inspection	CBER (b) (4) VAI

CBER conducted a pre-license inspection (PLI) of (b) (4) for the allogeneic processed thymus tissue DS and DP manufacturing. At the conclusion of the inspection, CBER issued a Form FDA 483 List of Inspectional Observations. The firm responded to the observations on August 24, 2019, October 14, 2019, November 1, 2019, February 13, 2020, and April 9, 2021, and the corrective actions were reviewed and found to be adequate. All inspectional issues are considered to be satisfactorily resolved. The inspection was classified as voluntary action indicated (VAI).

e. Container/Closure System

RETHYMIC consists of thymus tissue slices adhered to a filter membrane on top of a surgical sponge. The container closure system containing tissue, ancillary materials, and culture media is a sterile, non-pyrogenic 100 mm single-use (b) (4) polystyrene cell culture dish with lid supplied by (b) (4) The culture dishes are placed inside a sealable secondary DP container closure system, a single-use polycarbonate (b) (4) container supplied by (b) (4) . The cell culture dishes are visually inspected for leaks and damage prior to implantation.

(b) (4) , conducted aseptic process simulation of DP manufacture, packaging, and transport in lieu of the container closure integrity testing; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were conducted with thymus tissue to evaluate the effect of a variety of *in vitro* culture conditions on: 1) thymus architecture; 2) thymus epithelial cell (TEC) composition and function; 3) generation of a functional naïve T cell population; and 4) gene expression related to immune tolerance. Resulting data showed that a normal thymus phenotype was established and survival of TECs able to produce key regulatory genes that support thymopoiesis was observed. Analysis of biopsy samples obtained following transplantation of allogeneic postnatal thymus tissue in patients with Complete DiGeorge anomaly showed development of naïve T cells and the presence of a broad spectrum of T cell receptor beta variable regions, indicating that the cultured thymus tissue can maintain adequate numbers of TECs to drive development of a functional endogenous T cell population.

Animal studies were conducted in nude rats to identify potentially optimal culture conditions of allogeneic neonatal thymus that result in engraftment and development of an endogenous T cell population (i.e., thymogenesis) following transplantation. The *in vivo* data showed that: 1) thymopoiesis was observed at the pre-specified time points (1- and 9 months post-transplantation); 2) a progressive increase in endogenous generation of total and naïve T cells in the peripheral blood was detected; and 3) there was a time-dependent decrease in donor-derived T cells in the peripheral blood as the endogenous T cell population developed.

Based on the acceptable clinical safety profile of RETHYMIC and the lack of relevant animal species/models, no nonclinical toxicology studies with RETHYMIC were

performed. *In vitro* or *in vivo* genotoxicity, carcinogenicity, or developmental and reproductive toxicity studies were not conducted with RETHYMIC, nor were they indicated.

5. Clinical Pharmacology

Not applicable.

6. Clinical/Statistical

a. Clinical Program

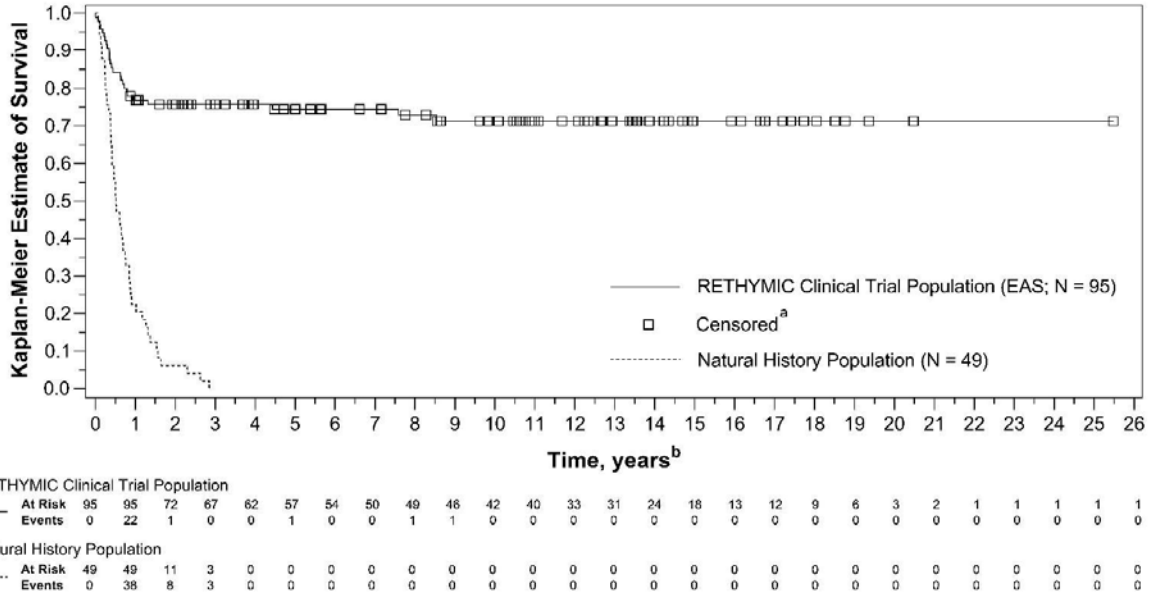
The clinical data to support safety and effectiveness are comprised of pooled clinical data from 10 open-label, prospective clinical studies in which 105 subjects were treated over 28 years at a single center, Duke University. Three of these studies were single-patient studies. All subjects received a single transplant of RETHYMIC at a dose of 4,500 to 24,000 mm^2 of RETHYMIC/Body Surface Area (BSA in m^2). The data from the interventional studies were compared to natural history data on untreated patients with cDGA.

Because of the similarities in study population, study design, study procedures including safety monitoring and efficacy endpoints, concomitant medications, and duration of follow-up, pooling the data from these studies was considered appropriate. The efficacy analysis set (EAS) was limited to 95 subjects with congenital athymia who had not previously received hematopoietic stem cell transplantation (HSCT) or fetal thymus transplantation. The diagnosis of congenital athymia was based on flow cytometry documentation of fewer than 50 naïve T cells/mm^3 ($CD45RA^+$, $CD62L^+$) in the peripheral blood or less than 5% naïve T cells. The EAS population was primarily composed of subjects with cDGA (93 subjects; 98%) and FOXN1 deficiency (2 subjects; 2%). Of the subjects with cDGA, 42 (44%) had an atypical phenotype. Fifty-nine percent (59%) of the EAS population were male, and 70% were White, 22% were Black, 4% were Asian/Pacific Islander, 2% were American Indian/Alaskan native, and 2% identified as multi-race. The median age at time of transplant was 9 months (range 33 days to 2.9 years; only 6 subjects were older than 24 months). The demographics of the safety population were similar to the efficacy population with the exception of age. The median age of the safety population was also 9 months, but included 4 subjects over 3 years-old, with an age range of 33 days-16 years. The safety population included 2 subjects with Severe Combined Immunodeficiency (SCID), 6 subjects with prior HSCT, 1 subject with prior thymic transplants, and 1 subject with athymia associated with TBX1 mutation.

<u>Efficacy</u>
The primary evidence of efficacy is based on a comparison of 1-year survival between the subjects in the EAS and natural history populations. Natural history data are from a contemporaneous population of 49 patients with congenital athymia who were observed from 1991-2017 and received only supportive care. The natural history population is sufficiently similar to the EAS population and appropriate to serve as a control. The 1-year survival for EAS subjects was 76.8% (95% Confidence Interval (CI): 67%, 84.1%)

at 1 year and 75.7% (95% CI: 65.8%, 83.2%) at 2 years. The lower limits of 95% CIs at Year 1 and Year 2 far exceeded the specified survival rate of 50% under the null hypothesis. For subjects treated with RETHYMIC who were alive at 1-year post-transplantation, the survival rate was 94% and was essentially unchanged thereafter. The median age of all surviving subjects was 11.4 years (3 years to 25.7 years), and censoring primarily occurred due to duration of follow-up rather than death. This is a large treatment effect size compared to what is observed in the natural history cohort, where 94% of subjects died by two years and all subjects died by three years of age (See Figure 1). RETHYMIC demonstrated a substantial and persistent survival benefit in this otherwise rapidly fatal disease, despite the heterogenous underlying genetic anomalies and diverse comorbid conditions.

Figure 1. Kaplan-Meier Survival of RETHYMIC Treated Subjects and Natural History Study Patients



[a]Patients were censored at the time of their most recent follow-up for the RETHYMIC clinical trial program. No patients in the natural history population were censored.
[b]Time is years after administration for the RETHYMIC clinical trial population and years of life for the natural history population.

The overall survival benefit of RETHYMIC was supported by evidence of immune reconstitution based on decreased frequency and severity of infections, evidence of thymopoiesis on biopsy, increasing numbers of naïve CD3, CD4 and CD8 T-cells, emergence of diverse T-cell receptor variable beta (TCRVβ) repertoires and increased T-cell proliferation in response to antigen/mitogen in the EAS population. With regard to infections, during the first 6-months following RETHYMIC, there were 346 infections of which 135 were serious. In the subsequent 6-month period following RETHYMIC, the number of infections declined to 109 infections of which 51 were serious. The number of total infections, serious infections and percentage of subjects with infections continued to decline through Year 2. Achieving a naïve CD4 count ≥ 100 cells/mm^2, generally considered sufficient to fight infection, usually occurred between 6-12 months following treatment with RETHYMIC. Specifically, median naïve CD4+ T cell counts were 1.0 (range: 0-38), 41.6 (range: 0-653), 212 (range: 1-751) and 274.5 (range: 33-858) cells/mm^3 at baseline, Month 6, Month 12, and Month 24 post-transplantation,

respectively. Median naïve CD8+ T cell counts were 0.2 (range: 0-45.9), 9.3 (range: 0-163), 57.9 (range 0-304.3) and 86 (range: 6.0-275) cells/mm^3 at baseline, Month 6, Month 12, and Month 24 post-transplantation, respectively. In addition, T cell proliferative responses to phytohemagglutinin (PHA), Concavalin A, Soluble CD3, Immobilized CD3, and tetanus toxoid were also increased and sustained through 2 years post-transplantation. The TCRVβ repertoire variability as assessed by immunoscope/spectratyping and flow cytometry demonstrated a diverse TCR repertoire through 2 years after transplantation. These data support the development and persistence of immune function through 2 years post-transplantation.

Safety

Overall, there were 29 deaths following RETHYMIC treatment in the safety population. The most common cause of death was infection (14, 48%), and most of these deaths occurred during the first year after RETHYMIC treatment, which is not unexpected as immune reconstitution following RETHYMIC occurred 6-12 months after RETHYMIC transplantation. There were 3 deaths possibly related to RETHYMIC study treatment; 2 were attributed to immunosuppressive agents, and one was due to CMV that may have been acquired from the donor thymus tissue.

Risk factors for death included pre-existing CMV infection; 3 of 4 subjects with disseminated CMV prior to transplant died in the first 4 months after transplant. Also, renal impairment at baseline was a risk factor for death; 6 of 10 (60%) subjects with baseline impairment of renal function died within 3 years of treatment, with 5 of 10 surviving less than a year. Additional risk factors for death included GVHD and baseline CD3+ T cells >6000 cells/mm^3. More patients with atypical cDGA died during the first year post-transplantation compared to typical cDGA patients.

The most common adverse reactions associated with RETHYMIC treatment included hypertension (19%), cytokine release syndrome (CRS) (18%), rash (15%), hypomagnesemia (16%), renal impairment (including renal failure) (12%), thrombocytopenia (12%), GVHD (10%). CRS was seen only in subjects treated with rabbit anti-thymocyte globulin and was generally mild or moderate in severity. GVHD resulted in death of 6 subjects (55%); risk factors for GVHD included atypical cGDA, prior HSCT and maternal engraftment, and elevated PHA T-cell response at baseline.

Other important adverse reactions in the safety population were autoimmune reactions, which occurred in 35% of treated subjects. They included thrombocytopenia (12%), neutropenia (9%), proteinuria (7%), hemolytic anemia (5%), alopecia (4%), hypothyroidism (2%), autoimmune hepatitis (2%), autoimmune arthritis (2%), hyperthyroidism (1%), transverse myelitis (1%), albinism (1%) and ovarian failure (1%). Most autoimmune conditions developed within the first 2 years after transplantation.

There were 2 subjects treated with SCID, both of whom died. There was no benefit observed in patients with SCID, and based on mechanism of action, patients with SCID are not anticipated to benefit from RETHYMIC. RETHYMIC is not indicated for patients with SCID.

The Applicant has provided substantial evidence of effectiveness and safety based on an adequate and well controlled clinical investigation with confirmatory evidence. RETHYMIC has a favorable benefit risk profile in pediatric patients with congenital athymia and the recommended dose is 5,000-22,000 mm^2 of RETHYMIC surface area/m^2 recipient BSA.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

A Bioresearch Monitoring (BIMO) inspection was issued for one sponsor-investigator who participated in the conduct of Protocols: 668-1, 668-2, and 25966. The inspections did not reveal substantive issues that impact the integrity of the data submitted in this Biologics License Application (BLA).

c. Pediatrics

The clinical data to support the safety and efficacy of RETHYMIC was obtained solely in children, median age of 9 months, ranging from 33 days – 16 years. All subjects in the EAS population were less than 3 years of age, as survival without RETHYMIC treatment is unlikely past 3 years of age. There was no trend in survival based on age at transplant. There were 4 subjects older than 3 years of age; 2 of these subjects had prior HSCT, 1 subject had prior thymic transplants, and 1 subject had a TBX1 mutation. There were no new safety signals identified in children over 3 years of age. Given the rarity of the disease and that the condition is fatal in early childhood without treatment, we believe that there are sufficient clinical data to support the indication of RETHYMIC for all children with congenital athymia.

A PeRC meeting was not held as there were no issues that needed to be discussed with PERC for this disease with orphan designation.

d. Other Special Populations

There are no data in pregnant or geriatric patients with congenital athymia.

7. Safety and Pharmacovigilance

Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint.

The Applicant independently proposed to conduct a 75-subject post-marketing study to assess survival, T-cell markers of immune reconstitution, and adverse events.

RETHYMIC is not marketed anywhere worldwide and thus there is no postmarketing information available.

8. Labeling

The proposed proprietary name, RETHYMIC, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on July 2, 2021 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on July 21, 2021.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information on August 26, 2021 and found the information acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

A Cellular, Tissue, and Gene Therapies Advisory Committee meeting was not held because information submitted in the BLA, including CMC and clinical study design and trial results did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

The original BLA submission was granted priority review.

Additionally, because of the rarity of the condition and the knowledge that without this product, congenital athymia is invariably fatal during early childhood, RETHYMIC qualifies for and is granted a Rare Pediatric Disease Priority Review voucher.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The review team recommends traditional approval of RETHYMIC for immune reconstitution in pediatric patients with congenital athymia.

b. Benefit/Risk Assessment

Congenital athymia is a rare disease characterized by profound, life-threatening T cell immunodeficiency due to the absence of a functioning thymus at birth. There is a substantial unmet medical need as there is no approved therapy for the treatment of congenital athymia. RETHYMIC improved survival of children with congenital athymia. 76% of subjects survived for at least the first two years following RETHYMIC treatment, compared to only 6% of the children in the natural history cohort who survived to at least 2 years of age. The survival benefit persisted in subjects for more than two years after treatment with RETHYMIC. The effectiveness of RETHYMIC is further supported by the decreased frequency of infections. The adverse reactions generally were not life-threatening and could be managed with routine medical care. In conclusion, the efficacy and safety data

in the BLA support a favorable benefit-risk profile for RETHYMIC for immune reconstitution in pediatric patients with congenital athymia.

c. Recommendation for Postmarketing Activities

Routine pharmacovigilance is recommended. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80. Routine surveillance includes 15-day expedited reports for serious, unlabeled/ unexpected adverse events, and quarterly periodic safety reports for 3 years and annually thereafter. Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.

Two CMC post-marketing commitments were proposed by FDA and agreed upon by the Applicant during review of the BLA.

1. Enzyvant commits to develop a (b) (4) assay to facilitate the assessment of quantitative changes in product quality for stability and comparability. The new (b) (4) assay will either measure (b) (4) . Enzyvant commits to submitting the proposed (b) (4) assay protocol in a product correspondence supplement by October 31, 2022. The assay method will be validated, and the sensitivity of the assay to detect shifts in (b) (4) will be established. Enzyvant will submit the final study report, which includes the validation report, as a Prior Approval Supplement by March 31, 2024.

2. Enzyvant commits to develop a (b) (4) . The level of comparability and stability data needed to support the (b) (4) will be commensurate with the degree of changes from the current (b) (4) . Enzyvant commits to conducting container (b) (4) . Enzyvant will submit the final study report, which includes the validation report, as a Prior Approval Supplement by October 31, 2024.