

Review Memo

BLA: 125685

Submission Date: 4/10/2019 (Rolling BLA)

Applicant: Enzyvant Therapeutics GmbH

BLA: RETHYMIC is proposed for the immune reconstitution of pediatric patients with congenital athymia

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Concurred by: Scott Brubaker (Director, DHT/OTAT)

SUMMARY

This section describes the review of procedures for donor eligibility determination and tracking of RETHYMIC manufactured using thymus tissue obtained from allogenic unrelated donors under the age of 9 months who are undergoing cardiac surgery.

Birth mothers and infant donors are evaluated for relevant communicable disease agents or diseases (RCDADs) in accordance with 21 CFR part 1271, subpart C. Thymus tissue from eligible donors and meeting other pre-established criteria qualify for licensure.

Based on the information received, the applicant's procedures for donor eligibility determination and tracking are acceptable.

DONOR ELIGIBILITY

Donor Screening

The applicant screens all infant donors of thymus tissue and the birth mother of all infant donors for relevant communicable disease agents and diseases (RCDADs). The

screening includes a medical history interview (Thymus Donor History Questionnaire- (b) (4)-TDS-001 FRM4, Thymus Donor Medical History Exclusion Criteria- (b) (4)-TDS-001 JA1), physical examination of the infant donors (Thymus Donor Physical Exam and Medical Review Form- (b) (4)-TDS-001 FRM1), and review of medical history and laboratory test results looking for clinical evidence of RCDADs (SOP (b) (4)-TDS-001). Nurse Practitioners, Physician Assistants, and Physicians are responsible for donor screening. All infant donors and birth mothers are screened for HIV types 1 and 2, HBV, HCV, HTLV type I and II, Vaccinia, Sepsis, WNV, Syphilis, Transmissible Spongiform Encephalopathy, Xenotransplantation, and Zika virus. Although not required, the applicant screens donors for Malaria, Chagas, and Babesiosis.

Reviewer comment: *The donor screening SOP (b) (4)-TDS-001) in the original submission does not adequately describe what clinical and physical evidence of RCDADs they look for when the relevant medical records are reviewed. The applicant submitted an updated SOP that includes additional details regarding the review of relevant medical records looking for clinical and physical evidence of RCDAD in the infant donor. Regarding physical examination of the birth mother, the applicant explains that at the time of the maternal blood specimen collection, the mother's arms are examined to rule out signs of IV drug use, but a more comprehensive physical examination of the mother would be challenging because the mother is not a patient of the (b) (4) [REDACTED]. For donors ≤ 1 month of age, physical examination of the birth mother is recommended when practical (2007 Donor Eligibility Guidance). The response is acceptable considering that the applicant completes a medical history interview of the birth mother for all infant donors regardless of donor's age (refer to updated SOP (b) (4)-TDS-001 in Amendment 19 received on 8/20/2019).*

Reviewer comment: *In response to information requests (Amendments 19 and 24, received on 8/20/2019 and 9/5/2019, respectively), the applicant updated several questions on the medical history interview questionnaire and the exclusion criteria (b) (4)-TDS-001 FRM4, (b) (4)-TDS-001 JA1). The questionnaire and the exclusion criteria are acceptable.*

Donor Testing

Blood specimens for donor testing are collected after consent for donation is obtained. For infant donors ≤ 1 month of age, the blood specimen for donor testing are obtained from the birth mother within 7 days of thymus tissue recovery. For donors ≥ 31 days to ≤ 9 months of age, both the birth mother and the infant donor are tested for communicable diseases. In such cases, the blood specimen from the infant donor is obtained on the day of tissue recovery, before the initiation of the cardiopulmonary

bypass and prior to blood product transfusion. The blood specimens from the birth mother are obtained within 7 days of thymus tissue recovery. The maternal specimens for testing are not accepted if the birth mother has received ≥ 2 liters of intravenous fluid within 1 hour, or ≥ 2 liters of colloid or any blood transfusion within 48 hours of specimen collection (b) (4)-TDS-001, (b) (4)-TDS-001-FRM3).

Reviewer comment: For infant donors who are “31 days to ≤ 9 months of age”, Form (b) (4)-TDS-003-FRM3 includes a question asking if the donor has received “steroids or fluid resuscitation in the last 48 hours, or ever had a blood transfusion, Yes/No”. The SOP (b) (4)-TDS-001 and the form do not include information about acceptability of the donor specimens if the response is Yes. In response to Information Requests (Amendments 19 and 24), the applicant updated the SOP regarding the acceptability of blood samples. The infant donor is excluded if the donor has received blood transfusion within 48 hours of blood specimen collection for donor testing. The applicant explains (Amendment 24) that the infant donors are generally in heart failure and on fluid restriction but receive “maintenance IV fluids” (crystalloids) (50 mL/Kg/24 hours). For donors weighing 3-9Kg, the maintenance IV fluid will range between 6.25-18.75 mL/hour. The staff confirms that the donor has not received more than the maintenance IV fluid in the hour before the donor testing specimen is obtained. The response is acceptable, because the maintenance IV fluid volume appears to be well below the calculated blood and plasma volume (using the algorithm in Appendix 2 of the 2007 donor eligibility guidance) for donors weighing 3-9Kg.

Donor information and assigned identification #, date and time of specimen collection, specimen volume, information regarding blood transfusion or fluid infusion, and the name of the specimen collector are documented on “Lab Collection and Distribution Log” forms (b) (4)-TDS-001 FRM 2, 3 and 5). The blood specimens for donor testing are prepared by (b) (4) and shipped to the (b) (4) in accordance with instructions in “Thymus Donor Screening Panel to (b) (4) document. The donor testing orders are entered and tracked in (b) (4), which is (b) (4) medical record system (Amendment 12, received on 6/28/19).

The donor testing laboratory, (b) (4) and registered with the FDA for testing donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under section 361 of the Public Health Service Act and blood donors (b) (4). The test results are electronically downloaded from (b) (4), printed and included in the thymus tissue batch record (SOP (b) (4)-TDS-001).

Reviewer comment: The applicant provided information about the donor specimen preparation and shipping, (b) (4) CLIA certificate number, and the FDA registration information in Amendment 12.

Reviewer comment: Regarding agreement/arrangements with the donor testing laboratory, the applicant explains that an on-site audit of (b) (4) was performed in February 2019 and no critical observations were identified. Under the established quality agreement, (b) (4) is required to provide notification regarding proposed changes in donor testing assays, deviations and investigation results (refer to Amendment 19). The response is acceptable.

The applicant performs the following communicable disease tests on blood specimens from the birth mother and the infant donors who > 1 month to ≤ 9 months (SOP (b) (4) TDS-001, (b) (4)-TDS-003 FRM1, (b) (4)-TDS-001 FRM3, and (b) (4)-TDS-001 FRM5):

Table 1: Communicable Disease Tests

Assay	Test kit	Lab
Cytomegalovirus (CMV) Antibody	(b) (4)	(4)
Hepatitis B Surface Antigen (HBsAg)		
Hepatitis B core (HBc) Antigen Antibody		
Hepatitis C Virus (HCV) Antibody		
Human Immunodeficiency Virus (HIV)-I/II/O Antibodies		
Human T-Lymphotropic Virus (HTLV)-I/II Antibodies		
Treponema pallidum Antibody		
Nontreponemal Syphilis Screen		
Trypanosoma cruzi (chagas)		
HIV-I/II/O / HCV / HBV (b) (4)		
HIV-I/II/O discriminatory (b) (4)		
HCV discriminatory (b) (4)		
HBV discriminatory (b) (4)		
West Nile Virus (b) (4)		
Zika Virus (b) (4)		
* Testing performed only if combined (b) (4) is positive		

All test results, except for CMV antibody, must be negative or non-reactive. Regarding the CMV antibody test results, the applicant determines the donor ineligible if the birth

mother's CMV antibody test result is negative and the infant donor's CMV antibody test result is positive (SOP (b) (4)-TDS-001, (b) (4)-TDS-003 FRM1).

Reviewer comment: According to SOP (b) (4)-TDS-001, for donors who test positive with the treponemal specific test, reflex testing using a non-treponemal specific test is performed, however, it is unclear how the results of the two assays are considered for making the donor eligibility determination. In response to Information Request (Amendment 19), the updated SOP explains that the donor is ineligible if the result is positive or reactive on treponemal specific test. The donor is eligible if the result is positive or reactive on a non-treponemal specific test but negative or non-reactive on a treponemal specific confirmatory test. The response is acceptable.

Reviewer comment: Because of a discrepancy between information in SOP (b) (4)-TDS-001 and form (b) (4)-TDS-003 FRM1, the applicant was asked to clarify whether an infant donor who is ">31 days to ≤9 months of age" would be determined "ineligible" if the RCDAD test results for the infant donor are negative/non-reactive and the birth mother tests positive/reactive for an RCDAD. In response to Information Request (Amendment 24), the applicant clarified that in such scenarios, the infant donor will be considered "eligible" but not "qualified". The response is acceptable because testing the birth mother is not a regulatory requirement for infant donors >1 month of age.

All infant donors are also tested for CMV (b) (4) (performed by (b) (4)) EBV (b) (4) and Toxoplasma gondii (b) (4) (performed by (b) (4)) and the acceptance criteria is "not detected" (SOP (b) (4)-TDS-001, (b) (4)-TDS-003 FRM1).

Reviewer comment: CMV (b) (4) EBV (b) (4) and Toxoplasma gondii (b) (4) assays are reviewed by other CMC reviewers.

Final donor eligibility (DE) determination

The DE determination procedures are described in SOPs titled "Summary of Donor Screening, Testing for Communicable/Infectious Disease, Chromosomal Abnormalities, and HLA Typing and Eligibility Determination of the Thymus Donor" (SOP (b) (4)-TDS-001) and "Final Eligibility Determination of the Thymus Donor" (SOP (b) (4)-TDS-003). The applicant determines the donor to be eligible if the donor screening does not identify any risk factors for RCDADs and all the infectious disease test results are negative or non-reactive, except for CMV (CMV results are reported). Only thymus tissue from eligible donors are accepted for use in allogeneic unrelated thymus transplantation. The final donor eligibility is determined and documented on the "Thymus donor Screening and Testing: Eligibility Checklist FRM1 (b) (4)-TDS-003 FRM1) by responsible physicians. The final DE determination is also reviewed by the

Quality Unit. The donor eligibility records are retained for at least 10 years after the transplantation of the product (SOP (b) (4)-TDS-001, Amendment 19).

Reviewer comment: Although step 8.1.1 SOP (b) (4)-TDS-003 state “only thymus tissue from eligible donors are accepted for use in allogeneic unrelated thymus transplantation”, other steps in this SOP and SOP (b) (4)-TDS-001 state that if risk factors are identified in donor screening and testing, the physician makes assessment of risks and benefits to determine suitability of the donation. In response to Information Request (response dated 8/20/2019, Amendment 19), the applicant clarifies their terminology and process: 1) Donor Eligibility (DE): process of donor testing and screening for RCDADs, 2) Ancillary Testing (AT): additional testing performed on the infant donor and the birth mother to rule out other medically significant findings (e.g., (b) (4) for 11q22, HLA typing, EBV (b) (4)), 3) Donor Qualification (DQ): the overall process to clear a donor. DQ consists of both DE and AT. The applicant also confirms that if RCDAD risk factors are identified, the donor is determined ineligible regardless of any risk assessments by the physician and thymus tissue from ineligible donors are not accepted, and negative or nonreactive ZIKV test result would not override any risk factors identified in donor screening. The response is acceptable (refer to updated BLA modules 3.2.A, 2.3.S, 2.3.P, 2.3.A, 3.2.S.2.3, 3.2.P.5, SOP (b) (4)-TDS-001, and (b) (4)-TDS-003-FRM1 in Amendment 19).

Reviewer comment: The revised form (b) (4)-TDS-003-FRM1 submitted in Amendment 19 appears to have some errors (e.g., donor screening tests for infants > 1 month to ≤ 9 months are listed under “Ancillary Testing” section). Additionally, it was unclear why donor screening and testing information is under “Ancillary Testing” section on the flow chart- Figure 1- Overview of Donor Eligibility and Qualification in SOP (b) (4)-TDS-001. In Amendment 24, the applicant corrected the form and the SOP, and clarified that for donors >1 month to ≤9 months, the physical examination referenced in the “Ancillary Testing” section of the flow chart is to rule out genetic disease associated with immune deficiency. The response is acceptable.

At time of distribution, the “Certificate of Analysis”, “Thymus donor Screening and Testing: Eligibility Checklist”, Batch Record for “Transplant Day Packaging of Transport Container and Transport”, and the package insert accompany the product that is delivered to the operating room. The “Thymus donor Screening and Testing: Eligibility Checklist” includes the summary of records information required under 21 CFR 1271.55, except for the statement that donor testing was performed by a CLIA certified laboratory.

Reviewer comment: The report of donor testing results provided by (b) (4) include the laboratory’s CLIA certificate number. In Amendment 24, the applicant

confirmed that the report from (b) (4) is included in the accompanying records. The response is acceptable.

Reviewer comment: The donor screening, testing, and DE determination procedures are acceptable and in compliance with 21 CFR part 1271.

TRACKING

The identification and tracking procedure are described in the BLA sections 2.3.S, 3.2.P.3, 2.3.P, SOPs (b) (4)-TDS-001, (b) (4)-GEN-003, and (b) (4)-QA-011. After consent for donation is obtained, the infant donor is assigned an identifier number with pre-fix “MLM” (e.g., MM XXX). The number is assigned and tracked electronically by the staff participating in the consent process. The MLM # is then paired with a “ZZ” number in order to keep the donor information confidential. The infant donor of the thymus tissue is identified with “ZZThymus” and a medical record number (MRN), which is also linked to the recipient’s medical records. The birth mother information and signature are documented on the last page of the Thymus Donor Health History Questionnaire. The birth mother is identified “ZZThymus, Mother” and a MRN. The MRN for the infant donor and the birth mother are in the same format (DXXXXXX) and assigned by (b) (4). These identifications are used for the donor testing specimens and are included on the donor test result reports, the Thymus Donor Health History Questionnaire, and other donor eligibility related records.

The surgical team recovers and places the thymus tissue in a sterile specimen container. The container is labeled with a barcode, donor’s name and (b) (4) medical record number by the O.R. staff. The (b) (4) facility personnel retrieves and transports to the processing laboratory by the (b) (4) facility personnel. A chain of custody form is signed by the O.R. staff and the (b) (4) facility personnel and the form is maintained in the batch record.

The (b) (4) facility assigns a lot number (b) (4)-XXX) and an ISBT-128 barcoded number to the thymus tissue from a single donor. The ISBT-128 number consists of a 5-character site code (W4529 assigned to the (b) (4) facility), 2-digit year code, a 6-digit sequential number. The ISBT-128 labels are used on the in-process containers and batch records. The final product label includes the Lot number (b) (4)-XXX) and the National Drug Code (NDC) number.

A confidential thymus donor information form is used for documenting and maintaining link between the donor thymus donor MRN, ISBT 128 number, MLM number, and the final product lot #. Additionally, the “Transfer of Drug Product for Transplant” form that accompanies the final product to the operating room for transplantation includes the Lot #, the thymus donor MRN and the ISBT-128 barcode label.

The following table in the BLA section 3.2.P.3 summarizes the use of different identifiers for tracking and maintaining linkage:

Table 2: List of Identifiers for Tracking

Identifier	Purpose
ZZThymus Number	Separate ZZThymus numbers are assigned to the thymus donor and the mother of the donor. They are used by the hospital to link to the MRN for confidentiality during billing & ordering of screening tests. The numbers link donor screening samples drawn and sent for testing to specific test labs. The numbers are assigned by (b) (4)
MRN	Medical record numbers are assigned to the thymus donor and the thymus recipient. They are assigned by (b) (4)
MLM Thymus ID	Assigned by Clinical group of DUHS during donor screening after consent is obtained
ISBT number	The ISBT-128 barcode is specific to the product lot number. The product code portion of this number is "02" for thymus tissue slices. The ISBT number is assigned by the (b) (4) facility and released by the Quality group.
Operation Number	The operation number is used as the drug substance and drug product lot number. This number is assigned sequentially by the (b) (4) facility.
Lot Number	The operation number is used as the drug substance and drug product lot number. This number is assigned sequentially by the (b) (4) facility.
NDC - Drug Product	The product identifier number, specific to RETHYMIC.

Reviewer comment: In Amendment 24, the applicant clarified that "lot number" is referred to as "operation number" in site documents, but there is no difference between the two numbers. The applicant also explained that the ZZThymus number is created in the electronic medical system (EMR) as a dummy MRN and date of birth for confidentiality purposes. The dummy numbers are linked to the actual infant donor and birth mother and are recorded on an enrollment log. The response is acceptable. Although several identification numbers are used from the time the donor consent is obtained to the labeling of the final product, the batch record information and the final product labeling allows tracking of the product from the donor to the recipient and vice versa. The tracking procedure is acceptable.