Application Type	Original BLA
STN	125685/0/65
CBER Received Date	April 5, 2019 (original submission) April 4, 2021 (response to CR letter)
PDUFA Goal Date	October 8, 2021
Division / Office	DCGT/OTAT
Committee Chair	Thomas Finn, Ph.D.
Clinical Reviewer(s)	Gumei Liu, M.D.
Project Manager	Jean Gilder / Adriane Fisher, M.P.H., M.B.A.
Priority Review	Yes
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renee C. Rees, Ph.D. Team Leader, Therapeutics Evaluation Branch
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	John Scott, Ph.D. Director, Division of Biostatistics
Applicant	Enzyvant Therapeutics GmbH
Established Name	Allogeneic processed postnatal thymus tissue (RVT-802)
(Proposed) Trade Name	RETHYMIC
Pharmacologic Class	Allogeneic cultured postnatal thymus tissue product
Dosage Form(s) and Route(s) of Administration	Single administration by surgical implantation
Dosing Regimen	(b) (4) to 22,000 mm^2 of thymus tissue/recipient body surface area in m^2
Indication(s) and Intended Population(s)	For the immune reconstitution of pediatric patients with congenital athymia

1. Executive Summary

This Biologics License Application (BLA) seeks licensure of RETHYMIC as a tissue therapy for the immune reconstitution of pediatric patients with congenital athymia. The original BLA, 125685/0, was submitted on 4/5/2019 and a Complete Response (CR) letter was issued on 12/4/4019 because of several Chemistry, Manufacturing, and Controls (CMC) deficiencies. There were no clinical or statistical deficiencies.

On 4/9/2021, the applicant submitted a full response to the CR letter under Amendment 60, addressing the CMC deficiencies listed in the letter. On 6/5/2021, the applicant submitted the latest datasets under Amendment 65 based on the FDA's request for clinical datasets on 5/11/2021.

Twelve additional subjects were added to the clinical database in this amendment. The full analysis set (FAS) includes 105 subjects, and the efficacy analysis set (EAS) includes 95 subjects. The primary efficacy endpoint, the survival rate at Year 1, was 76.8% (95% confidence interval [CI]: 67.0%, 84.1%) in the EAS based on the Kaplan-Meier (KM) method. The supportive efficacy endpoint, the estimated survival rate at Year 2, was 75.7% (95% CI: 65.8%, 83.2%). Both lower limits of 95% CIs at Year 1 and Year 2 are greater than the pre-specified survival rate of 50% under the null hypothesis. There were 29 deaths in the FAS, including 2 additional deaths (on 5/5/2018 and 1/8/2021) reported in this amendment. The results are very similar to those in the statistical memo dated on 12/04/2019.

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

2. Introduction

The original 125685/0 statistical review was conducted by Dr. Cong Wang and the statistical review memo was completed on 12/04/2019. The clinical development program for RETHYMIC included nine IND studies (Study 668-1, 668-2, 884&884-1, 931, 932, 950&950-1, 25966, 33170, 51692) and one non-IND study (Study 735). Please refer to Dr. Wang's memo for more details for the clinical development program, inclusion/exclusion criteria, study design, etc. Compared with datasets of 125685/0 reviewed by Dr. Wang, datasets reviewed in this memo include additional 12 subjects (4 from Study 25966 and 8 from Study 51692). The database lock date for datasets submitted under Amendment 65 was 5/18/2021.

3. STATISTICAL EVALUATION

The datasets submitted in this amendment include 105 subjects in the FAS, 95 subjects in the EAS, and 93 subjects in the analysis set of all EAS subjects except those with FOXN1 (Forkhead box protein N1) deficiency (EAS-cDGA).

Table 1 summarizes the demographic information for subjects in the three datasets (data are pooled from the 10 clinical studies).

Table 1: Pooled demographics for all analysis populations

	FAS (N=105)	EAS (N=95)	EAS-cDGA (N=93)
Age on the day of implantation (days)			
Mean (SD)	493.34 (923.64)	297.9 (213.95)	296.9 (215.84)
Median (min, max)	269 (33, 6163)	256 (33, 1087)	256 (33, 1087)
Sex n (%)			
Female	45 (42.9%)	39 (41.1%)	38 (40.9%)
Male	60 (57.1%)	56 (58.9%)	55 (59.1%)
Race n (%)			
White	76 (72.4%)	66 (69.5%)	65 (69.9%)
Black or African American	21 (20.0%)	21 (22.1%)	20 (21.5%)
Other	8 (7.6%)	8 (8.4%)	8 (8.6%)
Ethnicity n (%)			
Hispanic or Latino	20 (19.0%)	18 (18.9%)	18 (19.4%)
Other	85 (81.0%)	77 (81.1%)	75 (80.6%)

With the latest datasets under Amendment 65, I updated the important tables and figures in the previous statistical memo. The primary efficacy endpoint is the survival rate at Year 1 from transplant and the survival rate at Year 2 is a supportive efficacy endpoint. Table 2 provides the updated survival rates for the three populations.

Table 2. Survival rate results for all analysis populations

	FAS (N=105)		EAS (N=95)		EAS-cDGA (N=93)	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Alive, n	81	74	72	67	70	65
Dead, n	23	25	22	23	22	23
Censored, n	1	6	1	5	1	5
Alive + dead, n	104	99	94	90	92	88
Survival rate estimated as a proportion	77.1%	70.5%	75.8%	70.5%	75.3%	69.9%
95% exact binomial CI	(67.9%, 84.8%)	(60.8%, 79.0%)	(65.9%, 84.0%)	(60.3%, 79.4%)	(65.2%, 83.6%)	(59.5%, 79.0%)
Two-sided p-value*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Survival rate estimated using KM method	78.1%	76.1%	76.8%	75.7%	76.3%	75.2%
95% CI	(68.9%, 84.9%)	(66.7%, 83.2%)	(67.0%, 84.1%)	(65.8%, 83.2%)	(66.3%, 83.7%)	(65.1%, 82.8%)

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

For the EAS, the estimated survival rates at Year 1 and Year 2 based on the Kaplan-Meier method were 76.8% (95% CI: 67.0%, 84.1%) and 75.7% (95% CI: 65.8%, 83.2%), respectively. The survival rates at Year 1 and Year 2 estimated as the proportion of {#alive subjects} among {#alive and dead subjects} at the specific time points were 75.8% (95% CI: 65.9%, 84.0%) and 70.5% (95% CI: 65.8%, 83.2%), respectively. Similar results are observed for FAS and EAS-cDGA.

Figure 1 shows the Kaplan-Meier survival plot for two years of follow-up in the FAS, EAS and EAS-cDGA. Figure 2 shows a swimmer plot that gives detailed survival status for each individual subject in the EAS.

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

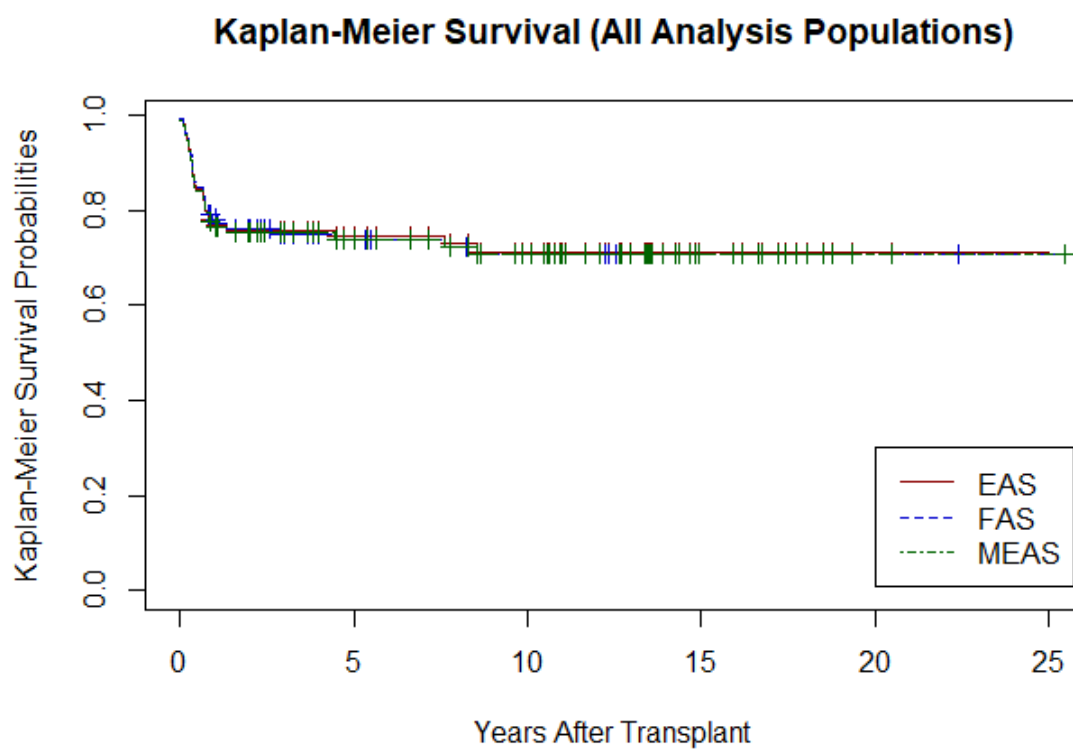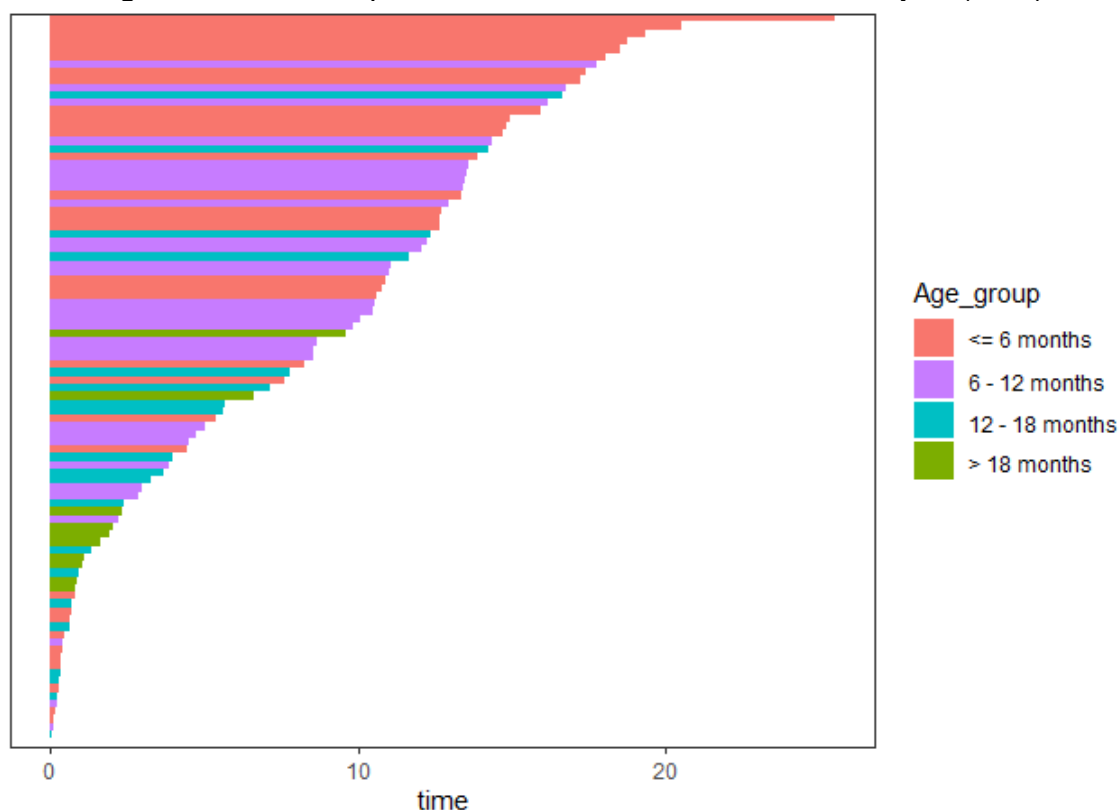Kaplan-Meier Survival (All Analysis Populations)

Figure 2. Swimmer plot of survival for each individual subject (EAS)

There are two additional deaths (one in Study 25966 and one in Study 51692) reported in Amendment 65 compared to 125685/0, on (b) (6) and 1/8/2021. The death that occurred on (b) (6) was not included in the previous dataset despite the data cutoff date of 7/16/2018. Both subjects died within 2 years of follow-up. Table 3 summarizes the distribution of deaths among individual studies.

Table 3. Deaths in each individual study (FAS)

	Total subjects	Within 2 years follow-up (%)	At the time of analysis data cutoff (%)
668-1	14	6 (42.85%)	6 (42.85%)
668-2	12	2 (16.67%)	4 (33.33%)
884 & 884-1	12	2 (16.67%)	3 (25.00%)
931	5	1 (20.00%)	1 (20.00%)
932	7	1 (14.29%)	2 (28.57%)
950 & 950-1	15	4 (26.67%)	4 (26.67%)
25966	28	7 (25.00%)	7 (25.00%)
(b) (6)	1	1 (100.00%)	1 (100.00%)
51692	10	1 (10.00%)	1 (10.00%)
735	1	0 (0)	0 (0)
Pooled dataset	105	25 (23.81%)	29 (27.62%)

Reviewer Comment: The above results are very similar to those in the statistical memo dated on 12/04/2019.

4. CONCLUSIONS

With the updated datasets submitted in 125685/0/65, the survival rate at Year 1 was 76.8% (95% CI: 67.0%, 84.1%) in the EAS. For the supportive efficacy endpoint, the survival rate at Year 2 was 75.7% (95% CI: 65.8%, 83.2%) in the EAS. These estimates were obtained using the Kaplan-Meier method. Both lower limits of 95% CIs at Year 1 and Year 2 were greater than the pre-specified survival rate of 50% under the null hypothesis. The median survival time for all subjects was yet to be reached as of the data cut-off date.

There are two additional deaths (one on (b) (6) and one on 1/8/2021) reported in 125685/0/65 compared to 125685/0. The overall number of deaths is 29.

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