



Our STN: BLA 125685/0

**LATE-CYCLE
MEETING MEMORANDUM**
October 25, 2019

Enzyvant Therapeutics
Attention: Kevin Healy, Ph.D.
C/O 324 Blackwell Street, Suite 1220
Durham, NC 27701

Dear Dr. Healy:

Attached is a copy of the memorandum summarizing your September 27, 2019 Late-Cycle teleconference with CBER. This memorandum constitutes the official record of the teleconference. If your understanding of the teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

If you have any questions, please contact Jean Gildner at (240) 402-8296.

Sincerely,

Raj K, Puri, MD, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Late-Cycle Meeting Summary

Meeting Date and Time: September 27, 2019 1300 - 1430
Meeting Location: Teleconference
Application Number: BLA 125685/0
Product Name: Allogenic processed thymus tissue - agdc
Proposed Indications: For the treatment of primary immune deficiency resulting from congenial athymia associated with complete DiGeorge Anomaly (cDGA) or forkhead box protein N1 (FOXP1) deficiency.
Applicant Name: Enzyvant Therapeutics GmbH
Meeting Chair: Dr. Thomas Finn
Meeting Recorder: Jean Gildner

FDA ATTENDEES

Ekaterina Allen, PhD, RAC, CBER/OCBQ/DMPQ
Rachael Anatol, PhD, CBER/OTAT
Kimberly Benton, PhD, CBER/OTAT Qiao
Bobo, PhD, CBER/OCBQ/DMPQ
Michael Brony, CBER/OCBQ/DCM/APLB
Melanie Eacho, PhD, CBER/OTAT/DCGT
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ
Thomas Finn, PhD, CBER/OTAT/DCGT
Jean Gildner, MSHS, MT (ASCP), CBER/OTAT/DRPM
Sukhanya Jayachandra, PhD, CBER/OTAT/DCGT
Alyssa Kitchel, PhD, CBER/OTAT/DCGT
Matthew Klinker, CBER/OTAT/DCGT/CTB
Lily Koo, PhD, CBER/OCBQ/DMPQ
Wei Liang, PhD, CBER/OTAT/DCEPT
Randa Melhem, PhD, CBER/OCBQ/DMPQ
Steven Oh, PhD, CBER/OTAT/DCGT
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Ramani Sista, PhD, CBER/OTAT/DRPM
Irina Tiper, PhD, CBER/OTAT/DCGT
Cong Wang, PhD, CBER/OBE/DB

APPLICANT ATTENDEES

Rachelle Jacques	Chief Executive Officer, Enzyvant Therapeutics, Inc.
Alan Kimura, MD, PhD	Chief Medical Officer, Enzyvant Therapeutics, Inc.
Alex Tracy, PhD	Vice President, Pharmaceutical Development & Manufacturing, Enzyvant Therapeutics, Inc.
Kristin Marks	Senior Process Engineer, Enzyvant Therapeutics, Inc.
Allison Lim, PharmD	Senior Medical Director, Clinical Development, Enzyvant Therapeutics, Inc.

Karin Pihel, PhD

Director, CMC Regulatory Affairs, Enzyvant Therapeutics, Inc.

Kevin Healy, PhD

Vice President, Regulatory Affairs and Quality, Enzyvant Therapeutics, Inc.

(b) (4)

Quality Consultant for Enzyvant Therapeutics, Inc.

(b) (4), MD, PhD

Professor of Pediatrics and Immunology, (b) (4)

(b) (4), MD

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(b) (4), PhD

Director of Regulatory Affairs and Quality, (b) (4)

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(b) (4) Laboratory Manager, (b) (4)

(b) (4)

(b) (4) Laboratory Director, (b) (4)

(b) (4)

(b) (4) Administrative Director, (b) (4)

(b) (4), PhD

Director of Product Development, (b) (4)

BACKGROUND

BLA 125685/0 was submitted on April 5, 2019, for Allogenic processed thymus tissue - agdc.

Proposed indication: Treatment of primary immune deficiency resulting from congenial athymia associated with complete DiGeorge Anomaly (cDGA) or forkhead box protein N1 (FOXP1) deficiency.

PDUFA goal date: December 4, 2019

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on September 17, 2019.

DISCUSSION

1. Discussion of Substantive Review Issues

- a. **Final product stability in new container closure.** The switch from the (b) (4) culture dish final container to the (b) (4) container involved numerous significant changes including: (b) (4)

(b) (4)

The full impact of these changes resulting from the change of the final container closure in the BLA is still under review. However, of greatest concern is the stability of the product under these new conditions. Our review to date indicates that the stability data for the final drug product in the (b) (4) container to support an expiration of (b) (4) is insufficient because of the following issues:

- Your stability and shipping study were appended to your process validation study. Only (b) (4) process validation lots used to assess stability were exposed to the full (b) (4) of holding time in the final container, and that lot was not exposed to the full (b) (4) formulation step time, nor the full (b) (4) allowable shipping time, nor the full extent of processing step times during manufacturing. Only one slice from that lot was used for histology. Histology data from the shipping study was not provided in the submission.
- The proposed shelf life does not take into consideration the time it will take to perform the transplant. Drug products should not expire during administration.
- There is no (b) (4) assay that is indicative of stability. The only means to assess stability was (b) (4) histology, for which the sensitivity of the assay for assessing changes in product quality of the drug product is unclear.
- The additional clinical data submitted on 09/13/2019 for the three patients to support the use of (b) (4) final container closure is not interpretable at this time because data on naive T cell counts at 6 and 12 months as well as 12 month survival are not yet available on these 3 patients. Since these data will not be available in time to review within the PDUFA clock, all clinical evidence of efficacy will be based on the patients who received product lots in the (b) (4) final container.
- The (b) (4) studies for demonstrating the resiliency of the tissue to strong insults were conducted on Day (b) (4) thymus cultures and the slices were placed back in culture out to 12 days, or as long as 21 days for some conditions. If the quality of final product slices decreases during the (b) (4) expiry, they will have no such opportunity to recover prior to transplant. In addition, you have not studied clinically whether thymus slices would recover in vivo at early time points post-transplant. The earliest biopsies were performed 2 months post-transplant. It therefore remains unknown how slices stored for a longer period with the new container closure will respond in vivo. Further, the (b) (4) studies were not replicated on Day 12 or 21 culture slices. It is therefore not clear how resilient the actual product would be compared to early stage culture slices.

In the absence of additional stability data, it is unlikely that we can approve the product using the (b) (4) final container at this time. Alternatively, approval of the BLA with the existing (b) (4) culture dish final container may be possible,

and if the BLA is approved, you could submit a PAS supplement for the (b) (4) container when additional supporting data becomes available.

In order to support the (b) (4) culture dish final container for approval, you will need to submit the following to the BLA:

- Details on the shipping configuration for the (b) (4) culture dishes. IND amendment 9836.209 submitted Nov 9, 2015 provides a description of the (b) (4) container system used to hold the dishes, and an insulated cooler it is transported in. Submit updated details and procedures on these materials and your experience using them.
- Conduct a new study demonstrating that the final container closure is providing adequate protection (physical and microbial) post-release and during transport and submit the results.

Discussion: FDA began discussion by informing the applicant that we appreciate their efforts to respond to information requests quickly; however, in order to meet the Dec 4 PDUFA deadline there is limited opportunity to be reviewing significant amounts of new information going forward. FDA already needs to process the considerable amount of information provided to date and there are still outstanding information requests we are awaiting a response to, and possibly more information requests that are needed. The applicant needs to be aware that information provided after Oct 31st may not allow us sufficient time to incorporate it into our review. Thus it is critical that any outstanding information we need be provided by that date.

Applicant stated that the (b) (4) container is superior to the (b) (4) container because of the much higher level of container integrity compared to the (b) (4) culture dishes with loose fitting lids. Enzyvant clarified that the (b) (4) shelf life of the product does include the time it takes to perform the surgical procedure. Enzyvant also announced that preliminary results on one patient treated with a product lot using the (b) (4) container now shows elevated naïve T cell levels consistent with other patients at the same time point who received product in the (b) (4) container and later went on to have improved survival.

Enzyvant also clarified that information provided in the pre-BLA about increased surgical times using the new container due to longer handling times was inaccurate. They have personally observed surgeries using both types of containers and now know that the surgeries take (b) (4) regardless of container type. From their perspective there is no delay in tissue getting to the surgeon. Enzyvant stated they have recently provided the histology data as requested from the process validation study that included the shipping step. They would be willing to assay (b) (4) samples from that study using the (b) (4) assay under development.

FDA commented that it is important that we are provided with accurate information in the BLA so that our decisions are based on a correct understanding of their manufacturing process and product handling. FDA cited two examples where the information provided has caused confusion: 1) that

surgeries performed would take about an (b) (4) longer with the (b) (4) container than the (b) (4) container, then revised to (b) (4) longer, and now stated to be the same, and 2) that the way tissue is handled in the surgery room, including the method diagramed in the package insert for removing the slice from the filter has been described in different ways in different parts of the BLA, in information requests, and on inspection by different Enzyvant and (b) (4) personnel. Since the review process is at a late stage any corrections that need to be made should be provided as soon as possible. FDA also expressed difficulty in evaluating the new container because very little information was provided on the (b) (4) container that has been in use for 26 years under the IND and was the basis for all the safety and efficacy data submitted. FDA recommended the sponsor submit additional information to the BLA on their experience with the (b) (4) container. FDA agreed that the (b) (4) container offers better container integrity which is important to protect the product, but imposes numerous risks that they have not fully evaluated or mitigated. FDA did not feel that the information available at this time would support the (b) (4) container, but possibly could in the future after additional information and stability data is provided. Due to the late stage of the review process, we would need them to make a decision quickly on which container they want us to consider for approval.

Applicant stated that they will discuss this internally after the meeting and get back to FDA with their decision. If they decided on revering back to the (b) (4) culture dish container they would like to discuss what would be necessary for a study to support transport of the product. The sponsor outlined details of a possible study for FDA to review and would like feedback. FDA agreed to look at the plan more in-depth and provide timely comments. If a teleconference is necessary the Applicant will be notified. FDA expressed that given the short time left in the PDUFA time frame that it is important that neither side be waiting on the other to proceed forward. The Applicant agreed. FDA pointed out that regardless of which container they choose that the eCTD submission needs to be updated with more complete information, especially if they will revert to the (b) (4) container because there is so little information included in the original submission. Since the same container is used for culturing they can refer to that level of information, and reference those eCTD sections to help support the (b) (4) container, if they decide to choose that container.

Applicant asked about whether they can continue to use the (b) (4) container under IND. Enzyvant stated that because they have already switched under IND to the (b) (4) container, revering back to the (b) (4) container would require re-instituting previous SOPs and forms and that would take a considerable effort. FDA acknowledge the difficulty in quickly revering back to the previous container under GMP. FDA will have to discuss the matter internally and provide advice in the near future on the best course of action. FDA pointed out that such a change should not have been implemented under IND without first providing a detailed summary of risk management and supporting manufacturing data with the new container for FDA to review.

Applicant stated they understand FDA's concerns, but felt that the (b) (4) container provides better protection for patients and long term would like to follow-up with the FDA about what would be needed to support that container.

Applicant sought clarity on whether container closure and shipping validation data involving thymus tissue would be required to support the (b) (4) container, and if so, whether such data can be provided in the form of a post marketing commitment.

FDA explained that they can refer to their extensive experience under IND using the (b) (4) culture dish container. It is FDA's understanding that there has not been evidence of product contamination or adverse events associated with using the (b) (4) dish as the final container closure for their clinical studies. Whether additional studies are needed using actual thymus tissue product would depend on how closely they adhere to how the container was used under IND. As long as the formulation and handling procedures are very similar, no additional studies would be needed to support the (b) (4) container for BLA review. However, FDA again pointed out the lack of information in the BLA on their previous experience using the (b) (4) container closure, or the acrylic secondary container. All appropriate sections of the eCTD submission need to be updated to provide this information so that we have a better understanding. For example, it is unclear what shelf life has been used for the (b) (4) container prior to switching to the (b) (4) container. Enzyvant should indicate what shelf life they have established and provide appropriate justification.

In summarizing the discussion of the container, FDA indicated they will review the proposed (b) (4) dish transport study, and Enzyvant will inform the FDA about which container they will propose for the BLA.

- b. **Timing of histology testing.** We acknowledge your revised proposal to perform identity, potency, safety, and viability testing by histology on Day (b) (4) samples. We also note that you have referred to process validation data intended to show that histological features remain at all stages of culture, and the resiliency of the thymus tissue and slices based on (b) (4) studies. We understand that because of the nature of your product and its manufacture process, some allowance of testing (b) (4) of the final formulated drug product may be justifiable. However, your current testing strategy is unacceptable as it is still too (b) (4). A more appropriate range with a shorter gap between testing and final product release (e.g. (b) (4) days prior to release) will be necessary. No additional validation would be needed as long as the range is more in line with what was used to under IND. [Note: You provided information on the sampling time point of (b) (4) of the (b) (4) clinical lots reported in Module 5. The time of histology sample collection relative to the final harvest was (b) (4) days prior to drug product formulation (average (b) (4) days prior)].

Discussion: FDA expressed concerns about a final product histology sampling window of either (b) (4) days. Testing so far upstream is inconsistent with FDA regulations and guidance, and is not how product lots were tested under IND for clinical lots used to support safety and efficacy. FDA clarified that since

histology testing is used to evaluate multiple parameters, some (b) (4) testing is appropriate. For example, for the purpose of evaluating the level of allogeneic thymocyte reduction, FDA agrees that a large reduction occurs by Day (b) (4). If they wish to perform such testing for that purpose at Day (b) (4) that would be acceptable. Further, identity testing by histology is performed at Day (b) (4). The interim identity test at Day (b) (4) is not really necessary. However, the determination of product quality, including potency, by histology should be conducted as close to the final harvest as is feasible. FDA related concerns about how the sponsor would assess the impact of a product deviation if key product attributes such as potency had already been performed prior to the deviation. Enzyvant indicated that repeat testing is a possibility, though that would reduce the amount of tissue available for transplant and they would like to transplant as much as possible.

Applicant explained that patient treatment is dependent on a number of factors outside of manufacturing control. There are clinical considerations about the health status of the patient that may require the date of transplant to be moved. The approach to testing by Day (b) (4) would allow histology results to be available for all lots that will be collected at Days 12-21. This will simplify coordination with product transplant. Restrictions on the time window for histology testing could jeopardize the ability to be able to treat the patient and given the shortage of source material they feel it would not be in the patient's best interest to not be able to use the product lot. They also stated that most patients are treated with RATGAM 5 days prior to scheduled transplant. This is a sensitive patient population and they do not want to expose the patient to RATGAM unless they are sure that the product would meet release specifications. Thus, they need to know the results of histology testing at least (b) (4) days in advance.

FDA acknowledge the challenges with coordinating manufacturing and testing with scheduled product administration. FDA explained that for many cell therapy products manufacturing and QC testing logistics are a significant challenge. This is why it is so important to use clinical studies as an opportunity to develop and demonstrate that the manufacturing process is feasible. The sponsor has yet to explain why a strategy that has been in place for so long under IND that was never reported as creating significant logistical issues is no longer tenable. It is the responsibility of the manufacturer to optimize the process to work suitably for the intended purpose. FDA further explained that as part of product development processes are typically set with wider criteria and more flexible step times and windows, and that these are narrowed and optimized as the product life cycle progresses. It appears that Enzyvant is proposing a broader strategy for licensure compared to what was used under IND. By the time the BLA is submitted these details should have been worked out and demonstrated as adequate under IND. FDA appreciates that no formal phase 3 study was conducted and so the sponsor did not have the benefit of that experience, but any change will have to be justified. FDA reminded Enzyvant that these concerns were raised at the midcycle meeting and we had advised them to provide justification for the need for Day (b) (4) test window. To date, such amendment has not been provided. Additional discussion was held going over FDA's concerns, emphasizing the importance of trying to minimize the difference in time between

product sampling for testing and final product preparation. Enzyvant suggested that testing within (b) (4) days of harvest might be a possibility. FDA indicated we would have to consider that proposal.

The applicant indicated they performed a comprehensive analysis of all key variables associated with manufacturing, testing, and patient treatment. In their final analysis a test window of Day (b) (4) is what is needed, and some examples were provided on complications that can occur in the treatment schedule that might delay transplant which are outside of the (b) (4) facility's control. FDA recommended that since they have already performed this analysis they should consider providing us with a copy of that assessment. FDA suggested they propose a test plan that incorporates both a time window for what days sampling can occur, along with a specified amount of allowable time between testing and product release. FDA asked that they submit a final proposal as an amendment as soon as possible.

- c. **Assessment of microbial contamination is based on samples from too large of a culture** (b) (4). Your product is administered with material from (b) (4) cell culture dishes in the order they were established. Samples used for sterility, endotoxin, and mycoplasma are (b) (4) from multiple dishes. The degree of (b) (4) should adequately take into consideration the limit of detection of each assay; therefore, we have requested microbiological testing (sterility, endotoxin and mycoplasma) be performed on media (b) (4) from (b) (4) culture dishes. Please provide the date by which you plan to address our concern.

Discussion: Enzyvant agreed to not (b) (4) medium from more than (b) (4) culture dishes and will work on revising their test methods. However, they pointed out that volume requirements for the assays will exceed the available volume for mycoplasma testing on Day (b) (4) cultures. Enzyvant asked if performing the test on Day (b) (4) cultures where more volume would be available would be acceptable. FDA agreed with the proposal.

- d. **Module 1 is vague about your intentions for how and where this therapy will be used.** Currently, only the (b) (4) facility is designated as source material provider/treatment center and manufacturing facility, respectively. Your DSCSA exemption request indicates it is your intention to add other treatment centers, and you may also add a new manufacturing facility:
- If the BLA is approved, the approval will only include (b) (4) facility as source material provider and manufacturing facility. Adding an additional supplier of thymic tissue source material or shipment of product to other centers would require BLA supplements that include additional shipping and stability data. Such data should include (b) (4) measures of product quality.
 - Future addition of a new manufacturing site would require a prior approval supplement that includes analytical product comparability data composed of (b) (4) measures of critical quality attributes of the drug substance

and drug product. If analytical product comparability studies cannot be performed (e.g., due to the lack of biologically or functionally meaningful (b) (4) assays evaluating critical quality attributes) or fail to demonstrate comparability, additional clinical studies may be necessary to demonstrate comparable clinical safety and efficacy.

- A future discussion can be held on Enzyvant's plans for additional centers or facilities, and the strategy you will use to qualify new centers and how the logistics would be handled.

Discussion: Enzyvant clarified it is their intention to initially restrict manufacturing and patient treatment to (b) (4). To make the product available to a larger number of patients in the future may necessitate the addition of other hospitals as thymus tissue providers or treatment centers, and additional information would be provided post-licensure as these plans mature. Language provided in the DSCSA exemption request were meant to be forward thinking statements and not an indication that they had any immediate plans in place.

- e. **Outstanding issues from the inspection remain.** There were many issues noted during the inspection and many are pending a risk assessment to determine what appropriate corrective actions, if any, should be taken. We are concerned since many issues deal with:

- The overall quality oversight of the process
- Lack of sterility assurance of product contact materials
- Controls designed to prevent microbiological and cross contamination (environmental monitoring and cleaning procedures).

We also note that some of the proposed dates for the corrective actions occur after the action due date for this submission.

Discussion: This items was not discussed as these issues and Enzyvant's proposal and timeline to address FDA concerns was already discussed in a recent telecon with the FDA.

2. Discussion of Minor Review Issues – 5 minutes

- a. **Relationship between starting material and final product dose.** The correlation between starting material weight and the amount of product generated is still unclear. You have set (b) (4) of tissue as the minimum amount of source material that you would accept to initiate processing.
- We previously commented that it was not clear that you would always achieve the minimum dose of final product based on (b) (4) and your manufacturing history. You indicated that this was a business decision, and that you agree that situations may arise where the minimum dose might not be generated. Given the scarcity of donors, the great medical need of the product, and your intention to increase the number of patients

treated per year, it was your intention to attempt manufacturing in such cases, even though there was no guarantee. However, in going over the batch history we note the that the following lots were manufactured using less than the minimum amount you now specify, and 3 of 4 subjects are still alive.

Lot #	Patient #	Year	(b) (4) tissue	Status
(b) (4)	(b) (4)	1993	(b) (4)	alive
		1998	(b) (4)	alive
		2002	(b) (4)	dead
		2004	(b) (4)	alive

If you are willing to take a calculated risk, it is not clear why smaller amounts of source material are not processed.

- Product dose is based on the surface area of the tissue and the body surface area (BSA) of the targeted patient. Our understanding is that product lots are targeted to the next subject on the waiting list. The body surface area calculation for the targeted patient is not recorded in the BR until close to the time of transplant and the surface area of the culture slices is determined the day before harvest. Your intention is to increase the number of patients that are treated each year, and multiple lots will be generated at the same time. It is unclear how the calculated dose will be factored in to which patient will receive which lot, and when in the production cycle that determination is made.
- In Discussions with (b) (4), one of the advantages to having a commercial product would be the likelihood that patients could be treated earlier from diagnosis compared to the clinical product. Younger patients might translate into lower BSA. Please comment.
- **Discussion:** Enzyvant agreed that there have been cases when less than (b) (4) of tissue resulted in a sufficient product dose. They will take FDA's observations under advisement and will continue to evaluate going forward. However, the (b) (4) source material acceptance criterion is based on their analysis of their manufacturing records and they feel that this represents the best minimum criterion to help ensure successful product lot manufacturing .

3. Information Requests

IR#1 May 2, 2019 request to perform a mycoplasma (b) (4) study; Enzyvant responding to IR #6 June 12, 2019 Enzyvant agreed to perform the study with results coming before October 2019.

IR#20 clinical ISS and ISE Information

IR#21 CMC MVD Calculations/Microbiology/endotoxin testing

IR #22 Clinical data discrepancies and #23 CMC September 18, 2019 – dose calculation and Process Validation stability histology

4. Current assessment of risk management activities, e.g, REMS – There is no anticipation of a REMS at this time.
5. Postmarketing Requirements/Postmarketing Commitments

At this time, we have identified the following PMC, but there may be additional ones depending on the strategy the Applicant and the Agency negotiate going forward.

- The need for development of a (b) (4) stability-indicating assay that reflects product quality or can indicate manufacturing issues if manufacturing changes are implemented in the future.

6. Major labeling issues

Insufficient detail in proposed labeling: The proposed package insert should accurately describe product handling and distinguish the responsibilities of health care professionals from those responsibilities of the (b) (4) personnel who will be present in the operating room. Also, you have procedures in place and a form that is used to keep track of which tissue slices were transplanted, which should be detailed. Further, information provided in response to information requests differs in what will happen to tissue that is not transplanted, how the dose will be calculated and recorded, and who will discard the tissue.

Discussion: The recently submitted 508 compliant updated package insert addresses some of the concerns raised. Enzyvant and FDA indicated remaining issues can be corrected during labeling discussions between both parties in the weeks ahead. Enzyvant agreed to try to make the labeling clearer.

7. Review Plans

A separate teleconference was scheduled for 9/20/2019 to discuss the Applicant's response to 483 items. The Agency will set up meetings with the Applicant on as-needed basis.

8. Applicant Questions

Protocol to be submitted to BLA

Initial BLA ACK section – accelerated approval

9. Wrap-up and Action Items

Container closure

Stability; shelf-life concerns

Requested updates and plans