BLA 761152

COMPLETE RESPONSE

Omeros Corporation
Attention: Catherine Melfi, Ph.D.
Vice President, Regulatory Affairs & Quality Systems
Chief Regulatory Officer
201 Elliott Avenue West
Seattle, WA 98119

Dear Dr. Melfi:

Please refer to your biologics license application (BLA) dated and received November 17, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for OMS721.

We acknowledge receipt of your major amendment dated April 23, 2021, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL AND STATISTICAL

The data presented in BLA 761152 fails to demonstrate substantial evidence of effectiveness for OMS721 for the treatment of hematopoietic stem cell transplantation-thrombotic microangiopathy (HSCT-TMA). We describe the rationale for this conclusion in further detail below.

It appears you are attempting to establish substantial evidence of effectiveness by proposing a single adequate and well-controlled trial plus confirmatory evidence, instead of two adequate and well-controlled trials.

1. With regard to your proposed adequate and well-controlled trial, there were major issues that made the estimation of the treatment response challenging. A significant number of patients (11/28 or 39%) did not meet the predefined inclusion and exclusion criteria but were included in the study. The magnitude of serum creatinine change is difficult to interpret for patients who did not meet the inclusion criterion of doubling of serum creatinine from pre-HSCT levels. Concurrent diseases (82% of patients with infections and 68% with graft versus host disease) requiring treatment with concurrent medications and the lack of an appropriate control made it difficult to attribute a treatment effect of OMS721 on

HSCT-TMA. Based on our analysis, 59% of patients that you considered to be responders had a change in immunosuppression compared to only 27% of the patients you classified as non-responders. In addition, your protocol stated that improvement in TMA markers was defined as achieving improvement in both platelet count and lactate dehydrogenase (LDH), or in just LDH if patients were not included in platelet count analysis due to failure of platelet engraftment. We do not agree with this approach, as it is unknown if data missingness would have affected the efficacy analysis. Patients with missing data that are needed to determine response, should be classified as non-responders. We identified 5 patients (b) (6) among the 17 patients identified by you as responders that we concluded should not have been classified as responders:

- Patient (b) (6) had a non-evaluable platelet response as the patient never engrafted platelets. There is insufficient evidence that the patient is a responder based on only two parameters of the response endpoint definition. In addition, cyclosporin was stopped 10 days prior to starting OMS721, and we cannot exclude the possibility that the findings for the two other parameters were attributable to cessation of cyclosporin.

- Patient (b) (6) did not meet renal inclusion criteria and the baseline serum creatinine was trending down prior to OMS721 administration; therefore, the effect of OMS721 on the renal response was unable to be determined. The platelet response is non-evaluable as the patient had not engrafted platelets, and thus, the patient only met one response criteria, LDH.

- Patient (b) (6) had a non-evaluable platelet response due to failure to engraft platelets. The LDH response was transient, and tacrolimus was stopped the same day as OMS721 so we cannot conclude that the LDH response or renal response was due to OMS721.

- Patient (b) (6) did not meet renal inclusion criteria. The patient met platelet and LDH response criteria, but there was no evidence of clinical improvement, and thus, the patient did not meet response criteria. The patient also had diagnosis of microangiopathic hemolytic anemia (MAHA) and a positive direct antiglobulin test (DAT) 80 days prior to finally meeting inclusion criteria of a negative DAT, calling into question as to whether this patient truly had DAT negative HSCT-TMA.

- Patient (b) (6) s neurological response could not be clearly attributed to a treatment effect of OMS721. Additionally, we could not conclude that the 4-week transfusion free interval was due to OMS721 due to confounders. The patient did not meet three response criteria.

Therefore, we do not agree with your calculated response rate of 17/28 (61%). Our analysis classifying these 5 patients as non-responders yields a response rate of 12/28 or 43% (95%CI: 24%, 63%).

In addition, we are unable to conclude that you have conducted an adequate and well-controlled investigation. You had intended to demonstrate at least a 15% response rate (with the 15% threshold based on expert opinion of the probable response rate in an untreated group). We do not agree that the expert opinion is sufficient to justify the 15% threshold. In addition, you submitted a literature review intended to support the selection of 15%. The literature review you conducted was not adequate from a methodological standpoint for the following reasons: unknown validity and accuracy of data, potential measurement errors associated with endpoints (response rates), variation in the definition of 100-day survival across different publications, propensity score analysis performed on limited confounding variables, lack of standardization of the timing of treatment visits across different publications, and the fact that the study was conducted using convenience samples which can introduce selection bias affecting the generalizability of the results. Even if these methodological issues could be overcome, the estimated 32% rate from the literature review falls well within the 95% confidence interval for our calculated response rate of 43% (95%CI: 24%, 63%). Thus, your study data do not establish a treatment effect.

2. Your application does not contain sufficient data that could serve as confirmatory evidence of effectiveness. Although there appears to be partial attenuation of complement activation and a delay in thrombotic onset by OMS721 in animal and in vitro models, you have not shown evidence that this translates into a measurable clinical benefit, either directly or indirectly. It is possible that OMS721's inhibition of the lectin pathway is not sufficient to alter the outcome in HSCT-TMA by a sufficient magnitude to persuasively demonstrate a clinical benefit. Our assessment found no association between OMS721 exposure or trough concentrations or the extent of complement component 4d (C4d) inhibition and the response to OMS721 treatment in patients with HSCT-TMA. Almost all patients who did not respond to OMS721 treatment had consistently comparable or higher exposure than patients who responded to treatment. Therefore, although related to the mechanism of action of the drug, the extent of C4d inhibition does not appear to be predictive of treatment response in HSCT-TMA patients.

PATH FORWARD

Additional data will be needed to demonstrate efficacy of OMS721 in HSCT-TMA. Possible options for the adequate and well-controlled investigation include:

- If a reliable responder rate in an appropriate comparator group could be determined, that might allow for retaining the current approach (threshold

analysis). You could explore alternative external data (e.g., registries) to establish a responder rate. Prior to determining the responder rate in another external data source, you should discuss your planned approach for the external control with the Division to ensure it could be scientifically valid. You would need to increase the total number of evaluable patients in TMA-001 so that the new analysis is not entirely *post hoc*, for example, to 50 as we stated in page 3 of the minutes to the January 29, 2019, meeting (see lines 2-4 of the last paragraph of our response to Question 1).

- Alternatively, you could conduct at least one randomized, controlled trial to demonstrate the effectiveness of OMS721 for the treatment of HSCT-TMA.

In addition, if you use only a single adequate and well controlled trial to support your BLA, you will also need to provide adequate confirmatory evidence; what this evidence will consist of can be discussed in a post action meeting. For example, if the current trial in atypical Hemolytic Uremic Syndrome (aHUS) were to be successful, that data might be used as confirmatory evidence for HSCT-TMA.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated, February 12, 2021, which addresses the proposed proprietary name, Yartemlea. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the dropouts from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues, but that you should address in subsequent discussions and/or a resubmission:

Clinical and Statistical

1. The clinical significance of the observed magnitude of change in laboratory values was difficult to assess in patients who had LDH just above the upper limits of normal prior to the initiation of OMS721. As the criteria for LDH response was based on an LDH <1.5 times the upper limit of normal (<1.5x ULN), it is difficult to determine the significance of LDH reduction in patients who already had an LDH <1.5x ULN prior to OMS721 treatment. The magnitude of improvement in patients with neurological or gastrointestinal dysfunction was also difficult to evaluate as these clinical manifestations could be due to a variety of potential underlying causes and treated concurrently.

2. The median time to response based on all three components of the response endpoint was 57 days, with a wide range of 13 to 228 days, and with two patients reported to have a response 100 days after the start of OMS721 treatment. Durability of response is also between 13 days to 794 days. The latency between treatment and response, as well as the wide range of durability of response, calls into question whether the 'response' is due to OMS721.

3. No studies in a pediatric population were conducted to support the proposed pediatric indication. We do not agree that full extrapolation from adults will be sufficient to support a pediatric indication. If you are seeking a pediatric indication we recommend that you discuss your data-package proposal with the Agency before initiating a pediatric assessment.

Product Quality

4. Provide low endotoxin recovery (LER) hold time study summary report and data from two additional lots of OMS721 drug product.

5. Submit the container closure integrity test (CCIT) method validation study summary report and data. The CCIT method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (*i.e.,* less than or equal to 20 µm) and note that a more sensitive and consistent method for dye detection (*e.g.,* spectrophotometry) is recommended. Perform annual sterility test in lieu of CCIT in the stability program until the CCIT method validation is complete.

Clinical Pharmacology

6. [redacted] (b) (4) you did not provide a justification for the selected supplemental OMS721 dose of 2 mg/kg. In addition, there are inconsistencies regarding the timing of administration (relative to PE) and the number of supplemental OMS721 doses. Unlike plasma infusion, PE is expected to remove large molecules such as proteins and monoclonal antibodies from the systemic circulation. The PK sampling design and the collected PK data from clinical studies were not informative enough to allow for a reliable assessment of the effect of PE on OMS721 clearance, thus impeding our ability to verify the proposed OMS721 supplemental dose of 2 mg/kg. To identify a precise dose and frequency for OMS721 supplementation following PE, we recommend that you conduct further clinical assessment in patients with appropriate collection of PK samples immediately before and after PE to methodically assess the effect of PE on OMS721 clearance.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Courtney Hamilton, Regulatory Project Manager at 301-796-6849 or at Courtney.Hamilton@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
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