

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761152Orig1s000

**ADMINISTRATIVE and
CORRESPONDENCE DOCUMENTS**

IND 120524

MEETING PRELIMINARY COMMENTS

Omeros Corporation
Attention: Catherine A. Melfi, PhD
Vice President, Regulatory Affairs & Quality Systems
201 Elliott Avenue West
Seattle, WA 98119

Dear Dr. Melfi:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OMS721.

We also refer to your August 29, 2019, correspondence, received August 29, 2019, requesting a meeting to discuss and reach agreement on information to be included in the biologics license application (BLA) for OMS721.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Kris Kolibab, PhD
Senior Regulatory Health Project Manager
On behalf of Division of Hematology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

¹We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

ENCLOSURE:

- Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: November 21, 2019; 1:00PM – 2:00PM (EDT)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, MD 20903

Application Number: 120524
Product Name: OMS721
Indication: For the treatment of patients with hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA).
Sponsor Name: Omeros Corporation

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 21, 2019 between Omeros Corporation and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Omeros Corporation requested a Type B Pre-BLA meeting with FDA on August 29, 2019, to discuss and reach agreement on the analyses and overall package for the administrative, nonclinical, and clinical information to be included in the BLA for OMS721.

Omeros is developing OMS721, a human IgG4 monoclonal antibody directed against MASP-2, for both SC and IV administration to treat lectin complement pathway-

mediated diseases. OMS721 has been evaluated in two Phase 1 studies in healthy volunteers, one Phase 2 study in patients with TMAs, including HSCT-TMA, atypical hemolytic uremic syndrome (aHUS), and thrombotic thrombocytopenic purpura (TTP), and one Phase 2 study in patients with glomerulopathies.

Preamble:

We strongly recommend that you submit a pre-BLA meeting package to discuss and review the the top-line efficacy data from your phase 2 trial prior to submission of final clinical portion of the application. It is important that the topline efficacy data is statistically persuasive and clinically meaningful to support a regulatory decision. We have several comments regarding your proposed analyses plan (see response to question 5).

Provide your justification and data to support the proposed dosing regimen for the Agency's review prior to the pre-BLA meeting. Provide your justification to support the proposed dosing regimen prior to the pre-BLA meeting. See FDA Response to Question 12.

2.0 DISCUSSION

2.1. Regulatory and Administrative Questions

Question 1:

Does FDA agree that providing the items described in the proposed Table of Contents for the submission will constitute a complete, reviewable package?

FDA Response to Question 1:

We cannot fully agree with items in proposed Table of Contents until we review your top line efficacy and safety data. Please see preamble. The decision as to whether the submission is complete for review is made during the filing review.

We have the following additional comments:

From your proposed table of content, it is unclear where you are planning to include an Integrated Summary of Immunogenicity within your BLA submission. We recommend that you provide an Integrated Summary of Immunogenicity in eCTD subsection 2.7.2.4 Special Studies or subsection 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should include:

- i. An immunogenicity risk assessment specific to your product
- ii. Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods used in the program

- iii. Links to method development and validation reports for the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from the pivotal clinical study(ies)
- iv. Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed
- v. Summary results of immunogenicity analysis for all clinical studies that collected immunogenicity data, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data
- vi. Traceability of drug product lots used in all your clinical studies
- vii. All immunogenicity assays, that were used during clinical development and a description of which assays were used for which studies or patient groups

Question 2:

Does the FDA agree with the approach and location for the information related to the 4-letter suffix?

FDA Response to Question 2:

The Agency recommends that you submit a request for FDA review of proposed suffix. This submission should occur no earlier than at request for a pre-biologics license application (pre-BLA) meeting for biologicals products to be submitted under section 351(a) of the PHS Act. It is acceptable to include information related to the 4-letter suffix in Module 1.12 in a BLA submission.

However, please see preamble.

Question 3:

Does the FDA agree with Omeros' proposal regarding development of a REMS for narsoplimab?

FDA Response to Question 3:

The decision on whether your product requires a REMS will be made during the review of the application. You will need to provide a comprehensive analysis of safety supported by data and literature to help the Agency make determination on need for REMS.

2.2. Clinical Questions

Question 4:

Does FDA agree with the clinical studies and associated study report formats for inclusion in the BLA?

FDA Response to Question 4:

We cannot agree until we review top-line data. Please refer to preamble and see response to question 5.

Question 5:

After review of the draft SAPs, does FDA agree with the analyses proposed to demonstrate efficacy and safety of narsoplimab in the treatment of patients with HSCT-TMA?

FDA Response to Question 5:

No, we have several comments regarding proposed analyses plan.

- Provide clarification for the information provided on page 73 of the meeting package in the sample size calculation section. It is unclear what is meant by the response rate and the observed response rate and if these are results from the 27 HSCT-TMA patients in the trial. Confirm the status of the data analyses from the 27 patients.
- With regards to the sample size calculations, propose a decision rule for determining the drug's efficacy (e.g., the response rate that you plan to rule out for your 95% CI).
- We acknowledge that you have proposed to use non-responder imputation to handle missing data for the binary efficacy endpoints. Since this is a small study with only approximately 27 patients to be enrolled, we recommend you also conduct the analysis based on the observed data (i.e., no imputation) and provide a lattice plot of patient profiles over time for platelet count and LDH. In addition, for any planned pooled analyses provide analyses for the original groups.
- We are concerned that the measurement of neurological improvement may be subjective and open to bias. We recommend that you incorporate an objective neurological assessments for determining the cessation of seizures or other neurological events in the clinical benefit component of the primary endpoint
- We are concerned that the 27 patients in the HSCT-TMA cohort comprising the primary analysis include both fixed and body weight dosing schemes. Refer to response to Question 12 for inclusion of this mixed patient population in the primary analysis.

Question 6:

Does FDA agree with this approach around the patient narratives?

FDA Response to Question 6:

The approach you propose for the patient narratives are acceptable.

Question 7:

After review of the example narratives, does FDA agree with the content and format of the HSCT-TMA patient narratives? Does FDA agree with the location of the patient narratives in Module 5?

FDA Response to Question 7:

In the graphical displays, we recommend that you include a line or marker indicating when the study drug was initiated as well as the transplant date and TMA diagnosis date.

Question 8:

Does FDA agree with the plan of presenting the efficacy information within Module 2.7.3, Summary of Clinical Efficacy?

FDA Response to Question 8:

There may be situations in which section 2.7.3, Summary of Clinical Efficacy would be sufficiently detailed to serve as the narrative portion of the ISE, while still concise enough to meet the suggested size limitations for Module 2. Clarify if you anticipate that the ISE (narrative and all tables/appendices) can fit the space requirements for Module 2.

It is possible that the narrative portion of the ISE can be split across Modules 2 and Module 5 with narrative portion located in section 2.7.3 and the appendices of the tables, figures and datasets located in section 5.3.5.3. If you choose to split the across the modules, it is critical to include clear explanations of where the parts are located and this should be placed in both Module 2 (section 2.7.3) and in Module 5 (section 5.3.5.3). Please refer to the following guidance for additional details: Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.

Question 9:

Does FDA agree with the approach to present the safety analyses by disease groups?

FDA Response to Question 9:

We recommend that you include datasets for safety for the patients who received narsoplimab on the compassionate use program. In Appendix C (Safety Narratives Template), include the time of resolution of the adverse event. Please also see preamble.

Question 10:

Does FDA agree with the approach not to re-code adverse events from healthy volunteer studies?

FDA Response to Question 10:

The proposal to not re-code the adverse events from healthy volunteer studies appears reasonable. Include the MedDRA code that was used to assess the adverse events in the healthy volunteers.

Question 11:

Does FDA agree with the location of the safety analyses?

FDA Response to Question 11:

It is possible that the narrative portion of the ISS can be split across Modules 2 and Module 5 with narrative portion located in section 2.7.4 and the appendices of the tables, figures and datasets located in section 5.3.5.3 if the narrative portion is concise enough to meet the suggested size limitations for Module 2. If you choose to split the across the modules, it is critical to include clear explanations of where the parts are located and this should be placed in both Module 2 (section 2.7.4) and in Module 5 (section 5.3.5.3). Please refer to the following guidance for additional details: Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.

Question 12:

Does FDA agree with the proposed population PK/PD analysis plan to support the recommended dose for treatment of patients with HSCT-TMA?

FDA Response to Question 12:

In addition to your proposed PK/PD analysis plan, your justification to support the proposed dosing regimen should also include dose-response and exposure-response analyses for efficacy and safety and an assessment of the effect of body size (e.g., body weight) on pharmacokinetics and pharmacodynamics of narsoplimab

to support body weight-based dosing. The final acceptability of your proposed dosing regimen for treatment of patients with HSCT-TMA will be a review issue.

Question 13:

Does FDA agree with the proposal around the 90-Day Safety Update?

FDA Response to Question 13:

The safety update should include any new safety information that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. If there are any new safety findings with the safety update than the appropriate safety documents would need updating.

Additional Clinical Pharmacology Comments:

Clinical Pharmacology has the following recommendations regarding your BLA submission:

- I. We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” (available at <https://go.usa.gov/xn4qB>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.
- II. Address the following questions in the Summary of Clinical Pharmacology:
 1. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 2. What are the exposure-response relationships for efficacy, safety and biomarkers?
 3. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
 4. What is the impact of immunogenicity on exposure, efficacy and safety?
- III. Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
2. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with range as appropriate.
3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
4. Submit the following for the population pharmacokinetic analysis reports:
 - Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
5. Submit the following information and data to support the population pharmacokinetic analysis:
 - SAS transport files (*.xpt) for all datasets used for model development and validation
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient

population. Refer to Guidance for Industry at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for population PK <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for exposure-response relationships, and <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and models submission guidelines.

3.0 OTHER MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 4, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.²

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new

² <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).³

³ <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants⁴ to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁵

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁶ and Pregnancy and Lactation Labeling Final Rule⁷ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

⁴ See the guidance for industry "*Formal Meetings Between the FDA and Sponsors or Applicants.*"

⁵ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁶ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁷ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the **U.S. Food and Drug Administration**
Silver Spring, MD 20993
www.fda.gov

time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁸

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR⁹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid¹⁰

⁸ <https://www.fda.gov/media/85061/download>

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

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/

KRISTOPHER KOLIBAB
11/08/2019 02:09:33 PM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120524

MEETING MINUTES

Omeros Corporation
Attention: Catherine A. Melfi, PhD
Vice President, Regulatory Affairs & Quality Systems
201 Elliot Ave West
Seattle, WA 98119

Dear Dr. Melfi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for OMS721.

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2018. The purpose of the meeting was to discuss phase 3 program design and the clinical studies to support submission of a BLA for OMS721 in the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (HCT-TMA).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B/EOP
Meeting Category: EOP2/Pre-P3

Meeting Date and Time: April 24, 2018; 1:00PM – 2:00PM (EDT)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 120524
Product Name: OMS721
Indication: Treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (HCT-TMA).
Sponsor/Applicant Name: Omeros Corporation

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Kris Kolibab, PhD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP):

Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Acting Clinical Team Leader
Patricia Oneal, MD, Medical Officer
Kris Kolibab, PhD, Senior Regulatory Project Manager

Office of Biostatistics, Division of Biometrics V (DBV):

Jingjing Ye, PhD, Statistics Reviewer

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology V:

Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Christopher Bral, PhD, VP, Nonclinical Development
Gregory Demopoulos, MD, Chief Executive Officer
Rafael Duarte, MD, PhD, FRCP, Clinical Consultant
Jonathan Harris, Sr. Director, Regulatory Affairs, CMC
Catherine Melfi, PhD, VP, Regulatory Affairs and Chief Regulatory Officer
David Monteith, PhD, Product Team Leader

Edmund Ng, PhD, Statistical Consultant
Alessandro Rambaldi, MD, Prof, Clinical Consultant
Steve Whitaker, MD, VP, Clinical Development and Chief Medical Officer

1.0 BACKGROUND

Omeros Corporation requested a Type B/End of Phase meeting with FDA on February 7, 2018 to discuss phase 3 program design and the clinical studies to support submission of a BLA for OMS721 in the treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy (HCT-TMA).

Omeros Corporation is developing OMS721, a human IgG4 monoclonal antibody directed against MASP-2, for both SC and IV administration to treat lectin complement pathway-mediated diseases. The drug product used in most of the clinical studies to date contains 100 mg/mL active ingredient, 20 mM sodium acetate, 50 mg/mL sorbitol, and 0.01% polysorbate 80 at pH 5.0. Omeros is using the higher concentration (185 mg/mL) drug product in ongoing Phase 3 trials, for future clinical trials, and for commercialization.

FDA sent Preliminary Comments to Omeros Corporation on April 18, 2018.

2. DISCUSSION

Preamble

While we are encouraged by your preliminary results in patients with HCT-TMA, we have several comments regarding your overall development plan of OMS721 in patients with TMA.

- Please provide an explanation why OMS721 demonstrated little efficacy in patients with TTP or aHUS.
- Provide an explanation why the biweekly or three times a week dosing of OMS721 was given to the compassionate-use patient compared to the weekly dosing used in Study OMS721-TMA-001.
- Given that the volume of distribution of OMS721 (0.071 L/kg) is similar to that of blood volume (~ 0.08 L/kg). Please address if changes in volume status (such as hypervolemia due to therapy interventions) may have an impact on the PK/PD and/or efficacy of OMS721 in patients with HCT-TMA.

2.1. Questions

Question 1:

HCT-TMA is a disease with a high mortality rate and, compared with a literature-based best-matched historical control, OMS721 shows a large improvement in estimated median survival in HCT-TMA patients. In addition, treatment with OMS721 is associated with a substantial reduction or complete cessation of transfusion requirements in patients with HCT-TMA. Given FDA's stated intention to make life-saving treatments available to patients

sooner, OMS721 for the treatment of HCT-TMA appears to be an ideal candidate for the accelerated approval pathway.

Can data collected to date together with additional data collected prior to the data cut-off date in HCT-TMA patients from the current Phase 2 trial be used as the basis for accelerated approval with the data from the proposed confirmatory study providing evidence in support of full approval?

FDA Response to Question 1:

The Agency may require evidence of effectiveness to support accelerated or traditional approval from two adequate and well-controlled trials. There are occasions in which a single trial with supportive data may be used support an application; however, the trial should be well designed, well conducted, internally consistent and provide clinically meaningful and statistically persuasive efficacy findings with an acceptable risk benefit profile.

In your study (OMS721-TMA-001), we note that no significant change was observed in the mean creatinine levels, the transfusion burden endpoints are not prospectively evaluated in your on-going study and that time-to-event data is not interpretable in a single arm trial.

The Agency stresses the importance of demonstrating a meaningful clinical benefit for patients with HCT-TMA which could include reduced transfusion burden and or improvement in end-organ function. Improvement in hemolysis/TMA parameters are supportive.

To strengthen a potential future initial application, we strongly recommend that you prospectively evaluate OMS721 on meaningful endpoints for this disease (i.e., reduction in transfusion burden or improvement in end-organ damage). The prospective evaluation should include pre-defined efficacy endpoints and adequate prospective and longitudinal collection of information on transfusion burden and end-organ involvement. We recommend that the preliminary data from OMS721-TMA-001 guide and inform you in the design of well-controlled trial evaluating clinical meaningful endpoints for this disease.

In addition, we have the following comments regarding your proposal:

1. You did not provide the clinical protocol and detailed statistical analysis plan (SAP) for your study in meeting package, so the evaluation is based on our understanding of your study design and analysis results.
2. You proposed to evaluate the efficacy based on a single-arm study with four different efficacy evaluations.
3. For survival data (#2 in efficacy justification), the trial is a single-arm phase 2 study OMS721-TMA-001, which treated 18 patients. Since time-to-event data cannot be interpreted by using single-arm trial, you tried to match historical control to justify the substantial improvement in OS. Two things are unclear:

- a) In the survival data from the literature, you did not include all patients in the published literature. For example, in the published literature of Arai 2001, there were 6 patients with OS data, while you included 4 out of 6. The reason why the patients were excluded should be justified clinically to match the inclusion/exclusion criteria of the trial. The patients and disease characteristics would need to be provided to sufficiently compare between your study population and the historical control. Ideally, you should have the protocol in place and match historical control patients prior to seeing the results of your clinical trial;
 - b) For survival data, it is unclear if you considered censoring in the OS when the comparison between your drug and historical control was done.
4. For change from baseline (#3 in efficacy justification), you did pair-wise comparison between each timepoint and baseline. There are two issues:
- a) The data are compared multiple times without adjusting for multiple comparison;
 - b) The missing measurements seem not to be considered.

Since the data is collected longitudinally, there are correlation for intra and inter-patients. An alternative statistical method considering mixed effect to test the trend of improving could be considered.

5. In addition, since multiple endpoints are proposed in the study, it is unclear which of those evaluations is considered primary or secondary. You would need to pre-specify how you would control the study-wise type I error control in the registration trial. In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analyses of the primary endpoint cannot result in (either singularly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Adjustments should be made for multiplicity to guarantee a study-wise one-sided 0.025 type I error rate.

Discussion:

The Agency and the Sponsor had a general discussion on the development plan for OMS721 for the treatment of patients with HSCT-TMA and potential paths forward that would support a future NDA application. The Sponsor is seeking to submit the data from the patients enrolled in OMS721-TMA-001 to support an NDA.

The Agency noted that the preliminary efficacy results with OMS721 in patients with HSCT-TMA appear encouraging however to support a potential application the Sponsor will need to provide data that adequately describes the treatment effect of their drug in a well-defined population.

The Agency reiterated that an improvement hematologic improvement (i.e hemolysis markers) is not sufficient for an approval and that there needs to be a demonstration of improvement on a clinical meaningful endpoint. Although the overall survival data from your single arm trial appears intriguing, there are challenges with the interpretation of OS in a single arm trial.

The Agency also stressed the importance of adequately defining the study population and inclusion of detailed narratives that describe type of transplantation(myeloablative/non-myeloablative), conditioning regimen, HLA mismatch, type of GVHD prophylaxis, donor source) will be critical to better define the population. The same scrutiny should be given to the matched historical controls to identify a similar population.

We recommend that you include and discuss your plans for the following items at a subsequent meeting with the Agency:

- Adequately define the study population [ie, type of transplantation, donor type, prior treatment for HSCT-TMA (plasma exchange, change in immunosuppression), underlying disease, HLA mismatch, and status of underlying disease, type of GVHD prophylaxis, conditioning regimen etc).**
- Define and describe in detail the matching procedures for the historical control**
- Detailed efficacy narratives for study patients in OMS721-TMA-001 and the matched historical controls**
- Detailed transfusion history for each patient to include platelet transfusion independence and PRBC independence after receiving OMS 721.**
- Clarify how missing data will impact assessment of hematologic parameters.**
- Clearly define what is meant by the “high risk” HSCT-TMA.**
- Consider the statistical methodology to address potential bias and variability when evaluating treatment benefit using historical controls**
- Determination or attempt to determine likely etiology for development of HSCT-TMA for each study patient and matched historical control.**

The Agency also recommends that the Sponsor explore data from registries such as Center for International Blood and Marrow Transplant Research (CIBMTR) or the European Society for Blood and Marrow Transplantation(EBMT) registry to provide information on the incidence, etiology, treatment and outcome to include such items as: age, donor type, HLA mismatch, GVHD prophylaxis. The data obtained from the registry may inform you to better describe and define patients who develop HSCT-TMA and thus help to further define study population.

The Agency noted that the Sponsor is proposing evaluating 2 dosage regimens in the confirmatory study. The agency stated that the Sponsor should evaluate the PD markers obtained from their ongoing study to assess the adequacy of their dose. The Sponsor stated that a PD marker data was not available yet and that they will be

evaluating this issue in the context of dose selection. The Agency reminded them that they should leverage the available PK/PD data for modeling and simulation for the determination of their dosing strategy.

The Agency is open to further discussions with the Sponsor regarding OMS721 in the treatment of patients with HSCT-TMA. We recommend that you request a follow-up meeting to discuss comments identified above as well as the comments discussed in the preliminary meeting comments sent on April 18, 2018.

Question 2:

Study OMS721-TMA-001 is an open-label, multicenter study of OMS721 that is currently enrolling only HCT-TMA patients with persistent HCT-TMA. To date, 18 patients with HCT-TMA have been enrolled in the study. One additional patient with HCT-TMA has been treated outside the clinical trial under compassionate use. A literature review was conducted to identify a best-matched historical control for comparison to the outcomes of patients with HCT-TMA treated with OMS721. The median overall survival across the combined historical studies was 21 days (95% CI: 15 to 29 days). The estimated median overall survival in the patients treated with OMS721 was 347 days (95% CI: 78 to NE), demonstrating that overall survival is far greater in patients who received OMS721 ($p < 0.0001$).

Does FDA agree that a single-arm, open-label study in patients with HCT-TMA and, for comparison, use of a historical control based on the literature is adequate to provide the efficacy data needed to support submission of a BLA in this indication?

FDA Response to Question 2:

No, please see response to question 1.

Discussion:

No discussion occurred.

Question 3:

Patients with high-risk HCT-TMA have complex ongoing co-morbidities and widely varying outcomes. In such a population at increased risk for mortality, overall survival represents an endpoint that can be obtained from a historical control and readily measured in a clinical trial.

Does FDA agree that overall survival is an appropriate primary endpoint for approval of the proposed indication?

FDA Response to Question 3:

You are proposing an indication based on results from a single-arm study. As stated above, time-to-event endpoints including overall survival are not interpretable in a single arm trial. For consideration of using comparison with historical control, please refer to comment #1.

Discussion:

No discussion occurred.

Question 4:

To date, approximately 200 subjects have been enrolled in clinical trials in the OMS721 clinical development program; over 160 subjects have been dose with OMS721. OMS721 has been well tolerated at doses up to 4 mg/kg IV three times weekly for more than 52 weeks.

Does FDA agree that data from patients with IgAN or aHUS treated with OMS721 can comprise a portion of the safety database to support approval of OMS721 for patients with HCT-TMA?

FDA Response to Question 4:

Please comment on the exclusion of patients with TTP from safety database.

In general, it is reasonable to include patients treated with IgA nephropathy or aHUS in a safety database to evaluate the safety of OMS721 in a potential future application. We recommend that you capture follow-up data for a minimum of 12 months in all subjects with HCT-TMA enrolled in your trial.

Discussion:

No discussion occurred.

Question 5:

Omeros is proposing a confirmatory single-arm uncontrolled study including patients having TMA diagnoses by the Jodele criteria with high-risk features as described. Patients will be treated with response-based criteria.

Does FDA agree with the single-arm confirmatory study design including patients with high-risk TMA as defined and response-based treatment?

FDA Response to Question 5:

We cannot agree with the study design until review of the full protocol. We have the following comments regarding your proposed study in patients with HCT-TMA:

- We recognize the importance of identifying patients with TMA who may benefit the most from therapeutic interventions and *Jodele et al* as you described has identified a risk stratification algorithm to identify the highest risk pediatric and young adult patients who may benefit from therapeutic intervention. It is unclear if you intend to enroll adolescents and young adults as well as older adults. If available, please provide the following information:
 - Clarify if you intend to enroll only adolescents and young adults
 - Describe if you expect to see a difference in response to OMS721 by patients with high risk versus non-high risk disease
 - Expected number of patients that would be considered high risk based on the algorithm by Jodele et al.
- A high risk population has not been adequately defined in the older adult population. Enrolling young adults and adults patients may pose challenges in describing the treatment effect of OMS721 as the population may be too heterogenous. If available, provide any information or data for risk stratification in the adult population with HSCT-TMA and or justification to apply the risk stratification used in the pediatric and young adults to the older adult population.
- Acknowledging the numerous diagnostic criteria and evaluation of clinical responses for HSCT-TMA, provide the rationale in the protocol for the diagnostic criteria chosen and applicability of the diagnostic criteria to proposed population.
- Clarify if your proposed trial intends to enroll patients with high risk TMA (identified by Jodele et al) and patients who do not meet the high risk features at time of TMA diagnosis and have not responded to withdrawal of calcineurin inhibitors or who have developed end-organ damage. We note that these may be two different populations and describing the treatment effect may be challenging as the populations may be different.
- We do not agree with overall survival as the primary endpoint as time-to-event endpoints are not interpretable in single-arm trial. You will need to demonstrate the OMS721 has demonstrated improvement on a meaningful clinical endpoint for this disease.
- Examples of meaningful clinical endpoints in patients with HSCT-TMA may include improvement in improvement or stabilization in renal function or other end-organ damage or decrease in transfusion requirements or transfusion independence provided adequately defined in the protocol and assessment not impeded by confounding factors. We note that what is appropriate clinical benefit may depend upon the exact population enrolled (i.e. high risk population).
- You will need to provide rationale and definitions for response criteria (i.e. definition of LDH response, platelet response) and the rationale for choosing the threshold for response if not including complete normalization.

- If evaluating improvement or stabilization in renal function, you will need to provide the rationale that measuring proteinuria in adults is a demonstration of improvement in renal function.
- You will need to provide the assumptions for expected response rates (i.e. hematologic parameters, renal function improvement, transfusion burden improvement) for sample size determination, depending upon study design and eventual patient population selected.
- Provide data supporting the use of a fixed dose of 370 mg IV rather than the weight based dose of 4 mg/kg in patients with HCT-TMA. We reiterate our recommendation that you optimize the dose regimen before starting trials intended to demonstrate safety and efficacy in support of a marketing application. Pool clinical pharmacokinetic, pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated dose-response and exposure-response analyses for dose optimization.

We can provide you additional details and comments once we review full protocol and proposed statistical analyses plan.

Discussion:

No discussion occurred.

Post Meeting Addenda:

The Agency wants to highlight two recent publications that may be useful in further defining the study population:

- **Li, A., Davis C., Pham P. et al. Transplant-Associated Thrombotic Microangiopathy (TA-TMA): Not a Singular Entity. Blood 2017 130:666**
- **Postalcioglu M. Characterization of Population of HSCT Associated Thrombotic Microangiopathy(TMA) Biol Blood Marrow Transplant 23 (2017) S18-S391.**

3.0 OTHER MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of

your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor provided the attached slide deck for the meeting.

23 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TANYA M WROBLEWSKI
04/30/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 120524
Request Receipt Date	February 28, 2018
Product	OMS721
Indication	Treatment of patients with hematopoietic stem-cell transplant associated thrombotic microangiopathy (HCT-TMA)
Drug Class/Mechanism of Action	Human IgG4 monoclonal antibody / Human IgG4 monoclonal antibody that binds to and inhibits manna-binding lectin associated serine protease 2 (MASP-2), an effector enzyme of the lectin pathway of complement.
Sponsor	Omeros Corporation.
ODE/Division	OHOP/DHP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	April 29, 2018

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Treatment of patients with hematopoietic stem-cell transplant associated thrombotic microangiopathy (HCT-TMA) who have persistent TMA despite modification of immunosuppressive therapy.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** YES NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹? YES NO

Hematopoietic stem cell transplantation (HCT)-associated thrombotic microangiopathy (HCT-TMA) is a well-recognized and potentially severe complication of HCT which can lead to death. The incidence of TA-TMA is 10–35% as reported in the largest retrospective reviews and studies.

Abnormalities of the vascular endothelium, independent of ADAMTS-13 activity, are believed to be critical to the pathogenesis of TMA, but the exact mechanisms of endothelial inflammation remains to be determined. HCT-TMA is identified when SCT patients present with microangiopathic hemolytic anemia, defined as de novo acute anemia and thrombocytopenia not explained by another process, elevated lactate dehydrogenase (LDH), excessive transfusion requirements, and schistocytes in the blood. While the kidney is most commonly affected, HCT-TMA involves organs such as the lung, bowel, heart, and the brain.

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

The diagnosis of HCT-TMA is very challenging and is often a diagnosis of exclusion. The diagnosis usually occurs at a median of 32 days after transplantation. Many if not most of these patients have concomitant illnesses such as steroid refractory graft-versus host disease (GVHD), ongoing infections and concomitant medications (nephrotoxic anti-microbials, and immunosuppressive agents).

There are no approved FDA treatments for HCT-TMA. Initial treatment usually consists of supportive measures such as withdrawal of calcineurin inhibitors, plasmapheresis and withdrawal of potential triggers. There are case reports of the use of rituximab, defibrotide, and eculizumab for the treatment of HCT-TMA with varying success rates. The mortality rates for patients with HCT-TMA who fail supportive measures is approximately 80-100% in initial 3 months after diagnosis. There is no spontaneous improvement.

If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES the BTDR is adequate and sufficiently complete to permit a substantive review
 - Undetermined
 - NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
 - i. Only animal/nonclinical data submitted as evidence
 - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Drug/Mechanism of Action:

OMS721 is a human IgG4 monoclonal antibody that binds to and inhibits manna-binding lectin associated serine portease 2 (MASP-2), an effector enzyme of the lectin pathway of complement. MASP-2 is an enzyme of the lectin pathway of the complement that initiates a proteolytic cascade leading to a membrane attack on the integrity of the cell membrane. It also leads to the production of C3a and C5a as anaphylatoxins that activates the endothelial membrane.

Animal models assessing tissue damage treated with MASP-2 monoclonal antibodies have shown improved outcome. Ex vivo models of TMA using activators like human sera, platelets and ADP were treated with OMS721. The endothelial damage plays a central role in the initiation of HCT-TMA causing further cell injury and worsening HCT-TMA.

Regulatory History

- IND 120524 submitted on March 3, 2014.
- Omeros granted fast track for treatment of atypical hemolytic uremic syndrome (aHUS) in July 2015.
- The Agency granted BTD in June 2017 for IgA nephropathy for reduction in proteinuria (4 patients average 73% reduction).
- The Sponsor was granted Orphan Drug Designation for OMS721 in the prevention of complement-mediated TMA and treatment of IgA nephropathy on December 16, 2013 and August 03, 2017, respectively.

Omeros submitted a preliminary BTD request in Oct 2016 for patients at high risk for HSCT-TMA. The agency recommended that the Sponsor continue to enroll additional patients due to low sample size (n=5) and recommended an increase of approximately 20 patients and demonstrate improvement in a clinically significant endpoint (renal function) as improvement in hemolysis or TMA markers alone is not sufficient. Another preliminary BTD request was submitted in Sept 2017. Supporting information on ten patients was included. The Agency recommended that the Sponsor including information to support BTD request that included a clinically significant endpoint aside from a reduction or normalization of hemolysis markers should include the following:

- Transfusion independence or
- Stabilization or improvement in renal function for consideration of a formal breakthrough designation.

Available therapies: There are no FDA-approved therapies. However, plasmapheresis, defibrotide, eculizumab, steroids and/or rituximab, renal transplantation are described in the literature in the management of HCT-TMA. The mortality rate for patients who fail supportive measures is in excess of 80% by 3 months after diagnosis.

7. Information related to endpoints used in the available clinical data:

- a. Endpoints considered by the Sponsor as supporting breakthrough therapy designation:
 - o Improvement in hemolysis parameters(thrombotic microangiopathy markers(LDH, platelets, haptoglobin)
 - o Reduction in transfusion requirements
 - o Overall Survival
- b. Endpoints accepted by the Division as a clinically significant endpoint (outcome measure) for patients with the disease:

- Reduced transfusion burden
 - Improvement in end-organ damage (i.e.kidney or neurological function)
 - Supportive: improvement in hemolysis parameters[thrombotic microangiopathy markers (LDH, Platelets, Haptoglobin) and overall survival
- c. Any other biomarkers the division would consider likely to predict a clinical benefit event if not yet a basis for accelerated approval.
- No
- 8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

There are no FDA-approved therapies for the treatment of HCT-TMA.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

None.

10.Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

OMS-721-TMA-001: Phase 2, 3-stage, open-label, multi-center study in atypical hemolytic anemia syndrome(aHUS), thrombotic thrombocytopenia purpura (TTP) or HCT-TMA. Stage 1 is dose finding stage and Stage 2 is dose expansion at 4.0mg/kg IV weekly x 4 weeks (HCT-TMA) and Stage 3 is an extension study for patients who are responding.

- Primary Objective: safety and efficacy/PK/PD, Anti-drug antibody
- Primary Endpoint: Overall survival
- Secondary Endpoints: Improvement in TMA markers: platelet count, LDH, haptoglobin
- Current enrollment for patients with HCT-TMA: 18 patients

Population for HCT-TMA: Onset of HCT-TMA at least 30 days from transplant or at least two weeks following modification of calcineurin inhibitor treatment, platelet count < 150,000, evidence of macroangiopathic hemolysis (presence of schistocytes, LDH > upper limit of normal, or haptoglobin < lower limit of normal, and renal dysfunction).

Compassionate Use: One (b) (6) treated on compassionate use protocol.

Sponsor evaluated efficacy in four ways for HCT-TMA population:

- Individual patient narratives (n=14) for 14 patients. Of the 18 patients enrolled, narratives only available for 14 patients. Five patients without sufficient duration on study and no narratives available. One narrative is for (b) (6) treated with OMS-721.
- Analysis of mean changes from baseline in hemolysis/TMA markers: platelet count, LDH, haptoglobin and creatinine

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- Analysis of transfusion data for 14 patients who had available charts and narratives
- Survival analysis from all 19(all OMS721 treated patients)

A total of 19 patients have been treated with OMS721 for HCT-TMA

Evaluable Population: N=14 (13 patients from OMS 721-TMA-001 and 1 compassionate use patient) consisted of the 14 patients with narratives.

Demographics (N=14):

Median age: 49 (14,68)

Underlying Diagnosis: AML, ALL, MF, MDS, refractory lymphoma, Diamond-Blackfan anemia

TMA diagnosis: median day post transplant: 60 (22,249)

Treatment duration: median 8 weeks (2,54)

Efficacy Evaluation

Efficacy Parameter	N=14
>50% Reduction in transfusion burden or cessation of transfusions (platelets and PRBC)	7/14(50%)
Transfusion independence (platelets or PRBC)	6/14(43%)
Improvement by at least 50% from baseline in all parameters (LDH, platelets, haptoglobin, creatinine)	4/14(28%)
Improvement by at least 50% from baseline in hemolysis parameters	8/14(57%)

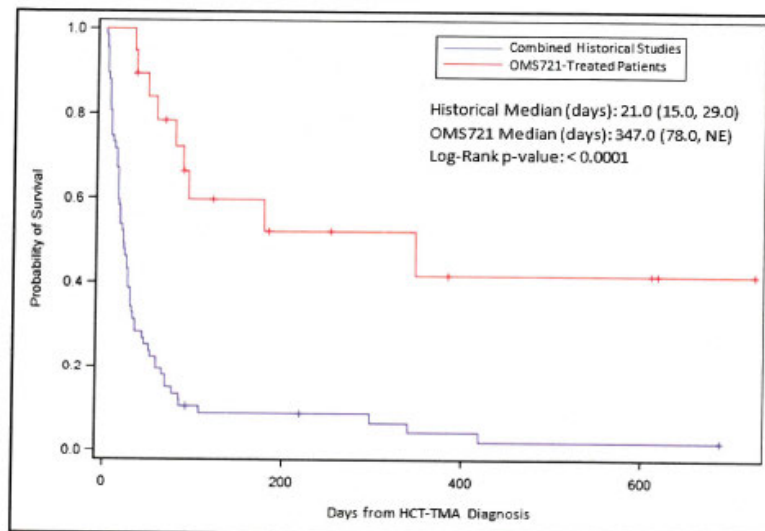
- At week 4, mean platelet count change increased from baseline of 1000/ul to greater than 25,000/ul for 11/14 (78%) of patients. Mean LDH change decreased to 300U/L below baseline in 10/14 (71%).
- Two patients had recurrence of worsening of TMA after stopping or reducing frequency of OMS721 and upon restarting OMS721 had improvement in HCT-TMA.
- Twenty-eight percent of patients had an improvement in renal function.

Supportive Data

This data is representative of the historical studies from published manuscripts from 2000 or later related to HCT-TMA survival among the best-matched historical control patients. The review of these studies demonstrated a median OS of 21 days (95% CI: 15, 29) (p = .102) (Figure 5). The median OS in the OMS721-treated patients was 347 days (95% CI: 78, NE) (p <0.0001) (Figure 6).

Ten patients out of 19 total treated patients are still alive with median number of days of 347.

Figure 6: Kaplan-Meier Plots of Overall Survival for OMS721-Treated Patients and for Combined Historical Studies



Notable Dramatic Improvement in Clinical Course

There are two patients with dramatic improvement in their clinical course that warrant further discussion as spontaneous improvement does not occur in this disease.

- (b) (6) with Diamond-Blackfan anemia and empty sella syndrome. (b) (6) received a 9/10 matched unrelated HSCT and diagnosed with TMA on Day 167 and required two admissions for persistent TMA. (b) (6) developed renal failure requiring hemodialysis and platelet transfusions. First dose of OMS721 given on day 404 and by day 432, hemodialysis discontinued to twice weekly and dose of OMS721 was reduced. TMA worsened and dose of OMS721 increased to three times a week and TMA improved. As of day 630, patient remains off hemodialysis.
- (b) (6) male with acute lymphoblastic leukemia(ALL) with complicated post transplant course with GVHD, CMV infection and development of HCT-TMA that did not respond to conservative measures. He developed tetraparesis and axonal myopathy after diagnosis of TMA and considered due to TMA. After starting treatment with OMS721, TMA resolved, neurological symptoms improved and patient was able to walk and return to work.

Safety

Based on safety population of 18 patients, treatment emergent adverse events in > 5% of patients consistent with expected TEAEs in this population.

Preferred Term	Safety Population Overall (n=18)
Anemia	3 (16.7%)
Neutropenia	4 (22.2%)
Fatigue	4 (22.2%)
Graft versus host disease	3 (16.7%)
AST increased	2 (11.1%)
ALT increased	2 (11.1%)
Acute renal failure	3 (16.7%)
Pulmonary edema	3 (16.7%)

11. Division's recommendation and rationale (pre-MPC review):

GRANT Provide brief summary of rationale for granting:

- Hematopoietic stem cell transplantation associated thrombotic microangiopathy (HCT-TMA) is a severe and potentially fatal complication of HCT. Mortality is in excess of 80% for patients that do not respond to conservative treatment (i.e. withdrawal of immunosuppression, TPE). Spontaneous improvement in transfusion requirements, hemolysis markers and end-organ damage does not occur in patients with HCT-TMA. There are no FDA approved therapies for HCT-TMA.
- The use of OMS721 in patients with HCT-TMA has shown an improvement over available therapy on clinically significant endpoints
 - Transfusion independence (43%)
 - > 50% reduction in transfusion burden or cessation of PRBCs/platelets (50%)
 - Stabilization or improvement in renal function (28%)
 - 10 patients still alive with median 247 days supports durability of response
- Supportive efficacy data demonstrates the following:

- Improvement in hemolysis parameters (57%)
- Two patients with dramatic improvement in clinical symptoms (cessation of dialysis and improvement in neurological symptoms)

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division has a meeting with the Sponsor on April 24, 2018 to discuss the Sponsor's proposed development plan. The Sponsor is seeking accelerated approval based on the data from the single arm Phase 2 study(OMS-721-TMA-001) for patients with HCT-TMA. The Sponsor is proposing a confirmatory study in 40 patients with HCT-TMA who are considered high risk for mortality defined by recently published criteria which includes evaluation of proteinuria > 30mg/dL, elevated C5b-9 or lack of TMA resolution by day 7 after change in immunosuppression. The Sponsor is proposing OS as primary endpoint for confirmatory study. The Division will discuss possible endpoints such as reduced transfusion burden, improvement in end-organ damage and analysis of OS in single arm trials and historical controls with the Sponsor.

13. List references, if any:

1. Jodele S, Laskin BL, Dandoy CE, Myers KC et al. A new paradigm: Diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial injury. Blood Rev. 2015 May;29(3):191-204.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/17/17/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA A ONEAL
04/25/2018

TANYA M WROBLEWSKI
04/25/2018

ANN T FARRELL
04/25/2018