CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214759Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 054552

MEETING MINUTES

medac GmbH
c/o Clinipace Inc.
Attention: Frank Schmidberger
US Agent, Senior Manager, Regulatory and Strategic Development
1434 Spruce Street, Suite 100
Boulder, CO 80302

Dear Mr. Schmidberger:[1]

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

We also refer to the teleconference between representatives of your firm and the FDA on April 2, 2020. The purpose of the meeting was to discuss the new drug application for treosulfan.

A copy of the official minutes of the meeting/telecon 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}

Donna Przepiorka, MD, PhD
Clinical Team Leader
Division of Hematologic Malignancies 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We 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.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 2, 2020; 1:00PM – 2:00PM (EDT)
Meeting Location: Teleconference

Application Number: 054552
Product Name: Treosulfan
Indication: As part of conditioning treatment prior to allogeneic hematopoietic stem cell transplantation (HSCT) in adult patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)
Sponsor Name: medac GmbH

Meeting Chair: Donna Przepiorka, MD, PhD
Meeting Recorder: Kris Kolibab, PhD

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/ Division of Hematologic Malignancies I (DHM1)
Angelo de Claro, MD, Acting Division Director
Donna Przepiorka, MD, PhD, Clinical Team Leader
Emily Jen, MD, PhD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Amy Baird, Chief
Kris Kolibab, PhD, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics IX
Jonathon Vallejo, PhD, Acting Statistical Team Leader
Alexei Ionan, PhD, Statistical Reviewer

OOD/Division of Hematology Oncology Toxicology
Haleh Saber, PhD, MS, Deputy Director

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Ruby Leong, PharmD, Team Leader
Runyan Jin, PhD, Clinical Pharmacologist

SPONSOR ATTENDEES

Anke Zens, MD, Medical Expert, medac GmbH
Joachim Baumgart, PhD, Clinical Scientific Program Lead, medac GmbH
Claudia Hemmelmann, PhD, Program Statistician, medac GmbH
Sonja Böhm, PhD, Pharmacology Toxicology, medac GmbH
Christine Buchsteiner, Programmer, medac GmbH
Jörg Schneidereit, MSc, MDRA, Global Regulatory Affairs – New Products, medac GmbH
Stephanie Roland Director, Regulatory and Strategic Development, Clinipace Inc. (Consultant)
Frank Schmidberger Sr. Manager, Regulatory and Strategic Development, Clinipace Inc. (Consultant)

1.0 BACKGROUND

Treosulfan is a cytotoxic alkylating agent being developed by Medac GmBH for use in preparative regimens for allogeneic hematopoietic stem cell transplantation (HSCT). Orphan drug designation was granted 4/8/2015 for treosulfan as a "conditioning treatment prior to HSCT in malignant and nonmalignant diseases in adults and pediatric patients." FDA provided advice at an EOP2 meeting on 9/4/2014, in written responses for a Type C meeting issued on 12/3/2015 and on 2/24/2020, and at a Type C meeting on 9/17/19.

On January 31, 2020, Medac GmbH requested a Type B Pre-NDA meeting with FDA to discuss additional question on the format and content of the new drug application for treosulfan.

FDA sent Preliminary Comments to medac GmbH on March 25, 2020.

2.0 DISCUSSION

2.1. Questions

Question 1:

Does the FDA agree with the content, organization and the cross-reference strategy of the NDA as outlined in the proposed content plan?

FDA Response to Question 1:

No. We reviewed the draft table of contents and the description of proposed content, and we have the following comments:

a. With regard to the nonclinical data portion of the NDA, the proposed content may be sufficient to support an NDA.

   We note that you are proposing to submit the application for treosulfan under the 505(b)(1) pathway. For a 505(b)(1) application, the nonclinical literature used to support your application must be data that you own or data you have the right to reference. If you are relying on literature that is necessary for approval of your application for which you do not own or have right of reference, your application would be a 505(b)(2) application; see 505(b)(2) section below for recommendations regarding 505(b)(2) applications. Also, see the meeting minutes for the EOP 2 meeting in September 2014 regarding acceptability of published literature in support of a 505(b)(1) NDA application.

b. Module 1.3.1.2 Change in Contact/Agent is specific to the NDA submission and cannot cross-reference the IND.

c. Please also submit a right of reference to IND 054552 in Module 1.4.2 Statement of Right of Reference.

d. For any document for which you plan to cross-reference your IND (e.g. as listed under Modules 1.6, 1.7, and 1.14.4), submit either the exact location of the paper document (date of amendment submission, section, page(s), etc.) or an electronic cross reference to a document in eCTD. For additional information, see the eCTD technical conformance guide at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf

e. Since treosulfan has Orphan Designation, there is no need to submit a request for waiver of pediatric studies. You may submit a statement of exemption in Module 1.9.6.

f. There is no need to submit a request for waiver of a REMS in Module 1.16.2. You should submit a Risk Management Plan in Module 1.16.1.

Discussion:

See discussion under Question 4.

g. Given the number of studies to be included in this NDA, please plan to provide the actual individual study synopses in Module 2.7.6 instead of cross-referencing documents in other sections of the submission.

h. You have two study folders planned for MC-FludT.14/L (Trial II). This is not acceptable. Each study may have only one folder. You may submit both the Interim and Final Clinical Study Reports in that folder. The Appendices (16.1

through 16.3) should be cumulative documents. Do not submit two versions of the Appendices.

Each study folder may have only one folder for data sets, and that folder should contain a single cumulative SDTM data set and a single cumulative ADAM data set.

We understand that you wish to make available the data used for the interim analysis. As discussed at the Type C meeting on 9/17/2019, it is preferable to do this using flags and additional time-to-event variables in the efficacy data files. If that is not feasible, the interim analysis data set should be submitted in the MISC subfolder of the MC-FludT.14/L (Trial II) study folder.

Discussion:

The Sponsor stated that the Clinical Study Report Appendices from the last analysis of Study MC-FludT.14/L (Trial II) were comprehensive as they included data on all patients and longer follow-up, and they proposed to include only the Appendices from the last analysis. The Agency agreed with the Sponsor's plan.

The Sponsor requested advice on the structure of the MISC folder. The Agency indicated that there is flexibility in the structure of the MISC folder as the names of the subfolders will depend on the nature of the material submitted.

i. The report justifying the noninferiority margin of MC-FludT.14/L (Trial II) should be placed in the ISE folder 5.3.5.4 Other Study reports and related information.

Discussion:

See discussion under Question 3.

j. The study report and data sets for MC-FludT.16/NM should be placed in Module 5.3.5.2 (do not use Module 5.3.5.4 for this study).

Discussion:

The Agency clarified that reports and data for MC-FludT.16/NM should be placed in (b) (4) under Module 5.3.5 (e.g., (b) (4)

k. Please clarify how many PSURs you intend to submit in Module 5.3.6 and where you will provide the overview of the postmarketing adverse event drug experience.

Discussion:

The Sponsor plans to submit two PSURs: one for ovarian cancer dating back to 2017 and one for transplantation dating back to approval. The overview of the postmarketing adverse event drug experience will be provided in the ISS and in Module 2.7.4. The Agency indicated that this plan was acceptable.

l. Please include executable, clearly commented, non-macro programs in ASCII format used to create tables and figures for primary and key secondary efficacy analyses and any additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. Ensure that programs call only data submitted to the Agency and can be easily used to reproduce the efficacy results in the Clinical Study Report. Ensure that variables used in the programs for generating efficacy results in the Clinical Study Report are described clearly in the define file. The code in programs should explicitly convert submitted .xpt files into the data format used by programs.

m. Please include in the related Data Definitions subfolder an index with clear descriptions of the programs.

n. Please include annotations for each figure and table in the CSR with a list of datasets and variables, as well as a link to the program used to generate results. Alternatively, annotations with programs, datasets, and variables for each figure and table could be included in the define file or reviewer's guide.

Question 2:

Does the Agency agree that the Summary of Clinical Efficacy (SCE) in Module 2.7 is adequate to describe the effectiveness of treosulfan and that a separate Integrated Summary of Effectiveness (ISE) in Module 5.3.5.3 is not needed in the NDA submission for treosulfan?

FDA Response to Question 2:

We have no objection to the plan to provide an SCE in lieu of an ISE. The text of the SCE should be provided in Module 2.7.4 and the tables, appendices and data sets should be provided in Module 5.3.5.3 (See "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" Example 4 available at: https://www.fda.gov/media/75783/download). We remind you that the maximum page limit of the Clinical Summary text (Modules 2.7.1 through 2.7.4 cumulatively) is in total 400 pages.

Discussion:

No discussion occurred.

Question 3:

medac GmbH intends to provide additional information needed to assist in interpreting the non-inferiority margin for the pivotal study MC-FludT.14/L Trial II in the following NDA sections: the clinical trial report for the last analysis, the SCE, and as a separate report under 5.3.5.3 (Reports of analyses of data from more than one study)? Is the Agency in agreement with the content, format and location of the requested information?

FDA Response to Question 3:

No. The report justifying the noninferiority margin of MC-FludT.14/L (Trial II) should be placed in the Module 5.3.5.4 Other Study reports and related information.

Additionally, we recommend following guidelines outlined in *Guidance for Industry: Non-Inferiority Clinical Trials to Establish Effectiveness* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials. We note the following limitations of the proposed "Justification of NI Margin" report contained in your briefing document Appendix V that you will need to address in your submission:

a. Your proposed pivotal trial is based on a primary endpoint of EFS. However, the proposed method of establishing the historical treatment effect of allogeneic HSCT vs. CCT is based on a variety of endpoints, including RFS, DFS, and LFS. The definition of such endpoints may vary across studies, as well as timing of assessment and length of follow-up. Justify using treatment effect from these other endpoints in the development of your noninferiority margin for EFS.

b. Your proposed margin depends strongly on the claim that BuFlu has an equivalent treatment effect vs. chemotherapy to other conditioning regimens. This is supported by evidence from studies designed to explore the difference between BuFlu and other regimens, and not explicitly designed to establish equivalent efficacy between BuFlu and other regimens.

c. Your noninferiority margin is based on a point estimate: "Hence, a survival benefit (whether called DFS, EFS, LFS or RFS) for allogeneic HSCT between 11% and 25%, as demonstrated in several studies as well as the meta-analysis by Koreth at al., can be transferred to BuFlu conditioning followed by allogeneic HSCT. In conclusion, a survival benefit of at least 10% can be claimed as the

treatment effect of allogeneic HSCT with BuFlu conditioning (as used in study MC-FludT.14/L) over a comparator, such as CCT for AML patients in CR1." In general, non-inferiority margins should incorporate the variability of the historical estimate, e.g. the 95-95 or synthesis methods (see FDA Guidance *Non-Inferiority Clinical Trials to Establish Effectiveness)*

d. Any noninferiority margin proposed post-hoc is considered exploratory and is suspect to bias. As such, its acceptability in the evaluation of efficacy will be a review issue at the time of a future NDA submission. In such a scenario, it is critical that the development of the margin is based on an unbiased assessment of the historical treatment effect and accounts for as many sources of variability as possible. The proposed post-hoc justification of the noninferiority margin should carefully document all studies considered for such developing such a margin, and the reasons for including or excluding studies in the subsequent analyses.

Discussion:

The Sponsor clarified that the noninferiority margin was prespecified and cannot be changed. The Agency acknowledged the Sponsor's clarifications on the noninferiority margin and reiterated that the noninferiority margin use and interpretation in efficacy assessment would be a review issue.

Regarding the demonstration of superiority for EFS, the Agency noted that the results from the interim and last analyses will be interpreted in the context of the prespecified statistical analysis plan. The Agency recommended that the Sponsor include in the CSR a description of trial conduct after the interim analysis and the rationale for the timing and conduct of the last analysis. The Agency noted whether the trial is adequate and well-controlled would be a review issue.

Regarding the placement of the information in the NDA, the Agency noted that the reference to the ISE folder was a typographical error. The report justifying the noninferiority margin should be placed in Module 5.3.5.4.

Question 4:

Does the Agency agree that a waiver from submitting a Risk Evaluation and Mitigation Strategy (REMS) is appropriate?

FDA Response to Question 4:

There is no need to submit a request for waiver of a REMS in Module 1.16.2. Whether a REMS is required will be a review issue. Submit a Risk Management Plan in Module 1.16.1.

Discussion:

The Sponsor acknowledged the Agency's comment and indicated they will provide a Risk Management Plan in Module 1.16.1.

Question 5:

Does the FDA agree that the NDA submission for treosulfan in the proposed indication meets the requirements for priority review?

FDA Response to Question 5:

Whether priority review is appropriate for the NDA submission will be a review issue.

Discussion:

No discussion occurred.

Question 6:

Does the Agency concur with the Sponsor's proposal as described below to include Case Report Forms in the NDA only for the pivotal phase III clinical trial?

FDA Response to Question 6:

Yes. However, we reserve the right to request other CRFs as needed during the review.

Discussion:

No discussion occurred.

ADDITIONAL CLINICAL COMMENTS

1. An Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, should be prepared and submitted for each data set in the NDA. Please refer to the *Study Data Technical Conformance Guide: Technical Specifications Document*, available at: https://www.fda.gov/media/131872/download.

2. Ensure that the define file and/or Reviewer's Guide for the Analysis Data Sets identify the coding dictionary and version for controlled terminology (e.g., MedDRA version, WHO Drug Dictionary version, etc.).

3. Provide sufficient comments, adequate bookmarks and hyperlinks in the define file(s) to ensure efficient review.

4. To assist with the adjudication of efficacy in the pivotal trial, submit an xpt data file that includes at least the following information:
   - Date of neutrophil recovery
   - Date of platelet recovery
   - Date of graft failure
   - Date of onset of Grade II-IV aGVHD
   - Date of onset of Grade III-IV aGVHD
   - Date of onset of chronic GVHD
   - Date of relapse
   - Date of death
   - Date last known alive
   - Date of salvage transplantation

5. To assist with the adjudication of causality of fatal adverse events, the submission should include an xpt data file with the date of death, study day of death, proximate cause of death (usually as reported by the investigator) and the root cause of death as determined by the sponsor for patients in the ISS. The root cause is generally categorized as a) direct effect of active disease, b) an adverse drug reaction or c) an unrelated intercurrent event (such as car accident).

Discussion:

No discussion occurred.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS

1. Address the following questions in the Summary of Clinical Pharmacology:
   a) What is the basis for selecting the doses and dosing regimen used in the trials intended 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.
   b) What are the exposure-response relationships for efficacy, safety and biomarkers?
   c) What is the effect of treosulfan on the QT/QTc interval?
   d) What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
   e) How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

2. Apply the following advice in preparing the clinical pharmacology sections of the original NDA submission:
   a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
   b) Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
   c) Refer to the FDA response to Question 4 regarding the preparation of the clinical pharmacology datasets for both adult and pediatric patients in the Written Responses letter conveyed on February 24, 2020.

3. Include the following items when you submit your QT study report:

   a) Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
   b) Electronic copy of the study report
   c) Electronic or hard copy of the clinical protocol
   d) Electronic or hard copy of the Investigator's Brochure
   e) Annotated CRF
   f) A data definition file which describes the contents of the electronic data sets
   g) Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
   h) Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
   i) Data set whose QT/QTc values are the average of the above replicates at each nominal time point
   j) Narrative summaries and case report forms for any:
      i. Deaths
      ii. Serious adverse events
      iii. Episodes of ventricular tachycardia or fibrillation
      iv. Episodes of syncope
      v. Episodes of seizure
      vi. Adverse events resulting in the subject discontinuing from the study
   k) ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
   l) A completed Highlights of Clinical Pharmacology Table

Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at http://cardiac-safety.org/ecg-database/.

4. Take the following recommendation about labeling into your consideration:

   FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support the NDA 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.

Discussion:

The Sponsor plans to submit a Type C WRO with a meeting package containing the QT/QTc evaluation plan for review and comment by the QT-IRT team. FDA indicated they would try to expedite the review, but that the actual timeline will depend on workload.

ADDITIONAL STATISTICAL COMMENTS

1. Please ensure compliance with Study Data Standards and the latest version of the *Study Data Technical Conformance Guide: Technical Specifications Document* https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

2. Programs written in SAS, R, or other language with adequate documentation may be acceptable. Per Statistical Software Clarifying Statement, "FDA does not require use of any specific software for statistical analyses, and statistical software is not explicitly discussed in Title 21 of the Code of Federal Regulations [e.g., in 21CFR part 11]. However, the software package (s) used for statistical analyses should be fully documented in the submission, including version and build identification." https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587506.pdf

Discussion:

No discussion occurred.

3.0 OTHER MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Agreement on content of complete application was reached.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated that you intend to submit a complete application, and therefore, there are no agreements for late submission of major application components. Agreements made with the Office of Product Quality regarding late submission of minor application components related to product quality will apply as documented in the CMC meeting minutes.

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 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.[2]

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

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] 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.[4]

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[5] and Pregnancy and Lactation Labeling Final Rule[6] 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

[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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)				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[7] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[8]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but

[7] We 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.
[8] http://www.regulations.gov

not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*

(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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*.[9]

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

[9] https://www.fda.gov/media/85061/download

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:

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[11]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached slide deck for the meeting.

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

DONNA PRZEPIORKA
04/03/2020 07:53:40 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 054552

MEETING MINUTES

Medac GmbH c/o Clinipace, Inc.
Attention: Stephanie Roland
Regulatory Affairs Manager
Clinipace Worldwide
4840 Pearl East Circle
Suite 201E
Boulder, CO 80301

Dear Ms. Roland:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (b) (4) ® (treosulfan).

We also refer to the meeting between representatives of your firm and the FDA on September 4, 2014. The purpose of the meeting was to discuss the clinical development program, pivotal studies, and planned NDA for treosulfan (b) (4) .

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, call Laura Wall, Regulatory Project Manager at (301) 796-2237.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
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
Meeting Category:	End of Phase 2
Meeting Date and Time:	September 4, 2014 from 11 a.m. to 12 p.m. (EDT)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 054552
Product Name:	(b) (4) ® (treosulfan)
Indication:	(b) (4)
Sponsor/Applicant Name:	Medac GmbH c/o Clinipace, Inc.
Meeting Chair:	Albert Deisseroth, MD, PhD, Clinical Team Leader
Meeting Recorder:	Laura Wall, MS, APHN, OCN, Regulatory Project Manager

FDA ATTENDEES

Division of Hematology Products (DHP)
Ann Farrell, MD, Division Director
Albert Deisseroth, MD, PhD, Clinical Team Leader
Donna Przepiorka, MD, PhD, Clinical Reviewer
Patricia Dinndorf, MD, Clinical Reviewer
Laura Wall, MS, Regulatory Project Manager
Amy Chi, MSN, Regulatory Project Manager

Division of Hematology Oncology Toxicology (DHOT)
Brenda Gehrke, PhD, Pharmacology/Toxicology Reviewer

Office of New Drug Quality Assessment (ONDQA)
Janice Brown, MS, Chemistry, Manufacturing & Controls Lead
Joyce Crich, PhD, Product Quality Reviewer

Office of Clinical Pharmacology (OCP)
Sarah Schrieber, PharmD, Clinical Pharmacology Reviewer
Vicky Hsu, PhD, Clinical Pharmacology Reviewer
Kevin Krudys, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology

Office of Orphan Products Development
Jeff Fritsch, RPh, Regulatory Review Officer

SPONSOR ATTENDEES
Kirsten Brass, PhD, Head, Drug Regulatory Affairs International
Michaela Rehberg, PhD, Director, Drug Regulatory Affairs/Pharmaceutical Development
Gretel Saß, Director, Research and Development
Dr. Joachim Baumgart, PhD, Head of Pharmacology/Toxicology
Uwe Pichlmeier, PhD, Head of Biometrics and Data Management
(b) (4) Medical Consultant
(b) (4), Regulatory Consultant, (b) (4)
Stephanie Roland, BS, Manager, Regulatory and Strategic Development

1.0 BACKGROUND

(b) (4)® (treosulfan) is not approved in the United States but is approved in Europe and several countries outside the European Union for the treatment of patients with ovarian carcinoma. In the United States, Medac is the Sponsor of IND 054552 for the use of treosulfan which was initially used in the treatment of acute leukemia but now is used as a conditioning treatment prior to hematopoietic stem cell transplantation (HSCT). The purpose of this End of phase 2 meeting is to discuss the clinical development program, pivotal studies, and planned NDA for treosulfan (b) (4).

The objectives and expected outcomes of the meeting are to obtain the Agency's concurrence on acceptability of the following:

- comparative Phase III trial (MC-FludT.14/L) as the pivotal study in adults
- clinical development program for a future application for marketing authorization for (b) (4)® in the United States (505 (b)(1) NDA submission) especially the clinical study design and Phase III study results (MC-FludT.14/L)
- (b) (4)

2. DISCUSSION

2.1. CMC

Medac GmbH's Position on Question 1

Medac GmbH has been granted marketing authorizations as early as 1973 for treosulfan 1000/5000 mg powder for solution for infusion and treosulfan 250 mg capsules for ovarian carcinoma in the following Member States of the EEA and worldwide: Belarus, Denmark, Germany (tradename Ovastat®), Ireland, Netherlands, Russia, Ukraine, and the United

Kingdom. Treosulfan ([redacted]®) for the indication of [redacted] is not registered in any country. Treosulfan ([redacted]®) is not approved in the USA.

IND 54,552 is up to date with respect to treosulfan drug substance covered by drug master file (DMF) [redacted] and for treosulfan drug product 1000/5000 mg powder for solution for infusion. This drug substance and drug product, as described in the DMF and IND, have been and will supply all of the sites (including US sites) that will participate in the ongoing adult and planned pediatric studies. Medac also plans to submit this same material in the future 505(b)(1) NDA. There are no questions regarding treosulfan drug substance or drug product.

The comparator to be used in the pivotal studies is busulfan. Busulfan is approved in the EU under the tradename Busilvex® (by Pierre Fabre Medicament) and in the US under the tradename Busulfex® (by Otsuka America; NDA 20-954). Because the approved labeling between the two products lists the same adult clinical trials for safety and efficacy (OMC-BUS-3 and OMC-BUS-4) and the same dosing regimen and preparation, Medac believes Busilvex® and Busulfex® are the same material.

Question 1: [redacted] Is this an acceptable approach to the Agency for the source of comparator drug?

FDA Response to Question 1: ***No.*** [redacted]

In your NDA submission, submit comparative characterization studies showing that the Busilvex® and the Busulfex® are comparable to bridge the drug products used in the clinical studies. You might consider performing these characterization studies now to confirm that these two drugs are identical.

<u>Meeting Discussion September 4, 2014:</u> The Agency agreed that the Sponsor could submit a comparability report analyzing the Busilvex® and the Busulfex® to establish the comparability of the two products for use in clinical trials.

2.2. Nonclinical

Medac GmbH's Position on Question 2

The pre-clinical data package to support the proposed NDA will be compiled from historic (non-GLP) studies, more recent Medac-sponsored GLP non-clinical study reports, and published data. Due to the long history of treosulfan non-clinical development (starting in the 1970s), the majority of toxicological data, however, were not obtained under GLP

regulations. There is, however, over 40 years of human clinical experience with the use of treosulfan in the postmarketing setting.

Non-clinical data on treosulfan are reviewed in Section 4 of the current Investigator's Brochure (IB), Appendix 1, and in Section 11. In addition, non-clinical data are summarized according to CTD-guidance as part of Module 2.4 and 2.6 which were submitted to IND 54,552 as part of Serial 0028/eCTD sequence 0002, dated April 03, 2013.

Question 2: Medac GmbH does not plan to conduct any further nonclinical studies and considers the nonclinical package complete to support a marketing application for the intended indication. Does the Agency agree?

FDA Response to Question 2: ***Your proposal may be acceptable. Published literature of studies conducted with treosulfan may be used to support a marketing application, however, the articles or information must be in the public domain. The adequacy of the non-GLP studies from the literature to support an NDA will be a review issue.***

We note that no article is available on reproductive toxicology studies. The embryofetal development toxicology studies may be waived if the submitted data demonstrate that treosulfan is genotoxic and targets rapidly diving cells in the general toxicology studies. A decision on whether or not the embryofetal development toxicology studies may be waived will be made following the review of genetic and general toxicology studies.

Meeting Discussion September 4, 2014: No discussion occurred.

2.3. Clinical

Medac GmbH's Position on Question 3

Due to the commercial availability of treosulfan (approved for treatment of patients with advanced ovarian carcinoma in several EU and non-European countries) starting from 1973, several thousand adult patients have been treated with treosulfan. In addition, a few thousand of adult and pediatric patients have been treated with treosulfan-based conditioning therapies not only in Medac GmbH- sponsored clinical trials, but also in numerous investigator-initiated-sponsored clinical trials in Europe, Israel, and the USA (IND 72,479). Clinical data on (b) (4)® are reviewed in Appendix 1 (Investigator' Brochure, Section 5) and in Section 12.

Medac GmbH plans to file for Orphan Drug Designation in the US and may seek FDA advice regarding opportunity for Fast Track as well.
The Medac-sponsored clinical development program for (b) (4)® for the proposed indication is summarized in Table 9.1.

Question 3: Does the Agency agree that the Phase III study MC-FludT.14/L (designed as an open-label, active-controlled, randomized, parallel-group, multicenter, group-sequential, non-inferiority study with event-free survival as primary study endpoint) supported by the Phase I

and II trials in adults represent an adequate safety and efficacy data package to support a future marketing application for treosulfan ([(b) (4)]®) in the USA for the proposed indication? Medac plans to have completed the two pediatric studies prior to the completion of the adult program (see Questions 6-8).

FDA Response to Question 3: ***No. The use of this protocol to support a marketing application is complicated by following potential major deficiencies in the protocol design:***

a) You have identified EFS as the primary endpoint with no alpha spending plan for other endpoints. OS is the accepted endpoint for regular approval, and you have not provided any data showing that EFS is a validated surrogate of OS in the population of patients transplanted for AML in CR and with MDS.

b) Your primary objective is to demonstrate noninferiority, but you have not provided any basis for the noninferiority margin. For additional information on determining noninferiority margins, please see "Guidance for Industry. Non-Inferiority Clinical Trials" available at
http://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf

c) The protocol is heterogeneous with regard to donor type and MHC compatibility, two factors that affect long-term outcomes, but your design does not provide any assurance that you will have sufficient power to test long-term outcomes within disparate groups to show that efficacy is independent of donor type and MHC compatibility.

Meeting Discussion September 4, 2014: The Agency established the regulatory precedence for the interpretation of clinical benefit being overall survival and advised the sponsor to submit data to support an alternative endpoint in accordance with the Cancer Endpoints Guidance. The link to the Cancer Endpoints Guidance is:
http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf

The Agency and the Sponsor discussed aspects of the noninferiority trial design and the fact that the EMA has already provided the Sponsor with its scientific advice concerning this issue. The Sponsor agreed to provide the Agency with the advice given to it by the EMA and a detailed description of the steps it intends to undertake to establish the noninferiority margin including a discussion of the prior clinical experience upon which it bases its estimate of the effect of the busulfan preparative regimen, and the evidence for assuming constancy between the historical data and the present time, and a description of what differences there may be between the advice of the EMA and the recommendations for the noninferiority design as outlined in the FDA non-inferiority guidance (see link above). In those instances in which there is a lack of agreement between the recommendations of the EMA and the FDA concerning noninferiority trial design, the Sponsor will provide a justification for design features which are not in agreement with FDA's noninferiority guidance.

The Sponsor acknowledges the Agency's comment and believes the trial design features will ensure no impact on the primary endpoint.

Medac GmbH's position on Questions 4 and 5

The pivotal Phase III protocol (MC-FludT.14/L) is designed as a non-inferiority study enrolling adult AML and MDS patients who are not eligible for standard myeloablative conditioning (MAC) regimens, but may receive reduced intensity conditioning (RIC) treatment only. Accordingly, a reduced dose of (b) (4)® is used within the treosulfan / fludarabine test arm of the protocol and is compared to a reduced duration (total dose) of busulfan treatment in the i.v. busulfan / fludarabine reference arm. Busulfan is given only on two consecutive days (a total of 8 doses), rather than for four days (a total of 16 doses) as classically used and authorized by FDA for myeloablative conditioning of CML patients.

For further information on the MC-FludT.14/L study design, please refer to Section 13.1 for the protocol synopsis.

Question 4: Does the Agency agree that the reduced intensity conditioning dose regimen of busulfan with fludarabine is an acceptable comparator arm for a pivotal study used to support a future marketing application for (b) (4)® in the USA for the proposed indication?

FDA Response to Question 4: ***We agree that IV busulfan in the regimen that you have described would be an appropriate comparator to treosulfan and that the design comparing outcomes with busulfan vs treosulfan given in addition to fludarabine correctly isolates the effect of treosulfan.***

Meeting Discussion September 4, 2014: No discussion occurred.

Question 5: Does the Agency have any further comments from a clinical perspective regarding the use of the EU-approved busulfan (Busilvex® by Pierre Fabre Medicament) (b) (4) compared to US-approved busulfan (Busulfex® by Otsuka America)? Please refer to CMC question 1 (b) (4) .

FDA Response to Question 5: ***See the response to Question 1.***

Meeting Discussion September 4, 2014: No discussion occurred.

Medac GmbH's Position on Questions 6, 7, and 8

Medac plans to conduct two clinical studies in the pediatric population, covering malignant and non-malignant diseases:

- MC-FludT.16/NM (designed as a randomized (1:1), multicenter, open-label, active-controlled, parallel-group Phase II study with freedom from transplant (treatment)-related mortality (TRM) as primary study endpoint and,
- MC-FludT.17/M (designed as a prospective, single arm, multicenter, non-controlled, open-label Phase II study with freedom from transplant (treatment)-related mortality (TRM) as primary study endpoint).

For further information on the study design for the pediatric studies, please refer to Section 13.2 for the protocol synopses and Appendix 3 for the EMA-PDCO agreed upon Pediatric Investigation Plan (PIP).

Question 6: (b) (4)

FDA Response to Question 6: ***No.*** (b) (4)

(b) (4) (b) (4) ***the adult dose is 10 g/m in your proposed Phase 3 study (MC-FludT.14/L). In addition, please also submit for our review the population pharmacokinetic report that was used to justify the dosing regimen in pediatric patients.***

Meeting Discussion September 4, 2014: (b) (4) .

Question 7: The pediatric clinical trials MC-FludT.16/NM and MC-FludT.17/M are estimated to be completed in 2016. The adult Phase III study (MC-FludT.14/L) is estimated to be completed in 2019. Medac GmbH plans to file for Orphan Designation in the US. (b) (4)

FDA Response to Question 7: ***No. See response to Question 6.*** (b) (4)

Meeting Discussion September 4, 2014: FDA recommended that the sponsor contact the Office of Orphan Drug Products directly for advice regarding an orphan indication. (b) (4)

Question 8: Medac believes (b) (4) . Does the FDA agree?

FDA Response to Question 8: (b) (4)

(b) (4)

(b) (4)

Meeting Discussion September 4, 2014: No discussion occurred.

2.4. Labeling/Target Indication

Medac GmbH's Position on Question 9

The planned clinical program to support the pediatric indication will include:

- Two planned studies in children eligible for standard myeloablative conditioning regimen (MAC) with a variety of malignant and non-malignant diseases (MC-FludT.17/M and MC-FludT.16/NM). Based on current clinical experience, treosulfan-based conditioning of patients (b) (4)

The planned clinical program to support the adult indication will include:

- ongoing phase III protocol MC-FludT.14/L includes adult AML and MDS patients eligible for reduced intensity conditioning (RIC).
- completed phase II trials MC-FludT.7/AML and MC-FludT.8/MDS in patients eligible for MAC.
- completed dose-range finding protocol (MC-FludT.6/L) in patients eligible for RIC.

There is additional experience in numerous investigator-initiated studies around the world, including those conducted under IND 72,479, which include a variety of adult and pediatric patients with other transplant indications in addition to AML and MDS (e.g. (b) (4)) who were eligible for RIC or MAC regimens (see Sections 12.6 and 12.7).

The safety and efficacy data (engraftment) across all studies for patients treated with treosulfan to date are at least comparable to published or registry data of standard myeloablative conditioning regimens.

(b) (4)

(b) (4)

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Question 9: Does the FDA agree with (b) (4):

(b) (4)

(b) (4)

Meeting Discussion September 4, 2014: The sponsor clarified that they are developing the target product profile.

Medac GmbH’s Position on Question 10

After the completion of the pediatric and adult studies, Medac’s proposed labeling indication is: “(b) (4)

Question 10: Does the FDA agree with (b) (4)

(b) (4)

FDA Response to Question 10: ***See response to Question 9.***

Meeting Discussion September 4, 2014: No discussion occurred.

2.5. Regulatory

Medac GmbH’s Position on Question 11

Medac GmbH plans to file for Orphan Drug Designation in the US and may seek FDA advice regarding opportunity for Fast Track as well.

Question 11: Does the FDA agree that treosulfan meets the definition of unmet medical need?

FDA Response to Question 11: ***No. A drug is not an unmet medical need. You have not articulated an unmet medical need for use of treosulfan. For examples of situations that are unmet medical needs, see "Guidance for Industry. Expedited Programs for Serious Conditions – Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf***

Meeting Discussion September 4, 2014: No discussion occurred.

Additional Clinical Comments

(b) (4)

2. Please clarify if you have identified any advantage with regard to safety or efficacy for use of treosulfan over busulfan.

Meeting Discussion September 4, 2014: The sponsor clarified that the expected reduction in regimen-related toxicity with treosulfan over busulfan (b) (4) **would not likely be measurable in a comparison of reduced intensity regimens.**

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies 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 PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP 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 at:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

ALBERT B DEISSEROTH
09/10/2014