# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761192Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 065448

**MEETING MINUTES**

MediWould, Ltd
c/o Kinexum LLC
Attention: Karen Wolfe-Kerker, MS, RAC
Regulatory Consultant
17165 Elm Trail Dr.
Eureka, MO 65025

Dear Ms. Wolfe-Kerker:

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

We also refer to the meeting between representatives of your firm and the FDA on July 29, 2019. The purpose of the meeting was to discuss the development program for Nexobrid (bromelain).

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, call Barbara Gould, Chief Regulatory Project Management Staff at (301) 796-4224.

Sincerely,

*{See appended electronic signature page}*

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- 7/22/2019 Sponsor's Revised Agenda
- 7/29/2019 Sponsor's PreBLA Meeting Slides

U.S. FOOD & DRUG ADMINISTRATION

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | Pre-BLA |
| **Meeting Date and Time:** | July 29, 2019, 10:00 – 11:00 a.m. EST |
| **Meeting Location:** | White Oak Building 22 |
| **Application Number:** | IND 065448 |
| **Product Name:** | Nexobrid (bromelain) |
| **Proposed Indication:** | Eschar removal (debridement) in adult patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns |
| **Sponsor Name:** | MediWound, Ltd. |
| **Meeting Chair:** | Kendall Marcus, MD |
| **Meeting Recorder:** | Barbara Gould |

## FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Brenda Carr, MD, Clinical Reviewer, DDDP
Kathleen Fritsch, PhD, Biometrics Reviewer, Division of Biometrics III
Cindy Pan, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) 3
Leslie A. Rivera Rosado,PhD, Product Quality Team Lead, Office of Biotechnology Products
Leopold Kong, PhD, Product Quality Reviewer, Office of Biotechnology Products

## SPONSOR ATTENDEES

Sharon Malka, Chief Executive Officer, MediWound Ltd
Prof. Lio Rosenberg, MD, Chief Medical Officer, MediWound Ltd
Ety Klinger, PhD MBA, Chief Research & Development Officer, MediWound Ltd
Smader Nestor, MSc, VP, Regulatory Affairs, MediWound Ltd
Keren David, MSc, VP, Clinical Affairs
Limor Dinur-Klein, PhD, Clincal Project Manager, MediWound Ltd
Merav REvach, PhD, Regulatory Affairs Project Manager, MediWound Ltd

(b) (4)

[redacted]

Julio Barrera-Oro, PhD, Health Scientist, Contracting Officer's Representative (COR), BARDA
Narayan Iyer, PhD, Program Chief, Burn Medical Countermeasures, BARDA
Nina El-Badry MS, RAC (US, EU), Subject Matter Expert – Regulatory Specialist, BARDA
Michael Halpin, MSc, Chief Operating Officer, Vericel Corporation
Joh Hopper, BSc, MB ChB, FRCSEd, Chief Medical Officer, Vericel Corporation
Anastacia Bilek, PhD, Associate Director, Regulatory Affairs, Vericel Corporation

## 1.0 BACKGROUND

The purpose of the meeting was to discuss the development program for Nexobrid (bromelain).

### Regulatory Correspondence History

We have had the following meetings with you:

- 04/19/2017: Guidance meeting
- 05/25/2016: Guidance meeting
- 07/25/2011: End-of-Phase 2 meeting
- 11/10/2010: Guidance meeting
- 05/20/2009: Guidance meeting
- 05/03/2005: Guidance meeting
- 08/03/2004: Guidance meeting

We have sent the following correspondences:

- 03/21/2019: Information Request letter (electronic)
- 11/05/2018: Advice letter
- 10/22/2018: Information Request letter (electronic)
- 11/17/2017: Information Request letter (electronic)
- 10/18/2017: Advice/Information Request letter
- 10/03/2017: Deny Fast Track letter
- 09/09/2016: Advice/ Information Request letter
- 07/21/2016: Advice letter
- 11/03/2015: Advice/ Information Request letter
- 05/14/2015: Advice/Information Request letter
- 12/05/2014: Special Protocol- No Agreement letter
- 09/19/2014: Special Protocol Assessment- Consultation Needed letter
- 12/26/2013: Special Protocol-No Agreement letter
- 11/01/2013: Special Protocol Assessment- Request Denied letter
- 10/30/2013: Advice/Information Request letter
- 07/29/2013: Special Protocol- No Agreement letter
- 12/05/2012: Advice/ Information Request letter

- 08/13/2012: Special Protocol-No Agreement letter
- 03/24/2011: Advice/ Information Request letter
- 08/31/2009: Advice/ Information Request letter
- 11/10/2005: Initiation of Clinical Trial letter
- 09/30/2005: Continue Clinical Hold Deficiencies letter
- 08/17/2005: Continue Clinical Hold Deficiencies letter
- 08/10/2004: Clinical Hold Deficiencies letter

## 2.0 DISCUSSION

### 2.1. BLA Content and Format

**Question 1a:**
Given the extent of the efficacy data from clinical studies, including two Phase 3 studies and the extent of the proposed safety data described in the briefing document, does the Agency agree that the application will provide sufficient information to allow for review of a BLA?

**FDA Response to Question 1a:**
We agree.

**Question 1b:**
Does the Agency concur with submitting a DETECT study CSR addendum containing the 12-month safety results, as a minor amendment within 30 days of the BLA original application?

**FDA Response to Question 1b:**
We do not concur. We recommend that the 12-month safety results from the DETECT study be included in the BLA original submission.

**Question 1c:**
Does the Agency concur that the DETECT study 24-month safety data can be submitted in a safety update report as a post-approval commitment?

**FDA Response to Question 1c:**
This is acceptable.

**Question 1d:**
Does the Agency agree with the proposed organization of the BLA, the content and format as described in Appendix 2 and described in Sections 13.1.1, 13.1.2, and 13.1.3?

**FDA Response to Question 1d:**

Pharm/Tox

The proposed content and format for the nonclinical section appear acceptable.

Product Quality (OBP)

The proposed content, format, and organization of the quality related modules to be submitted in the BLA appears acceptable.

Clinical/Statistical

You define the primary endpoint as "Incidence of complete eschar removal (≥ 95%)." As we have previously communicated, ≥ 95% eschar removal may not equate to complete (100%) eschar removal. Given this, address how the extent of eschar removal might be most accurately and meaningfully presented in the label.

Provide subject narratives and case report forms (CRFs) for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation. Also, include hyperlinks to this information. CRFs that are not submitted should be readily available upon request.

Include the full-text version of any referenced articles with hyperlinks to each article, as appropriate. For your clinical studies, include all components supporting the study report, such as protocols and amendments, SAPs, randomization lists, annotated CRFs, etc.

***Meeting Discussion:***
*Reference is made to the sponsor Powerpoint (PPT) presentation provided at meeting. The sponsor proposed draft language (see page 6 of the PPT); the Agency stated that final labeling will be determined upon review of the application.*

## 2.2. Integrated Summary of Safety, Integrated Summary of Efficacy

**Question 2a:**
Does the Agency agree with the planned studies to be integrated in the ISS for the BLA submission?

**FDA Response to Question 2a:**
The studies that you plan to integrate in the ISS may be acceptable. However, confirm that only studies that have evaluated the to-be-marketed formulation will be integrated.

***Meeting Discussion:***
*See sponsor PPT page 9. The Agency stated that the proposal appears reasonable. In addition, the sponsor will submit the safety data for each study.*

**Question 2b:**
Does the Agency have any comments on the proposed ISS SAP?

**FDA Response to Question 2b:**
Because you will be integrating results across studies that have different randomization ratios, patient populations, control arms, length of follow-up, etc., it will be important to use an integration method for your ISS that stratifies on study rather than simple pooling. See, for example Section V of guidance for industry "Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products" (https://www.fda.gov/media/117976/download).

You did not include mock tables. We request the following for each study report and for the integrated analyses:

1. Provide incidence rates of treatment-emergent adverse events (TEAEs) at ≥1% by treatment group. Because of the differing durations of follow-up, also include the exposure-adjusted rates (in patient-years) by treatment group. Also, include tables of all TEAEs. Present TEAEs in decreasing order of frequency by system organ class.

2. We do not agree with the sole, pooled NexoBrid group, as you propose for Cohorts 1 and 2. We recommend that the one vs two NexoBrid application groups also be considered separately in these analyses.

3. On p. 14 of the ISS SAP, you state that "(o)ne vs two NexoBrid applications" and "%TBSA ≤ 15% vs. TBSA > 15% of treated target wounds" will be among the subgroups that "will be used in the analyses of specific end-points." We see these as being important subgroups in the assessment of safety, and it is unclear why you would limit the assessment of safety for these sub-groups to "specific end-points." Please clarify.

4. Include separate discussion and analyses of "special events": pain, pyrexia and wound infection. Also, include sepsis as another element for separate discussion and analyses.

5. Include "time to wound closure" analyses on a patient level.

6. Include continuous pagination in all data listings for each study report and the ISS, including appendices and post-text tables. Provide a comprehensive index of all data listings contained within appendices and post-text tables. These indices should include the specific page number and hyperlink to the beginning of each data listing.

7. Include shift tables for all laboratory values and vital signs for outside the normal range and outside the range that is considered clinically significant. Provide the

reference values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate. To the extent possible, include reference ranges for all laboratory values in the data listings where those laboratory values are presented.

***Meeting Discussion:***
*The sponsor stated that they will include a study factor in the ISS analyses. The Agency noted that the proposal appears reasonable. The Agency noted that calculation of simple point estimates across studies can cause issues such as seen in Simpson's Paradox.*

*The sponsor inquired about submitting mock tables and a modified SAP for the ISS to the IND and the Agency timeframe for review of these items. The Agency stated that 90 days is the standard turnaround for the review of their modified SAP and ISS.*

*To request sample submission validation of eCTD and/or standardize study data see the guidance for industry Submit an eCTD or Standardized Data Sample to the FDA (https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda).*

*The sponsor stated that they believe their random-effect survival analysis can be interpreted as a patient-level analysis. The Agency reiterated that we would like to see an analysis based on the time to last wound closure in addition to the random-effect analysis assessing the average time. The Agency would conduct such an analysis if the sponsor does not provide it. The sponsor stated that they would provide a time to last wound closure analysis along with clinical and statistical context.*

**Question 2c:**
Does the Agency agree with the planned studies to be integrated in the ISE for the BLA submission?

**FDA Response to Question 2c:**
Including studies MW2002-04-01, MW2004-11-02, and MW2010-03-02 in the integrated analysis appears reasonable.

**Question 2d:**
Does the Agency have any comments on the proposed ISE SAP?

**FDA Response to Question 2d:**
Your proposed integrated analyses appear reasonable. Refer to guidance for industry *Integrated Summary of Effectiveness* (October 2015) (https://www.fda.gov/media/72335/download) for additional information on creating an ISE.

**Question 2e:**
Does the Agency agree with the proposal to split the ISE and ISS across Module 2 (Sections 2.7.3 and 2.7.4, respectively) and Module 5 (Section 5.3.5.3)?

**FDA Response to Question 2e:**
Yes. From a technical standpoint (not content related), the proposed format of submitting the ISS and ISE is valid considering the following:

- An overview of efficacy and safety results can be included in Module 2, sections 2.5.4, Overview of Efficacy, and 2.5.5, Overview of Safety.

- More detailed summaries of efficacy and safety should be provided in Module 2, sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety.

- Module 5.3.5.3 is the appropriate eCTD section for analyses containing large appendices of tables, figures, and datasets

**Question 2f:**
Does the Agency consider the data standardization plan acceptable?

**FDA Response to Question 2f:**
From a technical standpoint the data standardization plan is acceptable. Since only tabulations datasets will be submitted for phase II studies the review division is responsible to check if there are sufficient data for the review.

Your proposal to submit ADaM and SDTM datasets for Studies MW2010-03-02 and MW2004-11-02 is acceptable. We acknowledge that you propose to submit data from Phase 2 studies in legacy format. The adequacy of the data will be a review issue.

For the Phase 3 studies, submit the SDTM and ADaM datasets in SAS transport format (.xpt). The analysis datasets should include all variables needed for conducting the analyses included in the study report.

Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

Include statistical programs for the key primary, secondary, and safety analyses, including programs for the multiple imputation.

## 2.3. Administrative

**Question 3 - Risk Evaluation and Mitigation Strategy (REMS):**
Does the Agency concur with submission of a no REMS justification in the BLA submission?

**FDA Response to Question 3:**
A "no REMS justification'' is not needed at this time. However, the determination of a need for a REMS is a review issue based on the overall risk benefit assessment.

**Question 4, Electronic Submission Plan:**
Information and data already submitted to the IND in electronic format with the eCTD backbone files will not be submitted again in the BLA. Instead, the information will be included by cross- reference. A document placed in the appropriate CTD section of the BLA will contain (1) the application and amendment number, (2) the date of submission, and (3) the document of the referenced document name. A hypertext link to the location of the information will also be included. If a document replaces or appends a document previously submitted, these documents will be included in the BLA.

Does the Agency agree with this approach?

**FDA Response to Question 4:**
Your briefing meeting package does not contain enough information about which sections of the BLA application will be submitted by cross-referencing the IND. From a technical standpoint (and not content related), cross referencing previously submitted information is acceptable as long as –

- The link to the original study information is established using the eCTD XML backbones. Using the ich-stf.dtd with the ich-ectd-3-2.dtd by combining the referenced application type (e.g., IND) and application number, the submission-sequence number, appropriate path information to locate the original information, a leaf can be created in the index.xml file of a different application submission.

- Sponsor can also submit a sample application to test the eCTD cross-referencing by submitting two test samples. https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/submit-ectd-or-standardized-data-sample-fda

However, we do not agree that sections of Module 3 be included to the BLA by the way of cross-referencing the IND. Per 21 CFR 601.2, the license application must provide all relevant Chemistry, Manufacturing, and Controls (CMC) information, such as, descriptions of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the product. The BLA should also contain data establishing stability of the product through the dating period. Additionally, issuance of a biologics license is a determination that the product, the manufacturing process, and the manufacturing facilities meet applicable requirements to ensure the continued safety, purity, and potency of the product. Therefore, changes to the approved license, as presented in the

BLA submission, must be reported to the FDA (21 CFR 601.12), and cross-referencing the IND for CMC information is not appropriate.

Refer to the draft guidance for industry *Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products* (December 2017) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemistry-manufacturing-and-controls-changes-approved-application-certain-biological-products-draft

## 3.0 ADMINISTRATIVE COMMENTS

## DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 12, 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.[1]

## 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

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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.

## 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 Applicants[2] 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.[3]

## 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

[2] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] 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*.

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

**MANUFACTURING FACILITIES**

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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) | | | | |

**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.*[6]

**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.

***Post Meeting Comment:***
*Regarding the -4 letter suffix, Yes, per the Guidance: Nonproprietary Naming of Biological Products, "An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure" https://www.fda.gov/media/93218/download*

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

*Per the same guidance "For originator biological products, FDA intends to use a **core name** that is the adopted name designated by the United States Adopted Names (USAN) Council for the relevant biological substance when available."*

*Clarify why your product does not have USAN name and submit to the IND the USAN's Council response to your request for a name.*

## 4.0 ATTACHMENT

- 7/22/2019 Sponsor's Revised Agenda
- 7/29/2019 Sponsor's PreBLA Meeting Slides

# REVISED MEETING AGENDA

| | |
|---|---|
| Product Name | NexoBrid® (Debrase) |
| Proposed Indication for Use | Eschar removal (debridement) in adult patients with deep partial thickness and/or full thickness thermal burns |
| APPLICATION # | IND 065448 |
| Date of Meeting | July 29, 2019 |
| Sponsor | Name: MediWound Ltd<br><br>Address: 42 Hayarkon Street, North Industrial Area, Yavne 8122745, Israel<br><br>Phone: +972-77-9714172; +972-54-4642404; +972-77-9714100<br><br>Fax: +972-77-9714111 |

# FINAL QUESTIONS FOR DISCUSSION

## 1.1 BLA Content, Format, and Organization Questions

### Question 1, BLA Content and Format

**Question 1d**: Does the Agency agree with the proposed organization of the BLA, the content and format as described in Appendix 2 and described in Sections 13.1.1, 13.1.2, and 13.1.3?

### Question 2, ISS, ISE, and Dataset

***Integrated Summary of Safety***

**Question 2a**: Does the Agency agree with the planned studies to be integrated in the ISS for the BLA submission?

**Question 2b:** Does the Agency have any comments on the proposed ISS SAP?

MediWound assumes that some of the comments related to the ISS may be applicable to the ISE, and would like to discuss their relevance during the pre-BLA meeting.

## 1.2 Administrative Questions

### 1.2.1 Question 4, Electronic Submission Plan

Information and data already submitted to the IND in electronic format with the eCTD backbone files will not be submitted again in the BLA. Instead, the information will be included by cross-reference. A document placed in the appropriate CTD section of the BLA will contain (1) the application and amendment number, (2) the date of submission, and (3) the document of the referenced document name. A hypertext link to the location of the information will also be included. If a document replaces or appends a document previously submitted, these documents will be included in the BLA.

**Question 4: Does the Agency agree with this approach?**

## 1.3 Additional clarification

The FDA mentioned in their response letter the requirement for nonproprietary name. Can the Agency please confirm that a four-letter suffix will be assigned by the FDA for inclusion in the proper name.
For NexoBrid non-proprietary name, MediWound proposes the use of the core name "concentrate of proteolytic enzymes enriched in Bromelain" which was approved by EMA as well as by the regulatory authorities of additional countries in which the product is marketed. Can the Agency please clarify which steps should be performed by the Sponsor to ensure assignement of this core name for inclusion in the proper name?

**The following questions are considered as resolved:**
1a, 1b, 1c, 2e, 2f, 3



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/s/

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KENDALL A MARCUS
08/28/2019 03:02:22 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 065448

**MEETING MINUTES**

Teva Neuroscience
Attention: Michael J. McGraw, Pharm.D., M.S.
Regulatory Affairs Manager
425 Privet Road
PO Box 1005
Horsham, PA 19044-8005

Dear Dr. McGraw:

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

We also refer to the meeting between representatives of your firm and the FDA on July 25, 2011.

The purpose of the meeting was to discuss the development program for Debrase®.

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 Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** July 25, 2011; 1:00 pm
**Meeting Location:** WO 22 room 1415

**Application Number:** IND 065448
**Product Name:** Debrase®
**Indication:** Eschar removal in [redacted] (b) (4) patients with [redacted] (b) (4) deep partial and/or full thickness burns.
**Sponsor/Applicant Name:** Teva Neuroscience

**Meeting Chair:** Susan Walker, M.D., F.A.A.D
**Meeting Recorder:** Matthew White

## FDA ATTENDEES

Susan J. Walker, M.D., F.A.A.D., Director, DDDP
Tatiana Oussova, M.D., M.P.H., Deputy Director for Safety, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Joanna Ku, M.D., Clinical Reviewer, DDDP
Roxolana Horbowyj, Medical Officer, M.S.Ch.E., M.D., F.A.C.S., DSORD, CDRH
Shaw T. Chen, M.D., Ph.D., Leader, Botanical Review Team, Deputy Director, ODE IV
Jinhui Dou, Ph.D., Botanical Review Team Reviewer, ODE IV
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DB III
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Jie Wang, Ph.D., Clinical Pharmacology Reviewer, DCP3
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader, DCP3
Emanuela Lacana, Ph.D., Product Quality Team Leader, DTP
Cristina Ausin-Moreno, Ph.D., Product Quality Reviewer, DTP
Bo Chi, Ph.D., Microbiology Reviewer, MAPCB
Reyes Candau-Chacon, Ph.D., Biologist, MAPCB
Patricia Hughes, Ph.D., Product Quality Team Leader, MAPCB
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
Matthew E. White, Regulatory Health Project Manager, DDDP

## SPONSOR ATTENDEES

Gal Cohen, B.Sc., MBA, Chief Executive Officer, MediWound Ltd
Prof. Lior Rosenberg, M.D., Chief Medical Officer, MediWound Ltd
Keren Zarbiv, Clinical Project Manager, MediWound Ltd
Nina M. Moreno, Regulatory Affairs Specialist, Teva Neuroscience
Michael McGraw, Pharm.D., M.S., Senior Manager, Regulatory Affairs, Teva Branded Pharmaceutical Products R&D, Inc.

(b) (4)

**Purpose of the Meeting:**
To discuss the development program for Debrase®.

**Chemistry, Manufacturing and Controls (CMC)**

**Question 1:**
Taking into consideration the designation of Debrase® as a biologic and the botanical origin of the product, does the CMC information provided adequately support the planned Phase 3 study and the subsequent BLA submission?

**Response:**
The information you have provided is generally acceptable for the Phase 3 clinical study. In regard to your BLA submission, we have the following recommendations:

1. We recommend that you revise your release and stability protocols as follows:
   a. Acceptance ranges/limits should be tightened to reflect your manufacturing history and clinical experience. For example, the results provided for (b) (4) (b) (4) We recommend that you use multiple batches of drug substance and drug product in your clinical trial.
   b. You should establish acceptance ranges for peaks and peak groups for SEC and RP-HPLC (see our response to question 7 regarding RP-HPLC).
   c. The removal of process-related impurities should be validated or appropriate acceptance criteria should be established as part of the release protocol.
   d. You should develop and implement a stability protocol for the Bromelain Special Production material. The proposed protocol and stability data should be included in the BLA submission.

2. You should revise your qualification protocol for the Debrase In-House Reference Standard. Acceptance ranges/limits should be tighter than your Debrase DP release acceptance ranges/limits, in order to avoid product drift over time.

We recommend that you plan on implementing these revisions as soon as possible, so that sufficient information to support the changes can be submitted in the BLA.

Refer to the 2004 "Guidance for Industry: Botanical drug products" for general guidance on CMC information to be provided in the IND. In addition, note that adequate quality control of starting material (pineapple stems) should be ensured by applying the principles outlined in the above mentioned guidance and by following good agricultural and good collection practice for botanical raw materials. The manufacturing of Bromelain Special Production, drug substance,

and drug product should be in conformance with current good manufacturing practices (CGMPs).

**Additional questions and comments:**

See response to question 3 for additional comments for the BLA submission.

(b) (4)

(b) (4)

(b) (4)

[redacted]

**Question 2:**
The conduct of an adequate endotoxin test for Debrase is not scientifically/technically feasible. Therefore, the proposed release specifications will not include this test. Does the Agency concur?

**Response:**
This is acceptable. However, the manufacturing process should have adequate bioburden control to limit the endotoxin content in Debrase DP. See comments to question 1.

**Question 3:**
Is the proposed process validation concept conducted for Debrase drug substance (DS) and Debrase drug product (DP) sufficient to support a BLA submission for Debrase?

**Response:**
You did not provide sufficient information for us to answer your question. We recommend you consult the "Guidance for Industry: Process validation: General Principles and Practices" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf), to further develop your process validation strategy. Your BLA submission should include process development characterization studies, in-process controls, operating and performance parameters for all units of operations, a prospective process validation protocol and the result of the process validation studies on three consecutive lots of Debrase DP manufactured at the commercial scale. Process hold times should be validated to demonstrate that holding the product has no negative impact on product quality.

Since you are planning to manufacture Debrase at [redacted] (b) (4) should be validated, to ensure that the manufacturing process [redacted] (b) (4) yields a product with the expected quality characteristics.

To support the BLA submission for Debrase from CMC microbiology perspective, the following information should be provided in the BLA:

1. The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial control. The provided information should include, but not be limited to the following:

(b) (4)

(b) (4)

(b) (4)

[redacted]

**Question 5:**
The Sponsor's understanding is that prior to BLA submission, studies comparing between clinical batches used in the confirmatory pivotal study and the intended commercial product to be marketed should be conducted. The data from these comparability studies will be included in the BLA (see Section 10.1.10). Does the Agency agree to this approach?

**Response:**
If you are planning to introduce changes in the manufacturing process, you should provide studies supporting the comparability of the Phase 3 and commercial materials. Your submission should also include the comparability studies conducted in support of changes that occurred earlier in product development.

**Question 6:**
The SEC-HPLC is a chromatography identification test which evaluates the profile of the product. This test is one of three identification assays (FT-IR and UV) that compliment each other. There are also additional tests that quantitatively evaluate the product.

For further clarification on the use of this assay for identification of the Debrase see Section 10.1.11.

Due to the complexity of the product and the nature of its origin, the Sponsor suggests that the current identity specifications are sufficient to support a BLA. Does the Agency concur?

**Response:**
We understand that in such a complex mixture, the areas corresponding to small peaks can be variable. However, the current specification for SEC-HPLC corresponding to both Debrase DS and Debrase DP (according to Table 19 and Table 20, respectively) only refers to the peak area at [redacted] (b) (4) min. Revise the acceptance criterion to include a description of the chromatographic pattern and requiring the presence of [redacted] (b) (4) We also recommend that you consider improving the resolving capability of your SEC-HPLC method and developing additional analytical methods to better characterize Debrase DP.

**Question 7:**
The Sponsor plans to include group 2 in the release specifications according to the Agency's comment.

For further clarification on the use of this assay for identification of the Debrase see Section 10.1.12.

Due to the complexity of the product and its origin, the Sponsor proposes to include acceptance criteria for different clusters in group 4. Does the Agency concur with the proposed approach?

**Response:**
Yes, we agree as long as all the clusters in group 4 are specified.

**Additional CMC comments:**

1. Measurement of pH and viscosity are part of the routine testing of the Debrase DP and Gel Vehicle mixture (DGD). Justify why they have not been used in the qualification of the homogeneity of the DGD mixture.

2. In regard to your proposed plan to evaluate immunogenicity during the phase 3 clinical trial, to prevent the need for additional safety testing, we strongly recommend that clinical samples be appropriately stored and not tested until the proposed assays have been evaluated by the Agency. We also remind you of our recommendation on the sampling regimen. You are proposing to collect serum samples from patients up to day 56 from the start of treatment. This regimen is appropriate for negative serum samples. For confirmed positive serum samples, we recommend that patients be followed until the antibody titer reverts to baseline.

3. Be advised that the General Safety Test (GST) is a regulatory requirement (21 CFR § 610.11) for a non-specified biological product. Your product may qualify for an exemption as described under 610.11(g)(2) but you need to submit your justification as to why this test is unnecessary in your BLA. Include a request for an exemption from the GST along with your justification in the BLA.

4. Regarding the cultivation of the pineapple plants, provide:

    a. A list of all growers including their name and address.
    b. Specify the pineapple cultivars used, and their suppliers.
    c. Information on climatic conditions (length of day, rainfall, field temperature, etc.) in the area where the pineapple plants are grown.
    d. Information on the location of the pineapple plantations and any industries or other plantations that might be located upstream or downstream from them.
    e. Relevant information on the whole cultivation and collection processes.
    f. A certificate of authenticity of the pineapple cultivar and pineapple stem.

5. Due to the designation of Debrase as a biologic, the growth and harvest of the pineapple plants should comply with Good Agricultural Practices. For additional information refer to http://apps.who.int/medicinedocs/pdf/s4928e/s4928e.pdf. If available, provide certification that the farms are GAP compliant. Additionally, your manufacturing process should be conducted following current Good Manufacturing Practices (cGMP), starting with the crushing of the pineapple stems.

6. Be advised that any post-BLA changes in cultivars, farms or in the manufacturing process require prior approval from the Agency and additional pre-clinical or clinical studies might be necessary.

7. The botanical raw material (BRM) batches from all the available and accepted farms and cultivars should be represented in producing phase 3 Debrase DS batches. The final BRM specifications for BLA must be based on historical data of BRM batches, especially those batches used for producing Debrase DS batches tested in phase 3 trials.

8. Be aware that a USAN name should be adopted before the Marketing application is filed. Submit the corresponding application to the United States Adopted Names Council if you have not done so.

9. In regard to your stability studies, you should provide information on the cumulative stability of the drug product. For example, stability of the drug product should be evaluated under worst case scenario conditions, where drug product is manufactured with Bromelain Special Production that is at or near the end of its shelf-life.

**Pharmacology/Toxicology**

Submit to the IND an impurity profile for the lots of drug product used in nonclinical studies and the lots of drug product that will be used in clinical studies.

**Clinical Pharmacology/Biopharmaceutics**

The sponsor did not have any question for Clinical Pharmacology. However, we have the following comments:

1. (b) (4)

2. On April 15, 2011 you submitted the preliminary summary of PK results from an interim analysis of study MW 2008-09-03. In this summary, 7 of 8 available PK profiles had a Tmax of 2 hours, coinciding with the first sampling time. We recommend that future PK studies are designed to collect samples prior to 2 hours postdose to better capture Cmax.

3. It is not clear which moiety (or moieties) of Debrase, a complex mixture, is/are being measured in the PK study. The report titled "Validation of an Electrochemiluminescence (ECL) Method for the Quantitation of Debrase in Human Serum" states that rabbit anti-Debrase antibody was provided by the sponsor. However, no information on the target moiety and the specificity of the anti-Debrase antibody reagent was provided. Submit to the IND the information on what moiety(ies) of the mixture in Debrase is/are being measured by the PK assay and provide a rationale supporting that the selected moiety(ies) quantified by the assay is/are adequate to evaluate the systemic absorption of Debrase.

4. In the clinical development program, you should assess the impact of anti-Debrase antibody on the pharmacokinetics and clinical efficacy and safety; this requires a validated immunogenicity assay that is sensitive to detecting the circulating anti-Debrase antibody and not prone to interference by the presence of Debrase in the immunogenicity samples.

**Clinical/ Biostatistics**

**Question 8:**
Does the Agency agree that the co-primary endpoints for the proposed Phase 3 study are appropriate to support the intended indication?

**Response:**
No. You proposed two co-primary endpoints: 1) Superiority in eschar removal (debridement) as measured by a per wound survival analysis of incidence of complete eschar removal as a function of time; 2) Superiority in reduction in surgical need for eschar removal as measured by a per wound analysis of % area wound surgically excised performed as part of the eschar removal phase (debridement) (tangential/minor/avulsion/ Versajet/dermabrasion excision).

However, time to complete eschar removal and reduction in the need for surgical excision (measured by area of excision), alone, are not clinically meaningful, unless there is comparable or superior wound healing for 1) time to wound closure, 2) incidence of wound closure, and 3) final outcomes in function and cosmesis.

Reduction in need for surgery could be demonstrated by a number of different criteria, e.g., by decreased % skin area that requires excision as measured by planimetry, by decreased incidence of surgeries, by area that requires autograft, etc. However, reduction in surgery would be an acceptable an efficacy endpoint only if you also demonstrate that time to wound and incidence to wound closure, and function and cosmesis are not inferior.

Time and incidence to 100% wound closure (without drainage or need for a dressing) as well as function and cosmesis, are endpoints that can be assessed by the investigator, the subject and a blinded assessor (see additional Clinical Comments #1), and can be documented by standardized

photography and assessed by independent reviewers retrospectively; function can be documented by standardized video for masked assessor evaluation.

You use the term "eschar removal (debridement)". It appears that you intend to treat the wounds in the ER, shortly after arrival. "Eschar" usually refers to dead tissue, which may take time to develop. We will need you to clarify your definition of an eschar, and justify any differences between your definition of eschar and the definition provided by the American Burn Association (ABA: eschar is a slough (area of necrotic tissue), crust or dry scab resulting from a burn) as per the following ABA White Paper on Surgical Management of the Burn Wound and Use of Skin Substitutes: http://www.ameriburn.org/WhitePaperFinal.pdf

**Meeting Discussion:**
The sponsor concurred with the Agency's comments regarding end points. The Agency reiterated that the protocol, including the statistical analysis plan, should clearly define patient enrollment criteria, ensuring blinding when randomizing patients for treatment, appropriate measurement for the end points to be used for assessing efficacy and safety, and account for all subjects who are screened, randomized and/or treated.

**Question 9:**
Does the Agency agree that the patient population for the proposed Phase 3 study is appropriate? Please comment on the following:

- Total body surface area of the burn
- Burn depth
- Age

**Response:**

- Total body surface area of the burn (TBSA):

  No. It appears that you plan to include first degree, superficial- mid- and deep- partial, and full thickness (FT) wounds to count towards the TBSA of the burn (Section 10.2.4.7, p187 of briefing document). In addition, you state that adults and children, hospitalized in burn units, with mid/deep partial thickness and full thickness burns ranging from 4 – 30% but with no more than 30% TBSA burns in total will be enrolled. You state that "there is no obligation to treat first and second degree superficial burned area as they usually do not necessitate eschar removal". Indeed, such wounds usually do not form eschar. Finally, you state that it is impossible to separate these superficial areas from deeper ones (e.g., mixed depths on the same area/wound); these may be included as part of the Target Wound definition.

  However, your inclusion criteria include patients with:

  a. $\geq$ 4% TBSA partial (mid and deep dermal) and full thickness burn wounds.
  b. $\leq$ 30% TBSA total acute first – third degree total body surface area burned due to heat exposure, that is, adults with 4-30% of acute total body surface area burned due to heat exposure that does and does not need medical intervention.

c. At least 50% of mid and deep dermal and or full thickness wound area is intended for surgery as judged on admission by the investigator.

Your definition and criteria for clinical trial inclusion as well as outcome assessment do not distinguish burn surface area that needs treatment from burn surface area that you acknowledge to not need treatment (first and superficial second degree). This confounds poolability and assessment of wounds, treatment and outcome. It is also unclear how the above inclusion criteria can be applied based upon your statement that "it is impossible to separate these superficial areas from deeper ones (e.g.; mixed depths on the same area / wound); these may be included as part of the Target Wound definition". Additionally, in the US, TBSA in burn care is defined in general and formally by the ABA as total body surface area referring to the total body surface area affected by second and third degree burns or to the total body surface area treated (ref: Appendix 1, http://www.ameriburn.org/WhitePaperFinal.pdf). Therefore, your definition for TBSA is inadequate from the perspective of clinical trial design and standard US practice nomenclature.

1. Edit your US protocol to define TBSA as the total body surface area affected by second and third degree burns or to the total body surface area treated (ref: Appendix 1, http://www.ameriburn.org/WhitePaperFinal.pdf).

2. Edit your protocol to include nomenclature as per FDA and ABA definitions, including but not limited to the target wound of your product, which is only an acute wound due to heat exposure (refer to page 9, http://www.ameriburn.org/WhitePaperFinal.pdf ; page 8 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071324.pdf) .

3. If your TBSA definition is to be "total body surface area treated" and you intend to treat all first through third degree burn areas, then:

   a. Clearly state this is the indication for use and inclusion/exclusion criteria.

   b. Provide a method of distinguishing first and superficial second degree burn area, which you acknowledge do not need treatment, from deep second degree and third degree burn areas, which are acknowledged to need treatment. Otherwise, outcomes may be confounded and biased by wound enriched with surface area that does not need treatment. Such data is also clinically uninterpretable, especially as to claims and comparison of acute thermal burn wound areas that are not expected to heal without medical intervention.

4. Provide a summary of Debrase clinical data to date based upon TBSA defined as second and third degree thermal burn, compared to TBSA defined as all burn areas (first through third degree).

- Burn depth:

  No . Burn depth is a significant determinant of mortality and the primary determinant of the patient's long-term appearance and functional outcome. Therefore it is critical that you assess burn depth accurately. You state that burn depth will be visually assessed by the Investigator; however, this could introduce inter-observer variability, bias and error. Provide an objective method and criteria of burn- and debrided wound-depth assessment.

  Note that your wound depth definition (page 103 of protocol v 4/13/2011 for Study MW 2010-03-02) differs from that published in the American Burn Association White Paper: Surgical Management of the Burn Wound and Use of Skin Substitutes (2009). You define burn wound depths as 1st degree burn; 2nd degree burn (superficial partial thickness, mid partial thickness/mid dermal, deep partial thickness/deep derma); 3rd degree burn (full thickness burn). The White Paper defines: 1st degree burn (superficial); 2nd degree burn (superficial partial thickness or deep partial thickness); 3rd degree burn (full-thickness). Thus it appears that your definition has one additional category in the 2nd degree burn. Edit your protocol to use the standard convention for defining wound depth in the US. This will help to ensure clear communication, valid data collection interpretation, as well as proper use of your product during clinical trial as well as market settings.

- Age:

  You propose to study down to age 2. Acceptable safety (including adequate pain control) and some evidence of efficacy should be established in adult subjects before initiating testing in vulnerable population. At this time we have not found sufficient evidence to allow study in the pediatric population. Clarify enrollment of adults/ children in accordance to US Code of Federal Regulations Title 21 Part 50.3 (o), http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3

**Question 10:**
Does the Agency agree that the standard of care described in the protocol is an appropriate comparator to Debrase in the proposed Phase 3 study?

**Response:**
No. The SOC arm includes various modalities and no paradigm for reasonable consistency of intervention which would impact data poolability. Some subjects will undergo non-surgical (non-Debrase) debridement.

1. Clarify whether another form of enzymatic debridement will be applied to the wound.
2. Identify all forms of enzymatic debridement as well as non-enzymatic debridement to be used in control and or investigational product cohorts.
3. Record the timing, duration and name of each intervention as well as pre and post product use wound status, including objective (if possible) assessment of parameters such as surface area, drainage, edema, odor, pain and tenderness.

4. Provide paradigms for overall patient and wound standard-of-care that are appropriate for the US (e.g., such as established by investigator consensus).

As noted at the November 10, 2010 Guidance meeting, we recommend incorporating a vehicle arm in your Phase 3 program. It may be possible to enroll a smaller proportion of subjects on the vehicle arm than the SOC arm.

**Question 11:**
Does the Agency agree that hand burn wounds can be included in the proposed Phase 3 study?

**Response:**
Given that the hands are a sensitive anatomical location for both cosmesis and function, cosmesis and function should be established else where in the body before hands can be studied.

Also note that the US ABA Burn Center Referral Criteria (Appendix 2, http://www.ameriburn.org/WhitePaperFinal.pdf), include:

1. Partial-thickness burns of greater than 10% of the total body surface area.
2. Burns that involve the face, hands, feet, genitalia, perineum, or major joints.
3. Third-degree burns in any age group.
4. Electrical burns, including lightning injury.
5. Chemical burns.
6. Inhalation injury.
7. Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality.
8. Any patients with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient's condition may be stabilized initially in a trauma center before transfer to a burn center. Physician judgment will be necessary in such situations and should be in concert with the regional medical control plan and triage protocols.
9. Burned children in hospitals without qualified personnel or equipment for the care of children.
10. Burn injury in patients who will require special social, emotional, or rehabilitative intervention.

Edit inclusion/exclusion criteria to:

1. Address each of the above ABA criteria as an inclusion or exclusion criterion. At this time, your proposed clinical trial:
    a. enrolls adult patients with:
        i. $\geq$ 4% TBSA partial (mid and deep dermal) and full thickness burn wounds.

ii. ≤30% TBSA total acute first – third degree total body surface area burned due to heat exposure, that is, adults with 4-30% of acute total body surface area burned due to heat exposure that does and does not need medical intervention.

iii. At least 50% of mid and deep dermal and/or full thickness wound area is intended for surgery as judged on admission by the investigator.

b. is expected to not enroll:

i. As per current exclusion criteria.

ii. Children, based upon local US jurisdiction definition.

iii. Patients who will require special social, emotional, or rehabilitative intervention.

iv. Partial-thickness and third degree burn sum of greater than 30% of the total body surface area.

v. Burns that involve the face, hands, feet, genitalia, perineum, or major joints.

vi. Electrical burns, including lightning injury.

vii. Chemical burns.

c. is unclear as to an objective measure of the following:

i. Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality. For example, exclude patient with pre-injury American Society of Anesthesiologists Physical Status greater than 2 (ref: http://www.asahq.org/clinical/physicalstatus.htm ).

ii. Any patients with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient's condition may be stabilized initially in a trauma center before transfer to a burn center. Physician judgment will be necessary in such situations and should be in concert with the regional medical control plan and triage protocols. For example, exclude patients with APACHE 3 score greater than 30 within 4 hours of injury.

**Question 12:**
Does the Agency agree that the sample size and power calculations are appropriate for the proposed Phase 3 study?

**Response:**
We will need to reach agreement on the set of primary endpoints before we can discuss the adequacy of your power calculations. In general, the sample size calculations should be based on the best available (or conservative) treatment effect estimates for the primary endpoints from prior studies. It is not clear how your data from previous studies were used calculate sample sizes. In particular, you should

1. Provide all estimates needed to calculate the sample size for each primary endpoint, along with their justification.

2. Use a sample size calculation methodology that corresponds to the proposed primary endpoints (note that you proposed the "mean percent wound area excised" as one of the co-primary endpoints, but used estimates and methods for the "incidence of wound excision" to justify the sample size for this endpoint).

**Question 13:**
Does the Agency agree that the sponsor's clinical development plan is sufficient to support the submission of a BLA?

**Response:**
We do not yet have agreement on study design, the population to be studied, or primary endpoint/s, therefore it is not possible to address the sufficiency of your development plan at this time. Ultimately, the sufficiency of your clinical development plan will be a review issue. Efficacy and safety must be demonstrated in two adequate and well controlled studies, and endpoints need to be clinically meaningful. Safety assessment should extend to the time point where final wound outcomes (cosmesis and function) could be evaluated.

**Additional Comments Regarding the Proposed Phase 3 Protocol (MW 2010-03-02, version date 13April 2011):**

1. In order to maintain study integrity, assessor of efficacy endpoints (including time to and incidence of complete wound healing, and cosmesis and function) should be blinded. For example, results on whether the wound has closed could be measured at pre-specified time points by a blinded assessor.

2. Consider using multiple batches in Phase 3 studies to define the range of acceptable variation in CMC specifications. Propose your detailed design and analysis.

3. The description of SOC arm treatment lacks sufficient objective criteria and description. For example, it is stated that subjects in the SOC group may be treated with a "mixture of surgical and non-surgical debridement, according to the investigator's judgment." Leaving the treatment decision to the investigator's judgment will likely introduce variability to the SOC treatment. Or as another example, in subjects who are to receive the non-surgical debridement SOC treatment paradigm, it is not stated what other topical medication(s) will be used "to induce maceration and autolysis of eschar." See also FDA response to question 10.

4. Provide objective, pre-specified criteria in the protocol to describe whether, when and for what specific wound conditions a second application of Debrase will be applied.

5. You propose that function and cosmesis will be measured as safety parameters, by using the Modified Vancouver Scar Scale (MVSS), which measures pigmentation, pliability, height, vascularity, pain, and pruritus. The Vancouver Scar Scale is used widely in literature for

outcome measure in burn studies. However, we note that this scale does not measure functionality. Further, it has been noted in the literature that 1) the scale is best used to determine change within an individual rather than between individuals; 2) although frequently used in research settings and is beneficial to study small, linear scars, it is only minimally useful for studying large scars and for assessing functional affects of scarring; 3) the scale is prone to operator dependent errors.[1] Whether the MVSS can successfully measure cosmesis and function is uncertain. Provide scales for assessment of cosmesis and for assessment of anatomically specific function, e.g.: range of motion, motor strength, that have been validated for populations such as the proposed study population. A lower extremity function scale is referenced here: http://www.ncbi.nlm.nih.gov/pubmed/18849834. Include full text of literature supporting such validation. If you propose a new scale, provide a plan for scale validation in your protocol.

6. Safety monitoring should reflect the needs of this critically ill population. For example, EKG and labs should be obtained more frequently, not twice as proposed, before debridement and once within 24 hours after debridement); blood transfusions should be recorded until the subject is medically stable (such as at complete wound healing), not as proposed, only for the first 7 days post surgery. APACHE 3, Glasgow Coma Score and other population-specific validated assessments should be recorded.

7. The following are comments on the proposed analysis methods which can be taken into consideration once agreement on the primary endpoints and endpoint framework has been reached:

   a. You have proposed using per wound analyses, but it is not clear whether your proposed statistical analysis methods for the time to event endpoints address the repeated measures within a subject (multiple wounds per subject). In addition, the proposed time to event analysis proposes using both Kaplan-Meier and Cox regression analyses, and the roles of the two methodologies are not clear. You should clarify the proposed method and ensure that it adequately accounts for within subject effects (or alternatively use a per subject analysis), and clarify the roles of multiple methodologies (or propose a consistent analysis).

   b. Although the proposed analysis for continuous wound-based endpoints takes into account the within-subject correlation due to multiple wounds per subject, it is not clear how the varying number of wounds per subject will impact the analysis. In addition, the protocol proposes to use appropriate transformations if the normality assumption is not met, but the protocol is not clear on how an appropriate transformation would be selected, leaving room for the introduction of bias.

8. The protocol needs to include plans for handling missing data for the ITT population (for continuous and binary endpoints). In addition to a primary method of handling missing data, the protocol should also included two sensitivity analyses that use alternate methods or

[1] Fearmonti, R, Bond, J, Erdmann, D. et al. A review of scar scales and scar measuring devices (2010). ePlasty 10: e43

assumptions to ensure that the results of the study are not driven by the method of handling missing data.

9. Analyses based on the ITT population should be the principal analyses, with the analyses on the evaluable subset as supportive.

**Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, refer to 21CFR 54 and 21CFR 314.50(k).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

5. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Plan to address this issue early in development.

6. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website http://www.fda.gov/cder/regulatory/physLabel/default.htm for additional details).

7. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

**Data Standards for Studies**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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/s/

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SUSAN J WALKER
08/03/2011