ADDENDUM TO STATISTICAL ANALYSIS PLAN

Clinical Trial

A multicenter, multinational, randomized, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to Gel Vehicle and compared to Standard of Care (MW 2010-03-02) DETECT)

Sponsor:

MediWound, Ltd.

42 Hayarkon Street

North Industrial Area

Yavne, Israel 8122745

Trial protocol code: MW2010-03-02

EudraCT number: 2014-001672-55

IND No.: 65,448

Kompetenzzentrum für Klinische Studien Bremen

Competence Center for Clinical Trials Bremen - Biometry

Author: Dr. Martin Scharpenberg

Version of 23 August 2020, Addendum 2 to Version V03

1. Table of Contents

2. Study Administrative Structure

2.1. Sponsor

Sponsor: MediWound, Ltd
42 Hayarkon Street
North Industrial Area
Yavne, Israel 8122745

Represented by: Prof. Lior Rosenberg
Chief Medical Officer
MediWound Ltd.

Keren David Zarbiv
VP Clinical Affairs
MediWound Ltd.

Nimrod Leuw
VP QA/QC
MediWound Ltd.

2.2. Study Conduct

Study Conduct (CRO): Dr. Marco Schwarzer
GCP-Service International Ltd. & Co. KG
Anne-Conway-Str. 2
28359 Bremen

2.3. Statistics

Statisticians: Prof. Dr. Dr. h.c. Jürgen Timm
Dr. Martin Scharpenberg
Competence Center for Clinical Trials Bremen
University of Bremen
Linzer Str. 4
28359 Bremen
Germany

3. Signatures

Keren David Zarbiv
Sponsor Representative
MediWound Ltd.

DocuSigned by:
Keren David
Signature
Signer Name: Keren David
Signing Reason: אני מאשר את המסמך
Signing Time: PDT 2020-ספט-AM 4:52:58 | 01
B682E185C32B437D95874687D6005519
01/Sep/2020
Date

Dr. Marco Schwarzer
Study Conduct (CRO)
GCP-Service International Ltd. & Co. KG

Signature
25/08/2020
Date

Prof. Dr. Dr. h.c. Jürgen Timm
Principal Statistician
Competence Center for Clinical Trials Bremen,
University of Bremen

Signature
25/08/2020
Date

Dr. Martin Scharpenberg
Statistician/Author
Competence Center for Clinical Trials Bremen,
University of Bremen

Signature
24108/2020
Date

4. List of Abbreviations

abbreviation	meaning
ANOVA	Analysis of Variance
COVID-19	Corona virus infectious disease 19
MVSS	Modified Vancouver Scar Assessment Scale
POSAS	Patient Observer Scar Assessment Scale

5. Rationale for the Addendum

Due to COVID-19 restrictions, the sponsor has submitted a protocol memo, dated 09 Apr 2020, to sites allowing them to perform the 24-month visit with a deviation of up to 6 months (between April 1st to Sep 1st), or to perform the visit remotely. In addition, due to lack of resources, some sites may not be able to perform the 24-month MVSS and POSAS assessments. (See "Protocol Memo", attachment 1)

This addendum describes how deviations related to COVID-19 will be handled in the analysis.

6. Handling of missing values

Data missing due to COVID-19 will be handled in the same way as missing data for any other reason, i.e. the procedures for handling of missing data described in the SAP in section 10.1 will also be applied to missing values due to COVID-19.

7. Analysis of Safety Endpoint Cosmesis and Function at 24 months

7.1. Handling of data from earlier/delayed visits

One concern for the analysis of this endpoint is that, for some individuals, the 24-month visit was completed up to 3 months early (i.e. month 21) or up to 6 months late (i.e. month 30). From a medical perspective, it is assumed that data captured at an earlier or delayed visit will not be that different from data subsequently collected at 24 months; therefore, these data will be analyzed together with the data captured at 24 months (i.e. this endpoint will be analyzed as MVSS at 21-30 months).

All data handling procedures and analyses described in the SAP will be applied to the 21-30 months MVSS data.

As a sensitivity analysis, for subjects with a delayed 24-month visit (within the time frame 24-30 months) the MVSS at 24 months will be linearly interpolated from the delayed value and the last MVSS value captured before 24 months. In the same analysis, for subjects with an earlier 24-months visit (but within the time frame 21-24 months), the MVSS at 24 months will be linearly extrapolated from the earlier value and the last MVSS value captured before that. Following such interpolation, the same imputation techniques for missing data (regression imputation, best case, worst case) and the same analyses as described in the SAP will be applied. This implies that a new regression imputation model will be fitted to the data.

In addition, treatment groups will be compared with respect to the timing of the last visit (planned at 24 months). The allowed per protocol window for the 24-month visit is 23 months and 2 weeks to 24 months and 2 weeks. The following five categorical time-windows will be defined:

- 21 months to 23 months and 2 weeks,
- 23 months and 2 weeks to 24 months and 2 weeks,
- 24 months and 2 weeks to 27 months,
- 28 months to 30 months, and
- No visit between 21 months and 30 months.

A table of MVSS values (mean and SE) will be produced by these follow-up categories and treatment group.

In the event of imbalance of these time window categories across the treatment groups (defined as an absolute difference of 20% or more in the percentage of a category in the two groups) this categorical variable will be included as an extra explanatory variable in the regression model for comparing the treatment groups with respect to the 24-Month MVSS assessment, as additional sensitivity analysis.

7.2. Handling of remotely captured data

A small fraction of MVSS assessments are expected to be collected remotely. To account for this, the main analysis of the 24-month MVSS will be repeated, as supportive analysis, treating remotely assessed values as missing. I.e. the multiple imputation procedure described in the SAP section 10.1.2.2 will be repeated, fitting a new imputation model to the data.

The descriptive statistics table described in the SAP will be produced for all MVSS values with on-site collected values and remotely collected values listed separately. The p-values described in the SAP will be computed based on all values as a main analysis. As an additional analysis, the p-values will also be computed without remotely collected data.

8. Exploratory and Subgroup Analyses of MVSS and POSAS

The exploratory analyses of target wound and donor site POSAS and MVSS assessments, as well as the subgroup analyses of 24-month MVSS will be modified to account for the fact that some assessments of these scores were done remotely.

The descriptive statistics tables described in the SAP sections 11.3.4.3 and 11.3.5 will be produced for all POSAS/MVSS values as well as for on-site collected values and remotely collected values listed separately. The ANOVA p-values described in the SAP will be computed based on all values as a main analysis. As an additional analysis the p-values will also be computed without remotely collected data.

9. Further analyses

All endpoints apart from MVSS and POSAS assessments are self-reported. Therefore, no influence of remote study visits is expected. The analyses of the other endpoints will be conducted as described in the SAP sections 11.3.4.7-11 (including the first Addendum, dated 26 February 2020).

10. Attachment: Note to file

Protocol Number: MW 2010-03-02

MediWound

NOTE TO FILE

Originated by: Limor Dinur Klein	**Date:** 09/Apr/2020

☒ Study Specific ☐ Site Specific ☐ CRF Specific

For site specific/CRF specific, specify site number and name of PI: NA

For CRF specific, specify patient ID: NA

Specify Reason for File Note:

On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19. State of emergency was declared in response to COVID-19 in all countries currently participating in MW2010-03-02 study.

As a direct result of the COVID-19 pandemic, clinical trial conduct for the MW2010-03-02 study has been affected by restrictions due to quarantines, site closures, study staff required to work from home, and travel limitations.

The purpose of this note to file is to issue guidance and clarification on protocol modifications that can be implemented during the COVID-19 pandemic to assure the safety of trial participants, compliance with good clinical practice (GCP), and minimize risks to trial integrity.

You must immediately submit a copy of this protocol memo to your respective local Institutional Review Board/Ethics Committee and file these documents in the Investigator Site File. All modifications made to protocol visits and assessments should be approved by your local IRB/EC and local competent authorities, as required, prior to implementation. On parallel, MediWound will ensure regulatory agencies are notified of protocol modifications, prior to implementation. After COVID-19 hospital restrictions have been lifted, sites should continue to complete all remaining visits and assessments per the approved protocol.

All missed assessments or deviations from the approved protocol will be captured as a protocol deviation, documented using sponsor's standard processes, and the reason will be noted as due to the COVID-19 pandemic.

Action taken:

The following guidance and modifications should be taken into consideration:

Long Term Follow-up of Enrolled Study Subjects:

- At this time, all acute phase and 12 Month Long Term Follow- up subject visits have been completed for the MW2010-03-02 study, only the remaining final 24-Month Long Term Follow-up visits will require modifications to ensure these are completed.

Note to file Version: 04 Date: 31Mar2020

2

- As the MW2010-03-02 24 month Long-Term Follow-up Visit has several assessments which cannot be conducted remotely, such as Immunogenicity collection and Range of Motion, it is preferred that when possible, the visit be rescheduled to an onsite visit. The allowable visit window for the 24-Month Long Term Follow-up Visit is being extended as follows:
  - Any site/subject with a pending 24-Month Long Term Follow-up visit can be scheduled to occur between April, 1, 2020 until September 1, 2020, as hospital policy and restrictions allow (this may result with an out of window deviation of up to 6 months).

- If an onsite visit is not feasible and cannot be rescheduled within the window noted above due to COVID-19, to assure safety of trial participants and continued investigator oversight, at a minimum it is recommended that, if possible, a telephone interview be conducted to review any changes in adverse events or concomitant medications with the subject.

  One or more of the alternative follow-up methods can be implemented to conduct remote Long-Term Follow-up Visits. These methods include:
  - Telemedicine
  - HIPAA compliant (US only) Telecommunication
  - Subject interview via telephone call- at a minimum to collect adverse event and concomitant medication information
  - Wound assessment via photograph and/or videos that are taken by the subject and provided to the site. Note: In these cases, a study specific photograph label does not need to be utilized. The subject should be reminded not send any photographs of faces or tattoos to protect PHI. If photographs are transmitted by the subject and they contain PHI, they should not be made available to the sponsor..

  If a follow-up visit is conducted remotely via one of the methods listed above, the reason should be thoroughly documented in the source documents. Additionally, any assessments that were completed remotely should also be clearly documented within the study source.

- If a Long-Term Follow-up visit will be completed remotely, cosmesis assessments such as POSAS and MVSS should be completed to the best of the blinded assessor's ability through subject interview and photo/video assessment. A live video is preferred as the assessor can request the patient or family member to pinch/press the scars to assess pliability and vascularity while moving the camera around the area of the scar. Additionally, through live video, the height of the scars can be measured by a patient or family member with a ruler while moving the camera to a tangential angle in order to be able to see exactly where to measure and the height on the ruler. Note: Only a designated blinded assessor should complete POSAS and MVSS wound assessments.

- Additionally, if a Long Term Follow-up visit will be completed remotely, the subject should be mailed or emailed a copy of the applicable self-completed questionnaires (BSHS-B, EQ5D, POSAS (patient scale), Lower Extremity Function Scale, and QuickDASH) and patient diary. These should be completed by the subject, initialed and dated, and returned back to the site. If sending the questionnaires to the subject is not an option, the site may complete an interview with the subject on the phone/video call to discuss the questions. It should be clearly documented that the questionnaire was completed by site staff due to COVID-19.

- If, due to COVID-19, a subject is unable to return back to the site or complete a visit via telecommunication, or if the clinical site is unable to perform assessments as a result of a lack of resources then the missed visit should be documented in the source documents and the reason clearly noted as being due to COVID-19.

Note to file Version: 04 Date: 31Mar2020

3

- A table of the optional alternative methods for 24-Month Long Term Follow-up remote assessments is presented below (see table 1).

Notification of Study Subjects:

- Trial participants should be kept informed of changes to the study that could impact them.
- The Informed Consent Form (ICF) should be updated per local IRB/EC requirement and subjects re-consented via an IRB/EC approved method such as email/mail along with phone consenting procedures, if they are unable to return for an onsite visit.
- If the IRB/EC does not require subjects to re-consent updated ICF, sites are asked to send an IRB/EC approved subject memo to their participants to clarify that they may be asked to complete follow-up visits remotely via telemedicine/telecommunication, phone application, or phone and they may be asked to provide photos of their wounds and complete questionnaires at home

Study Monitoring Procedures:

- Due to travel restrictions, onsite monitoring visits may not be able to be performed during the COVID-19 pandemic. Alternative methods of monitoring will be implemented during this time to ensure that study conduct and subject safety are monitored.
- In lieu of onsite monitoring visits, remote interim monitoring visits may be conducted, if your site policies allow and has the capability. These visits would consist of electronically providing the study source documentation required for source data verification or any other required data. All provided source documents should be certified prior to sending to the CRA and any personal health information redacted.
- On-sites close out visits will not be completed remotely and therefore will be delayed to a later time, once COVID-19 hospital restrictions will be lifted.

Attachments/References: N/A

Signatures (Print name/Signature/Date)
If applicable, other responsible persons should sign as well (e.g. LM, PM, PI etc.):

PI Name:

Signature:

Date:

Originator (Sponsor PM or CRO PM/CRA; mandatory):
Limor Dinur Klein, PhD, MediWound Clinical Project Manager

Note to file Version: 04 Date: 31Mar2020

4

Distribution please specify (e.g. TMF section x, ISF section y, not applicable or other) and extend list if necessary:
Original: TMF
1. Photocopy: ISF
2. Photocopy:

Note to file Version: 04 Date: 31Mar2020

Running Title: A multicenter, multinational, randomized, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to Gel Vehicle and compared to Standard of Care		
Protocol: MW 2010-03-02	Version: 11- 23 June 2016 COVID- 19- Remote Follow-up methods	Page 1 of 1

Table 1- Optional Methods for Remote Completion of 24-Month Long Term Follow-up Visit

Assessment		Method of Contact				Comments
		Photo sent by Patient	Phone conversation	Video call/Telemedcine	Phone Application	
Wound photographs		X	N/A	N/A	X	Photos/Videos that will be sent by the patients will not include photo label.
Documentation	Adverse events	X Photo Assessment- Local TW related only	X	X	X	Any SAEs should be reported within 24 hours of knowledge of the event.
	Concomitant Medication review	N/A	X	X	X	
	Scar modulation procedures	N/A	X	X	X	
POSAS Observer Scale		X		X	N/A	Video method preferred, if available
MVSS		X		X	N/A	Video method, if available
ROM		N/A	N/A	N/A	N/A	Can be completed during an on-site visit only.
Patient questionnaires	POSAS Patient Scale	X Photocopy sent back to site	X Subject interview	X Subject interview	X	It is preferred to have questionnaires sent to subject via mail/email, completed, and returned to site, if possible.
	QOL (EQ5D,BOQ)	X Photocopy sent back to site	X Subject interview	X Subject interview	X	It is preferred to have questionnaires sent to subject via mail/email, completed, and returned to site, if possible.
	LEFS/ QuickDASH	X Photocopy sent back to site	X Subject interview	X Subject interview	X	It is preferred to have questionnaires sent to subject via mail/email, completed, and returned to site, if possible.
	Subject Diary	X Photocopy sent back to site	X Subject interview	X Subject interview	X	It is preferred to have questionnaires sent to subject via mail/email, completed, and returned to site, if possible.
Immunogenicity		N/A	N/A	N/A	N/A	Can be taken during an on-site visit only. May be performed in delay

Page **1** of **1**