AMENDMENT

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 (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 29 November 2018, SAP Version V02, Amendment 01

1. Table of Contents

2. Reason for the Amendment

The final Statistical Analysis Plan (SAP), version 02, dated May, 15 2018, was submitted to the Food and Drug Agency (FDA). The FDA gave four comments on the SAP (Advice letter from 05 November 2018) regarding the planned statistical analysis, suggesting changes to the analyses and requesting clarifications on the planned analysis. The FDA comments were:

1. For establishing efficacy in an adequate and well-controlled trial, the statistical analyses need to be fully prespecified to minimize bias and ensure control of Type I error. The description in the SAP regarding the analysis method for the primary endpoint mentions both logistic regression and Fisher's exact test, without clearly stating which analysis is the primary analysis. To ensure that the analysis for the primary endpoint is fully prespecified, clarify whether the primary analysis method is logistic regression or Fisher's exact test.
2. As we noted in our Advice Letter dated 5/14/2015, while we acknowledge that the number of subjects with missing data at the end of the topical agent soaking period for the primary endpoint of complete eschar removal at the end of the topical agent soaking period and the secondary endpoint of incidence of excision is likely to be very limited, you will need to account for any missing subjects in the primary analysis using the total number of randomized subjects.
3. You have proposed to analyze blood loss using either the Mann-Whitney test or the t-test depending on whether the results of the Shapiro-Wilk test are significant at the 5% significance level. Because the Shapiro-Wilk test may be likely to reject the normality hypothesis when you have larger sample sizes even for relatively trivial deviations from normality, we recommend using a smaller significance level.
4. You have proposed to use multiple imputation to handle missing data, however, if the normality condition is not satisfied, it is not clear whether the assumptions need for multiple imputation using the regression method would be satisfied or how the results from the multiple Mann-Whitney tests could be appropriately combined using Rubin's rules. Clarify how you will analyze the data, including missing data handling, if the normality assumption does not hold.

Following receipt of the comments from the FDA on the SAP, required changes were discussed. On November 20, 2018, Prof. Freedman, the statistician blinded to the data, recommended changes to the SAP which are implemented in this amendment.

3. Signatures

Keren David Zarbiv
Sponsor Representative
MediWound Ltd.
Signature: Keren David Zarbiv Date: 02 Dec 2018

Dr. Marco Schwarzer
Study Conduct (CRO)
GCP-Service International Ltd. & Co. KG
Signature: M Schwarz Date: 4/12/18

Prof. Dr. Dr. h.c. Jürgen Timm
Principal Statistician
Competence Center for Clinical Trials Bremen,
University of Bremen
Signature: Date: 4.12.18

Dr. Martin Scharpenberg
Statistician/Author
Competence Center for Clinical Trials Bremen,
University of Bremen
Signature: Date: 4.12.18

4. List of Abbreviations

abbreviation	meaning
FDA	Food and Drug Agency
KKSB	Competence Center for Clinical Trials Bremen
SOC	Standard of Care

5. Changes to the statistical analyses plan

Changes are highlighted in bold letters, reasons of change in italic.

FDA comment # 1:

5.1. Primary Endpoint: Incidence of complete eschar removal in the topical arms

5.1.1. Primary analysis method

Insert in Section 11.1.2 of the SAP after the second paragraph:

"Note: The primary analysis method is Fisher´s exact test."

Reason:
In comment 1, the FDA asked for clarification on whether the primary analysis method is logistic regression or Fisher´s exact test.

FDA comment # 2:

5.1.2. Handling of missing data

Replace in Section 10.1.1 of the SAP in the first paragraph

"The main analysis…of complete cases"

by

"The primary analysis of complete eschar removal will include patients with missing endpoint data in the analysis. Such patients will be counted as having failed on this endpoint, i.e. as not having achieved complete eschar removal."

In consequence, the following **switch** is incorporated in Section 10.1.1**:**

This analysis is currently one of the specified sensitivity analyses, so it will be **removed** from the sensitivity analyses. Instead, **the complete case analysis, initially planned as the main analysis, will serve as one of the sensitivity analyses.**

Reason:

In SAP version 02, the main analysis of the primary endpoint is described as a complete case analysis, only taking into account subjects without missing data. In comment 2, the FDA requests changing the analysis to an analysis using the total number of randomized subjects. This change is in response to the FDA´s comment.

5.2. Secondary Endpoint: Incidence of surgical excision

Replace in Section 10.1.1.1.1 the text by

"The same procedure as for the primary endpoint will be applied for this endpoint, i.e. the main analysis will include all randomized patients, with those having a missing value assumed to have "failed", i.e. to have received surgery. Two sensitivity analyses will be performed. First, in each treatment group, only patients with documented surgical excision will be counted and this number divided by the total number of randomized subjects with non-missing endpoint. A second analysis will include all randomized patients and count all patients with missing data (for this endpoint) as positive (i.e. no surgical excision performed)".

Reason:

In SAP version 02, the main analysis of the secondary endpoint is described as being the same as in the primary analysis. The above change in the text emphasizes that the changes in the analysis implemented for the primary endpoint will also be implemented for this secondary endpoint.

FDA comment # 3:

5.3. Secondary Endpoint: Blood loss

5.3.1. Significance level of the Shapiro-Wilk test

In Section 10.1.1.3 and 11.1.3.3, second paragraph (for Shapiro-Wilk test significance level) **replace "5%" by "0.5%".**

Reason:

The FDA noted that the specified significance level of 5% for the Shapiro-Wilk test might be too large, due to the high sensitivity of the test to relatively trivial deviations from normality (comment 3).

FDA comment # 4:

5.3.2. Multiple Imputation in the presence of non-normality

The description of imputation in 10.1.1.3 will be divided into two parts, depending on the normality test results. The text as written will be used for the case where the normality hypothesis is accepted, and the following addition will be inserted for the case where the normality hypothesis is rejected:

“If the normality condition is not satisfied, then the multiple imputation method known as predictive mean matching will be used. Random draws from the five nearest neighbors for each missing value, and five multiply imputed datasets will be used. Multiple imputation may indeed be used with the Mann-Whitney Test, combining the Mann-Whitney test statistics across multiply imputed datasets, as described in the paper by Mogg and Mehotra, Statistics in Medicine 2007; 26:484-497 [1]**. The predictive mean matching method is implemented in the SAS procedure PROC MI. In accordance with the imputations specified in the SAP, the random seed for the imputations of blood loss values on a procedure level will be 11468. The seed for the imputations for analysis of blood loss, which treats the whole eschar removal process as one continuous procedure, the random seed, will be 12467.”**

Reason:

FDA noted that it is not clear whether the assumptions needed for multiple imputation using the regression method described in the SAP would be satisfied in case the assumption of normally distributed data is rejected by the Shapiro-Wilk test. Furthermore, it was requested to clarify how the results from the multiple Mann-Whitney tests could be appropriately combined using Rubin's rules.

5.4. Additional changes

The following changes to the SAP will be employed, independent from FDA´s comments.

To ensure better comparability between descriptive statistics tables for continuous and categorical variables, the table for categorical variables (Table 5 in the SAP) will be transposed.

To ensure better comparability between the unequally sized treatment groups, bar plots for categorical variables will display percentages instead of counts (Figure 2 in the SAP). The sample sizes underlying the bar plots will be displayed in the legend.

6. Reference List

[1] R. Mogg and D. V. Mehrotra, "Analysis of antiretroviral immunotherapy trials with potentially non-normal and incomplete longitudinal data," *Statistics in Medicine,* vol. 26, pp. 484-497, 2007.