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 (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

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Version of 26 February 2020, Addendum to Version V03

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2. Study Administrative Structure

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3. Signatures

Keren David Zarbiv
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02.03.2020 — Date

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26.02.2020 — Date

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26.02.2020 — Date

4. List of Abbreviations

abbreviation	meaning
ADaM	Analysis Data Model
AE	Adverse Event
BLA	Biologics License Application
CSR	Clinical Study Report
FDA	Food and Drug Administration
INR	International Normalized Ratio
ITT	Intention to Treat
KKSB	Competence Center for Clinical Trials Bremen
PT	Preferred Term
PTT	Prothrombin Time
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TW	Target Wound

5. Rationale for the Addendum

This addendum describes safety data analyses to be performed in addition to the final SAP (Version 3, 29 November 2018). The decision to add these analyses was made after breaking the blinding and in knowledge of the primary statistical analysis results computed in accordance with the SAP.

All originally planned analyses, as described in the final SAP, version 3, were performed and summarized in a Statistical Analysis Report dated 20 June 2019. Changed outputs described in this document will be implemented in the study CSR. The sponsor requested these ad hoc analyses in order to support the interpretation of the safety data statistical analysis results and to fulfil the FDA request for treatment emergent Adverse Events analysis as noted in the pre-BLA meeting minutes.

Furthermore, the calculation of some variables is adapted to be conform with the Analysis Data Model (ADaM) Implementation Guide v1.1. and to be consistent throughout the analysis.

6. General changes

Some general changes to the layout of tables described in the SAP will be performed:

- For some tables, the treatment arms will be presented in columns rather than rows, to facilitate between-treatment-group comparisons.
- Descriptive statistics tables will be combined for some baseline characteristics.
- The number of censored observation will be added to the tables of descriptive statistics for time to event endpoints.

Statistical analyses for all safety parameters which were described in the SAP are included in the Statistical analysis report, yet will not be included in appendix 14 of the CSR and is available upon request.

Furthermore, the calculation of some variables is adapted as follows to be conform with the Analysis Data Model (ADaM) Implementation Guide v1.1. and to be consistent throughout the study:

- AGE (Age) = RFICDTC (Date of Informed Consent) – BRTHDTC (Date of Birth)
  In the SAP, the date of physical examination instead of the date of informed consent is used which leads to missing age for two screening failures.
- CHG (Change from baseline) = AVAL (Analysis Value) – BASE (Baseline Value)

According to the SAP, the change from baseline should be calculated as BASE – AVAL which is not conform with the ADaM Implementation Guide. The calculation of pre-post differences is adapted accordingly (i.e. pre-post difference = post value – pre-value) to be consistent with the calculation of the change from baseline. However, the calculation described in the SAP will still be done (variable: BCHG) and form the basis of the analyses presented in the CSR.

7. Additional Analyses

7.1. Central Laboratory values

Shift tables for central laboratory values indicating shifts from baseline to post every type of eschar removal procedure (first application, additional application, surgical application, additional surgical application, and nonsurgical application) will be produced (see Table 1).

Furthermore, shift tables indicating shifts from baseline to any low/high or no low/high values will be presented (see Table 2).

Additional tables will indicate shifts from baseline to any post treatment clinically significant result (see Table 3). A listing of subjects experiencing such shifts will be provided.

The above tables will be presented for biochemistry parameters, hematology parameters and urine analysis parameters separately, and for parameters with numeric values only.

7.2. Local Laboratory values

The following sets of tables will be produced separately for INR and PTT:

- Shift tables indicating shifts from baseline to post first application, 24 hours past start and 48 hours past start, similar to Table 1
- Shift tables indicating shifts from baseline to any low/high or no low/high values post treatment (see Table 2) as well as a listing of subject experiencing such shifts
- Shift tables indicating shifts from baseline to any post treatment clinically significant result (see Table 3) as well as a listing of subjects experiencing such shifts

7.3. Vital signs

For the vital signs assessments, shift tables will be produced indicating shifts from baseline to any post-treatment time point (post first treatment, post second treatment, and post third treatment), as well as to the daily assessments for day 1 to day 7 (see Table 4).

Furthermore, shift tables indicating shifts from baseline to any post treatment clinically significant result (as in Table 3) will be provided. A subject listing of patients experiencing such shifts will be provided.

7.4. Pain

For the pain assessment, shift tables will be produced indicating the shift from baseline to pre and post any treatment time point (first application, additional application, surgical application, additional surgical application, and nonsurgical application), as well as to the daily assessments for day 1 to day 7 (see Table 4).

Furthermore, shift tables indicating shifts from baseline to any post treatment clinically significant result (see Table 5) will be provided.

7.5. Adverse Events

The following tables will be produced in addition to the tables described in the SAP:

- Summary of Treatment Emergent Adverse Events (TEAEs) on a subject level (see Table 6)
- Summary of TEAEs by System Organ Class (SOC), and Preferred Term (PT) (see Table 7) separately for:
    - All TEAEs
    - Treatment related TEAEs
    - General TEAEs
    - Local, not TW-related TEAEs
    - Local, TW-related TEAEs
    - TEAEs with PTs related to fever (Pyrexia, Body Temperature Increased, Hypothermia)
    - TEAEs with Target Wound Infections (only if Local, TW-related: Wound Infection Bacterial, Staphylococcal Skin Infection, Wound Infection, Wound Infection Staphylococcal)
    - Pain TEAEs (Pain: Pain; Post-traumatic pain; Uncontrolled pain in TW1,2 and 3; Pain in extremity [if Local, TW-related])

    - TEAEs including Tachycardia PTs (Sinus Tachycardia, Tachycardia)
- Summary of TEAEs by SOC, PT, and time of onset (see Table 8) separately for:
    - All TEAEs
    - General TEAEs
    - Local, not TW-related TEAEs
    - Local, TW-related TEAEs
    - All Treatment Emergent Serious Adverse Events (TESAEs)
- Summary of TEAE by SOC, PT and maximum intensity (see Table 9). In this table, patients who experienced multiple AEs with the same PT, but different intensities will be counted only once per PT with their maximum intensity. Subjects with multiple AEs with the same SOC but different intensities will be counted only once per SOC with their maximum intensity in the SOC row. This table will be produced separately for:
    - All TEAEs
    - Treatment related TEAEs
    - General Treatment related TEAEs
    - Local, not TW-related Treatment related TEAEs
    - Local, TW-related Treatment related TEAEs
    - All TESAEs
    - Treatment related TESAEs

All AE/SAE/TEAE/TESAE tables will be produced separately for Adverse Events occurring in the acute phase, in the second stage (3-12 months), and combined for the time frame 0-12 months.

7.6. Subgroup Analysis

7.6.1. Target wounds in the anatomical area of the hand

Additional to the subgroup analysis described in the SAP, which was defined on a subset of target wounds, the primary and secondary endpoint were also analyzed on a patient level using the subgroup of patients having at least one target wound that is found, at least partly, in the anatomical area of the hand.

7.6.1. Target wounds that are entirely full thickness

Additional to the subgroup analysis described in the SAP, which was defined on a subset of target wounds (i.e. all target wounds that are entirely full thickness), the primary and secondary endpoint were also analyzed on a patient level using the subgroup of patients having at least one target wound that is entirely full thickness.

8. Lay-out and list of tables

Table 1: Laboratory Value Shift Table for Changes from Baseline

Lab Value	Treatment	Baseline	Time point				
			Low: <32 n (%)	Normal: 32-50 n (%)	High: >50 n (%)	Missing n (%)	Total n (%)
Value [unit]	NexoBrid (N = xxx)	<32					
		32-50					
		>50					
		Missing					
		Total					
Value [unit]	SOC (N = xxx)	<32					
		32-50					
		>50					
		Missing					
		Total					

			Time point				
Lab Value	**Treatment**	**Baseline**	**Low: <32 n (%)**	**Normal: 32-50 n (%)**	**High: >50 n (%)**	**Missing n (%)**	**Total n (%)**
Value [unit]	Gel Vehicle (N = xxx)	<32					
		32-50					
		>50					
		Missing					
		Total					

N = number of subjects with the respective eschar removal procedure; N/A = not applicable,
n = number of subjects with respective category,
% = n/N*100

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 2: Laboratory Value Shift Table, Shift to Any Low or High

			Any post-treatment time point			
Lab Value	**Treatment**	**Baseline**	**Any Low n (%)**	**No Low n (%)**	**Any High n (%)**	**No High n (%)**
Value [unit]	NexoBrid (N = xxx)	Low				
		Normal				
		High				
		Missing/not applicable				
		Total				
Value [unit]	SOC (N = xxx)	Low				
		Normal				
		High				
		Missing/not applicable				
		Total				
Value [unit]	Gel Vehicle (N = xxx)	Low				
		Normal				

			Any post-treatment time point			
Lab Value	**Treatment**	**Baseline**	**Any Low n (%)**	**No Low n (%)**	**Any High n (%)**	**No High n (%)**
		High				
		Missing/not applicable				
		Total				

N = number of subjects with the respective eschar removal procedure,
n = number of subjects with respective category,
% = n/N*100

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 3: Laboratory Value Shifts from Baseline to Any Post-treatment Clinically Significant Result

			Any post-treatment time point			
Lab Value	**Treatment**	**Baseline**	**Any pCS low n (%)**	**No pCS low n (%)**	**Any pCS high n (%)**	**No pCS high n (%)**
pCS low: ….. pCS high: ….						
Value [unit]	NexoBrid (N = xxx)	Low				
		Normal				
		High				
		Missing/not applicable				
		Total				
Value [unit]	SOC (N = xxx)	Low				
		Normal				
		High				
		Missing/not applicable				
		Total				
Value [unit]	Gel Vehicle (N = xxx)	Low				

	Normal
	High
	Missing/not applicable
	Total

N = number of subjects in the Safety Population,
n = number of subjects with respective category,
% = n/N*100
N/A = not applicable; ULN = upper limit of normal
pCS = potentially Clinically Significant

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 4: Vital Sings/Pain Changes from Baseline by Time Point

		Baseline Assessments											
		NexoBrid (N= XXX)				Standard of Care (N= XXX)				Gel (N= XXX)			
Time point	**Assessment**	**<90 n (%)**	**90-180 n (%)**	**>180 n (%)**	**Missing n (%)**	**<90 n (%)**	**90-180 n (%)**	**>180 n (%)**	**Missing n (%)**	**<90 n (%)**	**90-180 n (%)**	**>180 n (%)**	**Missing n (%)**
Post first treatment	pCS (Low)												
	no pCS												
	pCS (High)												
	Missing												
	Total												

N = number of subjects in the Safety Population,
n = number of subjects with respective category,
% = n/N*100
pCS = potentially Clinically Significant

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 5: Pain Assessment Clinically Significant Results Shifts from Baseline to Any Post-treatment Time Point

			Any post-treatment time point			
Visual Analog Scale	**Treatment**	**Baseline**	**Any abnormal (nCS) n (%)**	**No abnormal (nCS) n (%)**	**Any abnormal (CS) n (%)**	**No abnormal (CS) n (%)**
Pain Intensity (mm)	NexoBrid (N = XXX)	Abnormal (nCS)				
		Normal				
		Abnormal (CS)				
		Missing/not applicable				
		Total				
Pain Intensity (mm)	SOC (N = XXX)	Abnormal (nCS)				
		Normal				
		Abnormal (CS)				
		Missing/not applicable				
		Total				

			Any post-treatment time point			
Visual Analog Scale	**Treatment**	**Baseline**	**Any abnormal (nCS) n (%)**	**No abnormal (nCS) n (%)**	**Any abnormal (CS) n (%)**	**No abnormal (CS) n (%)**
Pain Intensity (mm)	Gel Vehicle (N = XXX)	Abnormal (nCS)				
		Normal				
		Abnormal (CS)				
		Missing/not applicable				
		Total				

N = number of subjects in the Safety Population,
n = number of subjects with respective category,
% = n/N*100

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 6: Summary of Treatment Emergent Adverse Events - Patient level

	Treatment					
	Topical:NexoBrid Gel (N=XXX)		Standard of Care (N=XXX)		Topical:Gel Vehicle (N=XXX)	
	n	%	n	%	n	%
With at least one TEAE						
With at least one mild or moderate TEAE						
With at least one severe TEAE						
With at least one TESAE						
With at least one TEAE not related or remotely related to study drug						
With at least one TEAE possibly, probably, or related to study drug						
With treatment-emergent outcome of death						

N = number of subjects in the Safety Population,
n = number of subjects with respective category,
% = n/N*100

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 7: Summary of TEAEs/TESAEs by System Organ Class and Preferred Term

System Organ Class Preferred Term	Topical:NexoBrid Gel (N=XXX) n (%)	Standard of Care (N=XXX) n (%)	Topical:Gel Vehicle (N=XXX) n (%)
System Organ Class 1			
Preferred Term 1			
Preferred Term 2			
Preferred Term 3			
Preferred Term 4			
System Organ Class 2			
Preferred Term 1			
Preferred Term 2			

N = number of subjects in the Safety Population,
n = number of subjects with respective category,
% = n/N*100

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 8: Summary of TEAEs/TESAEs by System Organ Class, Preferred Term and Time of Onset

System Organ Class Preferred Term	Time of Onset	Topical:NexoBrid Gel (N=xxx) n (%)	Standard of Care (N=xxx) n (%)	Topical:Gel Vehicle (N=xxx) n (%)
System Organ Class 1	Total			
	During the treatment session			
	1st week after treatment			
	Week 2 - 4 after treatment			
	Week 5 - 8 after treatment			
	Later			
	Missing			
Preferred Term 1	Total			
	During the treatment session			
	1st week after treatment			
	Week 2 - 4 after treatment			
	Week 5 - 8 after treatment			
	Later			
	Missing			
Preferred Term 2	Total			
	During the treatment session			

System Organ Class Preferred Term	Time of Onset	Topical:NexoBrid Gel (N=xxx) n (%)	Standard of Care (N=xxx) n (%)	Topical:Gel Vehicle (N=xxx) n (%)
	1st week after treatment			
	Week 2 - 4 after treatment			
	Week 5 - 8 after treatment			
	Later			
	Missing			

Adverse events are presented in alphabetic order of system organ class and descending order of preferred term in the Total row of the NexoBrid group
Classifications of Adverse Events are based on the MedDRA (version 21.1)

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX

Table 9: Summary of TEAEs/TESAEs by System Organ Class, Preferred Term and Maximum Intensity

System Organ Class Preferred Term	Topical:NexoBrid Gel (N=XXX) n (%)				Standard of Care (N=XXX) n (%)				Topical:Gel Vehicle (N=XXX) n (%)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
System Organ Class 1												
Preferred Term 1												
Preferred Term 2												
System Organ Class 2												
Preferred Term 1												

AE is defined as related if causality is possibly related, probably related or related
Subjects are counted at the maximum severity level, only once in each system organ class category, and only once in each preferred term category
Events are counted for maximum severity level on a patient level. If an event was reported multiple times in the same patient, only the maximum severity is counted.
Adverse events are presented in alphabetic order of system organ class and descending order of preferred term in the Total column of the NexoBrid group
Classifications of Adverse Events are based on the MedDRA (version 21.1)

N = number of subjects in the Safety Population,
n = number of subjects with respective category,
% = n/N*100

Program: xxx.sas / Output run time: xxx / Data Base Extraction Date xxx
Output File: xxx.rtf
Source Data Set(s): ADAM.ADXX