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END-OF-STUDY PATIENT REGISTRY REPORT

Final version



NexoBrid

Prospective Assessment of Efficacy of NexoBrid in the treatment of Adult Patients with deep dermal and full thickness burns in Belgium

Sponsor: Mediound
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Germany

Protocol number: MW Reg Be 01 - 20/02/2016

First patient enrollment date: March 1st 2016

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Study performed *<in accordance with EN ISO 14155-1 and>* in compliance with Good Clinical Practices

This report was written according to ICH E3: Structure and content of clinical study reports

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1. SYNOPSIS

Sponsor: Mediwound
Investigational products: NexoBrid
Title of study: NEXOBRID Belgian registry: Prospective Assessment of Efficacy of NexoBrid in the treatment of Adult Patients with deep 2 nd degree and 3 rd degree dermal burns in Belgium.
Studied period: March 1 st 2016 – August 16 th 2017
Objectives: The overall study objective of this trial is a population based prospective assessment of efficacy of NexoBrid in Belgium.
Methodology: Open label Patient Registry
Study population: Adult patients identified as having deep 2 nd degree and 3 rd degree dermal that necessitate surgery, who have signed an informed consent, and are treated with NexoBrid.
Diagnosis and main criteria for inclusion: Adult Patients with deep dermal and full thickness thermal burns in need of surgical eschar removal/debridement
Summary: It is a prospective, open, non-interventional patient registry to evaluate the efficacy of NexoBrid in adult patients with deep 2 nd and 3 rd degree thermal burns in need of eschar removal/debridement. The purpose of the registry is to document the efficacy of NexoBrid to fulfil the requirements of the Workgroup for Reimbursement.
Date of the report: 17 OCTOBER 2017

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Listing 2	Burnt area and surface treated by NXB, by STSG and conservative, details
Listing 3	NexoBrid usage, details
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6. LIST OF ABBREVIATIONS

6.1 Abbreviations

CI	Confidence interval
CIP	Clinical investigational plan
ICF	Informed consent form
IQR	Interquartile range
NA	Not applicable
NXB	NexoBrid
SAP	Statistical analysis plan
STSG	Split-Thickness Skin Graft
TBSA	Total burnt surface area

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7. ETHICS

7.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

7.2 Ethical conduct of the study

7.3 Patient information and consent

Patients have received information regarding data protection and signed an informed consent.

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8. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Prof. Dr. Stan Monstrey, University Hospital Ghent

Dr. Lieve De Cuyper, ZNA Stuivenberg Antwerp

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9. INTRODUCTION

The NexoBrid trial is a post-marketing patient registry to evaluate efficacy of NexoBrid in Belgium.

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10. STUDY OBJECTIVES

The overall study objective of this trial is a population based prospective assessment of efficacy of NexoBrid in Belgium.

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11. INVESTIGATIONAL PLAN

11.1 Overall study design and plan: description

It is a prospective, open, non-interventional patient registry to evaluate the efficacy of NexoBrid in adult patients with deep 2nd and 3rd degree thermal burns in need of eschar removal/debridement. The purpose of the registry is to document the efficacy of NexoBrid to fulfil the requirements of the Workgroup for Reimbursement (as stipulated in article 4-6 of the agreement between Mediound and the Belgian National Institute for Health and Disability Insurance).

The registry will include adult patients identified as having deep 2nd and 3rd degree dermal burns that necessitate surgery, who have signed an informed consent, and are treated with NexoBrid. The patients will be followed until the wound is closed.

11.2 Discussion of study design, including the choice of control groups

The Registry is designed to fulfil the requirements of the Workgroup for Reimbursement to document the indication of use, efficacy of debridement, burn depth, method of wound closure and time to healing using Nexobrid within approved indication. There is no control group.

11.3 Selection of study population

11.3.1 Inclusion criteria

Adult patients with deep 2nd and 3rd degree thermal burns in need of eschar removal/debridement.

11.3.2 Exclusion criteria

According to the label (contraindications).

11.4 Treatments

11.4.1 Treatments administered

All patients are treated with NexoBrid.

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11.4.2 Method of assigning patients to treatment groups

Not applicable.

11.4.3 Selection of doses in the study

Not applicable.

11.4.4 Selection and timing of dose for each patient

According to the labelling of Nexobrid.

11.4.5 Blinding

Not applicable

11.4.6 Prior and concomitant therapy

Not applicable

11.5 Efficacy and safety variables

11.5.1 Efficacy and safety measurements assessed and flow chart

Efficacy of eschar removal and time from injury to debridement.

11.5.2 Appropriateness of measurements

According to the requirements for the Reimbursement working group.

11.5.3 Primary efficacy variable(s)

The primary endpoint of the trial is the assessment of efficacy of debridement/eschar removal using NexoBrid to treat adult patients with deep 2nd degree and 3rd degree dermal burns:

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- Complete (100%)
- Excellent (90-99%)
- Good (80-89%)
- Partial (<80%)

11.5.4 Drug concentration measurements

Not applicable.

11.6 Data quality assurance

11.7 Statistical methods planned in the protocol and determination of sample size

11.7.1 Statistical and analytical plans

The NexoBrid registry is descriptive in nature for hypothesis generation. All analyses will be descriptive in nature and performed by means of SAS 9.4 (Copyright © SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA).

Further details are given in the SAP.

11.7.2 Determination of sample size

No formal sample size calculation is performed as this trial is a non-interventional patient registry.

11.8 Changes in the conduct of the study or planned analyses

Not applicable.

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12. STUDY PATIENTS

12.1 Disposition of patients

In total 23 subjects are enrolled in this study and treated with NexoBrid. 6 subjects were treated in ZNA Campus Stuivenberg and 17 subjects in UZ Ghent from March 1st 2016 until August 2017.

12.2 Protocol deviations

Not applicable.

13. EFFICACY EVALUATION

13.1 Datasets analyzed

The intent-to-treat (or ITT) population will be the primary analysis set for assessing the primary and secondary endpoints. For the ITT analysis, all subjects who sign the written ICF and are included in the trial and treated with NexoBrid will be included in the analysis population.

13.2 Efficacy results and tabulations of individual patient data

13.2.1 Analysis of efficacy

The **primary endpoint of the trial** is the assessment of efficacy of debridement/eschar removal using NexoBrid to treat adult patients with deep dermal and full thickness burns:

- Complete (100%)
- Excellent (90-99%)
- Good (80-89%)
- Partial (<80%)

12 out of 23 subjects (52.17%) had complete debridement/eschar removal using NexoBrid. 5 subjects (21.74%) had excellent result and another 4 (17.39%) had good efficacy outcome. Only 2 subjects (8.70%) had less than 80% debridement/eschar removal, which is defined as treatment failure. The total number of successes is 21 out of 23 subjects or 91.30% (95% Wilson CI [73.20%, 97.58%]). The failure rate is 8.70% (95% Wilson CI [2.42%, 26.80%] or 2 out of 23 subjects). These results are summarized in Tables 1 and 2.

Table 1: Efficacy evaluation		
Category	N	n (%)
Complete (100%)	23	12 (52.17%)
Excellent (90-99%)	23	5 (21.74%)
Good (80-89%)	23	4 (17.39%)

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Table 1: Efficacy evaluation		
Category	N	n (%)
Partial (<80%)	23	2 (8.70%)

Table 2: Failure and success rate			
Variable	N	n (%)	95% CI Wilson
Successes	23	21 (91.30%)	[73.20%, 97.58%]
Failures	23	2 (8.70%)	[2.42%, 26.80%]

In Listing 1 the efficacy evaluation per patient is listed together with each patient's reimbursement status. 1 stands for yes and 2 for no (reimbursement).

Listing 1: Efficacy evaluation, failure / success and reimbursement status

Unique center_subject ID	Efficacy evaluation	Success/failure	Reimbursement (yes=1 no=2)
NXB-03_SUBJECT1	GOED 80-89%	SUCCESS	1
NXB-03_SUBJECT2	GOED 80-89%	SUCCESS	1
NXB-03_SUBJECT3	GOED 80-89%	SUCCESS	1
NXB-03_SUBJECT4	MATIG <80%	FAILURE	2
NXB-03_SUBJECT5	EXCELLENT 90-99%	SUCCESS	2
NXB-03_SUBJECT6	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT1	COMPLEET 100%	SUCCESS	2
NXB-04_SUBJECT2	EXCELLENT 90-99%	SUCCESS	1
NXB-04_SUBJECT3	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT4	COMPLEET 100%	SUCCESS	1

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Unique center_subject ID	Efficacy evaluation	Success/failure	Reimbursement (yes=1 no=2)
NXB-04_SUBJECT5	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT6	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT7	MATIG <80%	FAILURE	2
NXB-04_SUBJECT8	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT9	GOED 80-89%	SUCCESS	1
NXB-04_SUBJECT10	EXCELLENT 90-99%	SUCCESS	1
NXB-04_SUBJECT11	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT12	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT13	EXCELLENT 90-99%	SUCCESS	1
NXB-04_SUBJECT14	COMPLEET 100%	SUCCESS	2
NXB-04_SUBJECT15	EXCELLENT 90-99%	SUCCESS	1
NXB-04_SUBJECT16	COMPLEET 100%	SUCCESS	1
NXB-04_SUBJECT17	COMPLEET 100%	SUCCESS	1

Table 3 provides summaries of the reimbursement rate. 18 subjects out of 23 (78.26% with 95% Wilson CI [58.10%, 90.34%]) are entitled to reimbursement whilst 5 out of 23 (21.74% with 95% Wilson CI [9.66%, 41.90%]) are not. Two of the patients due to treatment failure (<80% efficacy), two subjects because of off-label use of the product and one patient not being a Belgian citizen and thus not included in the Belgian insurance system.

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Table 3: Reimbursement rate

Variable	N	n (%)	95% CI Wilson
Reimbursed: yes	23	18 (78.26%)	[58.10%, 90.34%]
Reimbursed: no	23	5 (21.74%)	[9.66%, 41.90%]

The **secondary trial endpoints** are the following:

- To evaluate the depth of the burns treated with NexoBrid;
- To document the area treated as % TBSA;
- To document the usage of NexoBrid;
- To document the evolution of wound until wound closure.

A summary of burns, area and cm² treated with NexoBrid, area treated with STSG and treated conservative is presented in Table 4. Mean burnt area TBSA is 12.5 % (ranging from 1 to 40 %). On average 7.9 % (with range from 1 to 15 %) burnt area TBSA is treated with NXB. Total surface treated NXB is 1361 cm² (ranging from 159 to 3135 cm²). On average 3.8 % (with range from 0 to 10 %) burnt area TBSA is treated with STSG and 4.1 % (ranging from 0 to 15 %) is treated conservative.

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Table 4: Burnt area and surface treated by NXB, STSG and conservative, summaries

Variable	Mean	Std Dev	Median	IQR		Minimum	Maximum
Burnt area TBSA (%)	12.5	10.24	10.0	4	17	1	40
Burnt area TBSA treated by NXB (%)	7.9	5.10	5.0	4	15	1	15
Burnt area TBSA treated by STSG (%)	3.76	3.80	3.0	0	7	0	10
Burnt area TBSA treated conservative (%)	4.11	4.69	3.0	0	6	0	15
Cm² treated NXB (cm²)	1360.9	959.26	1000.0	708	2000	159	3135

All by patient details can be found in Listing 2.

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Listing 2: Burnt area and surface treated by NXB, by STSG and conservative, details

Unique center_subject ID	Burnt area TBSA (%)	Burnt area TBSA treated by NXB (%)	Burnt area TBSA treated by STSG (%)	Burnt area TBSA treated CONSERVATIVE (%)	Cm ² treated NXB
NXB-03_SUBJECT1	16	10	10	0	1000
NXB-03_SUBJECT2	10	10	10	0	1000
NXB-03_SUBJECT3	20	15	6	9	2000
NXB-03_SUBJECT4	24	5	5	0	800
NXB-03_SUBJECT5	2	2	2	0	300
NXB-03_SUBJECT6	40	15	7	8	3000
NXB-04_SUBJECT1	10	5	0	5	470
NXB-04_SUBJECT2	11	11	10	1	1969
NXB-04_SUBJECT3	3	3	3	0	500
NXB-04_SUBJECT4	19	15	4	11	2880
NXB-04_SUBJECT5	4	4	0.5	3.5	756
NXB-04_SUBJECT6	10	5	1	4	985
NXB-04_SUBJECT7	1	1	1	0	159
NXB-04_SUBJECT8	4	4	4	0	708
NXB-04_SUBJECT9	15	15	10	5	2670

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Unique center_subject ID	Burnt area TBSA (%)	Burnt area TBSA treated by NXB (%)	Burnt area TBSA treated by STSG (%)	Burnt area TBSA treated CONSERVATIVE (%)	Cm ² treated NXB
NXB-04_SUBJECT10	17	15	0	15	3135
NXB-04_SUBJECT11	6	6	0	6	1104
NXB-04_SUBJECT12	11	11	8.5	2	1869
NXB-04_SUBJECT13	10	5	0	5	1326
NXB-04_SUBJECT14	2	2	0	1.5	285
NXB-04_SUBJECT15	36	15	0	15	2748
NXB-04_SUBJECT16	12	4	1	3	804
NXB-04_SUBJECT17	5	4	3.5	0.5	832

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The NexoBrid usage details i.e. NXB/%TBSA and NXB/CM² are listed per patient in Listing 3. The minimum NXB/%TBSA amount equals 0.80 g/% for NXB-04_SUBJECT1 and the maximum amount equals 2.67 g/% for patient NXB-03_SUBJECT14. The amounts of NXB/CM² vary between 0.0062 g/cm² (subject NXB-04_SUBJECT16) and 0.0167 g/cm² (subject NXB-03_SUBJECT5). This was calculated from the quantity of product contained in the units used for mixing; this shows that dosing was within the recommended range according to the SmPc.

Listing 3: NexoBrid usage, details

Unique center_subject ID	NXB/%TBSA	NXB/CM ²
NXB-03_SUBJECT1	1.20	0.0120
NXB-03_SUBJECT2	1.00	0.0100
NXB-03_SUBJECT3	1.00	0.0075
NXB-03_SUBJECT4	1.00	0.0063
NXB-03_SUBJECT5	2.50	0.0167
NXB-03_SUBJECT6	1.33	0.0067
NXB-04_SUBJECT1	0.80	0.0085
NXB-04_SUBJECT2	1.36	0.0076
NXB-04_SUBJECT3	1.33	0.0080
NXB-04_SUBJECT4	1.67	0.0087
NXB-04_SUBJECT5	1.75	0.0093
NXB-04_SUBJECT6	1.80	0.0091
NXB-04_SUBJECT7	2.00	0.0126
NXB-04_SUBJECT8	1.75	0.0099
NXB-04_SUBJECT9	1.93	0.0109
NXB-04_SUBJECT10	2.00	0.0096
NXB-04_SUBJECT11	1.17	0.0063
NXB-04_SUBJECT12	1.90	0.0107
NXB-04_SUBJECT13	2.00	0.0075
NXB-04_SUBJECT14	2.67	0.0140
NXB-04_SUBJECT15	2.13	0.0116

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Unique center_subject ID	NXB/%TBSA	NXB/CM ²
NXB-04_SUBJECT16	1.25	0.0062
NXB-04_SUBJECT17	2.50	0.0120

The evolution of wound until wound closure is detailed in Listing 4. The average time between the incident and treatment is -2.4 days (ranging between -5 and 0 days). The average time to closure is 27.7 days (ranging from 7 to 95 days).

Listing 4: Time between incident and treatment and time to closure

Unique center_subject ID	Date incident	Date treatment	Time between incident and treatment (days)	Date of wound healing	Time to closure (days)
NXB-03_SUBJECT1	24SEP2016	27SEP2016	-3	13OCT2016	16
NXB-03_SUBJECT2	03OCT2016	06OCT2016	-3	13OCT2016	7
NXB-03_SUBJECT3	17APR2017	20APR2017	-3	11MAY2017	21
NXB-03_SUBJECT4	29MAY2017	01JUN2017	-3	04SEP2017	95 ¹
NXB-03_SUBJECT5	16APR2016	18APR2016	-2	09MAY2016	21
NXB-03_SUBJECT6	22JUN2017	24JUN2017	-2	17JUL2017	23
NXB-04_SUBJECT1	29APR2016	03MAY2016	-4	28MAY2016	25
NXB-04_SUBJECT2	14MAY2016	16MAY2016	-2	23JUN2016	38
NXB-04_SUBJECT3	13MAY2016	17MAY2016	-4	01JUN2016	15
NXB-04_SUBJECT4	27AUG2016	31AUG2016	-4	05OCT2016	35
NXB-04_SUBJECT5	05SEP2016	05SEP2016	0	14OCT2016	39
NXB-04_SUBJECT6	15OCT2016	16OCT2016	-1	21NOV2016	36
NXB-04_SUBJECT7	02NOV2016	07NOV2016	-5	22NOV2016	15
NXB-04_SUBJECT8	12DEC2016	12DEC2016	0	24DEC2016	12
NXB-04_SUBJECT9	31DEC2016	04JAN2017	-4	09FEB2017	36
NXB-04_SUBJECT10	07MAR2017	10MAR2017	-3	10APR2017	31

¹ Debridement failure caused by pre-treatment with Flammazine/Flammacerium, a substance known to decrease activity of Nexobrid as described in NexoBrid SmPC.

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Unique center_subject ID	Date incident	Date treatment	Time between incident and treatment (days)	Date of wound healing	Time to closure (days)
NXB-04_SUBJECT11	17APR2017	19APR2017	-2	15MAY2017	26
NXB-04_SUBJECT12	10APR2017	12APR2017	-2	04MAY2017	22
NXB-04_SUBJECT13	20APR2017	20APR2017	0	12JUN2017	53
NXB-04_SUBJECT14	04MAY2017	04MAY2017	0	25MAY2017	21
NXB-04_SUBJECT15	11JUN2017	13JUN2017	-2	30JUN2017	17
NXB-04_SUBJECT16	30JUL2017	02AUG2017	-3	15AUG2017	13
NXB-04_SUBJECT17	01AUG2017	04AUG2017	-3	25AUG2017	21

13.2.2 Statistical/analytical issues

13.2.2.1 Adjustments for covariates

Not applicable.

13.2.3 Tabulation of individual response data

See Listings 1 till 4 presented in section 13.4.1.

13.2.4 Efficacy conclusions

Primary efficacy endpoint:

The total number of successes is 21 out of 23 subjects or 91.30% (95% Wilson CI [73.20%, 97.58%]). A success is defined as obtaining at least 80% debridement/eschar removal using NexoBrid. The failure rate is 8.70% (95% Wilson CI [2.42%, 26.80%] or 2 out of 23 subjects). According to the investigator failure was caused by pre-treatment with Flammazine/Flammacerium, a substance known to decrease activity of Nexobrid, as described in the Nexobrid SmPc.

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Secondary efficacy endpoints:

Mean burnt area TBSA is 12.5 % (ranging from 1 to 40 %). On average 7.9 % (with range from 1 to 15 %) burnt area TBSA is treated with NXB. Total mean surface area treated with NXB is 1361 cm² (ranging from 159 to 3135 cm²). On average 3.8 % (with range from 0 to 10 %) burnt area TBSA is treated with STSG and 4.1 % (ranging from 0 to 15 %) is treated conservatively, allowing spontaneous healing.

Surgical excision of necrosis will always lead to surgical coverage of the wound with skin grafts. The mean reduction of surgical coverage in the Nexobrid treated areas is 53.

The average time between the incident and treatment is -2.4 days (ranging between -5 and 0 days). The average time to wound closure is 27.3 days using a combination of surgical coverage and conservative healing, in wounds healed by conservative treatment 28.8 days and by surgery only 27.5 days.

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14. SAFETY EVALUATION

14.1 Adverse events

14.1.1 Brief summary of adverse events

No adverse events attributed to Nexobrid were reported (spontaneous reporting)

14.2 Deaths, other serious adverse events, and other significant adverse events

14.2.1 Listing of deaths, other serious adverse events, and other significant adverse events

14.2.1.1 Deaths

No deaths or other serious/significant adverse events reported

14.3 Safety conclusions

No adverse events related to Nexobrid treatment were observed.

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15. DISCUSSION AND OVERALL CONCLUSIONS

A total of **23 patients** were included in the Registry from **2 Belgian Burn centers** and analyzed. NexoBrid has an **overall success rate equal to 91.30%** (95% Wilson CI [73.20%, 97.58%]). Only two patients experienced insufficient debridement (defined as <80% eschar removal), in the investigators opinion due to pre-treatment with Flammazine and Flammacerium, both known to decrease Nexobrid efficacy and should be avoided. The **average time between the burn injury and treatment is 2.4 days** (ranging between 0 and 5 days). It can be concluded that **surgical excision could be avoided in 91.30% of the cases**, preserving viable tissue and reducing the need for surgical cover of the wound with STSG.

On average 7.9 % (with range from 1 to 15 %) burnt surface area (BSA) is treated with NXB which is within approved indication.

The average amount of Nexobrid used per % BSA treated with Nexobrid is as recommended in the label. However, total amount of product used in all patients is slightly less than anticipated based on total %TBSA treated. No adverse events were observed.

Nexobrid treatment saves viable tissue and wound bed assessment after selective enzymatic debridement with Nexobrid, provides extra information to decide more accurate if a wound can heal by means of conservative treatment or that it needs coverage with skin grafts. With other words, **Nexobrid allows for a more precise burn depth assessment if compared to clinical burn depth assessment**. In this study 4.1 % TBSA (ranging from 0 to 15 %) is treated conservatively allowing for spontaneous healing, and 3.8 % (with range from 0 to 10 %) burnt area is treated surgically with STSG, which means that the need for surgical wound closure is reduced with at least 50%. The average time to wound closure is 27.3 days in wounds treated with a mix of surgery and conservative healing. In wounds closed by surgery only the time to closure was 27.5 days, and conservatively treated areas healed in 28.8 days (thus, no difference in healing time).

5 of 23 patients were excluded from reimbursement; 2 due to treatment failure, 2 because of off-label treatment and 1 patient not being a Belgian citizen and thus not included in the insurance system.

The analyses contained in this report of the Belgian Patient Registry confirm the efficacy and safety of NexoBrid in debridement of deep 2nd degree and 3rd degree burn wounds. Significant reduced need for surgical coverage with STSG is confirmed, which will lead to reduced morbidity (less donor sites and less hypertrophic scarring) without longer time to wound closure. The product is used as indicated in the label and reimbursed according to

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the contract. Efficacy is demonstrated above the requirements stipulated in the Working Group's agreement.

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16. TABLES, FIGURES AND GRAPHS

16.1 Demographic data summary

Not applicable.

16.2 Efficacy data summary

Not applicable.

16.3 Safety data summary

16.3.1 Displays of adverse events

Not applicable.

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17. REFERENCES

Not applicable.