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Confidential

END-OF-STUDY OS BURN 2014 REPORT



NexoBrid

A prospective, non-interventional multicenter study, performed in patients with burns, to evaluate efficacy and safety aspects of NexoBrid in clinical practice

Sponsor: MediWound
Eisenstr. 5
DE - 65428 Rüsselsheim
Germany

Protocol number: OS-BURN2014
First patient enrollment date: July 1st 2014

Sponsor's responsible medical officer: Roland Frösing, MD PhD, Medical Director Europe

Author: Roland Frösing, MD PhD

Date of issue: 15 January 2019

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 A prospective, non-interventional multicenter study, performed in patients with burns, to evaluate efficacy and safety aspects of NexoBrid in clinical practice.
Study period: July 1 st 2014 – June 30 th 2018
Objectives: The overall study objective of the study is to evaluate efficacy and safety of NexoBrid in clinical practice at two burn centers in Germany
Methodology: Open label Observational study
Study population: Adult patients identified as having deep dermal and full thickness burns 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 Study objectives are to gather data about the application of NexoBrid in clinical practice and to evaluate if application is performed in accordance to approval (indication and %BSA treated with NexoBrid) and in line with MediWounds extensive training program. Furthermore to gather data regarding outcomes of treatment and therapeutic experiences of NexoBrid in clinical practice, which are important for the acceptance of new medical product therapy aimed at removing eschar in patients with deep thermal burns (grade IIb - III: „deep partial“ and „full thickness“). Safety of the treatment will be evaluated and assessed.
Date of the report: January 15 th 2019

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3. LIST OF ABBREVIATIONS

3.1 Abbreviations

NXB	NexoBrid
ICF	Informed consent form
NA	Not applicable
STSG	Split Thickness Skin Graft
SAP	Statistical analysis plan
BSA	Burnt surface area treated
TBSA	Total burnt surface area

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4. ETHICS

4.1 Patient information and consent

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

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5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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6. INTRODUCTION

The OS Burn2014 was a prospective, open, non-interventional study to evaluate efficacy and safety of Nexobrid treatment at 2 burn centers in Germany.

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7. STUDY OBJECTIVES

Primary objective was to document efficacy of NexoBrid in clinical practice. Furthermore, the investigator assessed if there were any adverse events related to the treatment.

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8. INVESTIGATIONAL PLAN

8.1 Overall study design and plan: description

Open label, non-interventional study 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 study was to document efficacy and feasibility of NexoBrid in clinical practice, and to evaluate safety in conjunction with the treatment.

The study included adult patients identified as having deep 2nd and 3rd degree dermal and full thickness burns that necessitated surgery, who signed an informed consent, and were treated with NexoBrid.

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

The study was a part of the approved PMS plan, designed to fulfil the requirements of EMA following the approval of NexoBrid. There was no control group.

8.3 Selection of study population

8.3.1 Inclusion criteria

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

8.3.2 Exclusion criteria

According to the label (contraindications).

8.4 Treatments

8.4.1 Treatments administered

All patients were treated with NexoBrid.

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8.4.2 Selection of doses in the study.

According to the labelling of NexoBrid.

8.4.3 Selection and timing of dose for each patient

According to the labelling of NexoBrid.

8.5 Efficacy and safety variables

8.5.1 Efficacy and safety measurements assessed

Efficacy of eschar removal to allow for spontaneous healing or surgical coverage of the wound. Safety will be assessed if treatment related in the investigator's opinion, and AE/ADRs reported accordingly.

8.5.2 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 dermal and full thickness burns using a 10 graded Lichert scale (0-10): 0=insufficient, 5=fair, 7=good, 8= very good, 10= excellent.

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

8.6.1 Statistical and analytical plans

The OS Burn2014 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).

8.6.2 Determination of sample size

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

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9. STUDY PATIENTS

9.1 Disposition of patients

In total 41 subjects, 31 males and 10 females, were enrolled in this study and treated with NexoBrid. 11 subjects were treated in Offenbach and 30 subjects in Ludwigshafen from July 1st 2014 until June 2018.

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10. EFFICACY EVALUATION

10.1 Datasets analyzed

The intent-to-treat (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. All patients that signed the ICF were treated with Nexobrid.

10.2 Efficacy results

10.2.1 Analysis of efficacy and feasibility of Nexobrid

The **primary endpoint of the trial** was the assessment of efficacy and feasibility of debridement/eschar removal using NexoBrid to treat adult patients with deep dermal and full thickness burns judged by the physician on a 0-10 Lichert scale (0=insufficient, 10=excellent). In average the physician rated the efficacy of debridement to 7.49 (very good), the median being 8 (great) with a range of 3 to 10.

Efficacy of Debridement	7.49 (1.61) 8.00 (3.00; 10.00) n=41
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Judgement by Physician ranging from 1 (insufficient) to 10 (excellent)	
Efficacy of Debridement	
3	1 (2.4%)
4	2 (4.9%)
5	3 (7.3%)
6	2 (4.9%)
7	7 (17.1%)
8	16 (39.0%)
9	8 (19.5%)
10	2 (4.9%)

The investigator then was asked if the debridement with NexoBrid was helpful in diagnosing the burn depth, also using a 0-10 Lichert scale: 0= not helping, 5=helpful, 7=very helpful and 10=instrumental/crucial. The mean rating was 7.54 (very helpful), the median value being 8.

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Help on the initial diagnosis of depth of burn	7.54 (1.67) 8.00 (3.00; 10.00) n=41
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Help on the initial diagnosis of depth of burn	
3	2 (4.9%)
4	1 (2.4%)
5	3 (7.3%)
6	2 (4.9%)
7	4 (9.8%)
8	19 (46.3%)
9	8 (19.5%)
10	2 (4.9%)

Feasibility (ease of use) of the treatment compared to SOC (surgical debridement) was also evaluated using a 10-grade scale: 0=not feasible, 3=more difficult, 5=no difference, 7=easier than SOC, 8=very easy and 10=extremely easy. The treatment was rated as high as 7.73 (easy/very easy to use) on average compared to SOC, with a median 8 .

Easier to use than SOC	7.73 (1.98) 8.00 (3.00; 10.00) n=41
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Easier to use than SOC	
3	3 (7.3%)
4	1 (2.4%)
5	3 (7.3%)
7	6 (14.6%)
8	11 (26.8%)
9	11 (26.8%)
10	6 (14.6%)

The ultimate goal of debridement is to remove the eschar and dead tissue, while saving as much viable tissue as possible (e.g. minimize the trauma). On the 10-grade Lichert scale: <4=more traumatic than SOC, 5=as traumatic as SOC, 7=less traumatic, 8=much less traumatic than SOC. In general, enzymatic debridement with Nexobrid was considered less traumatic than SOC, on average rated 8.59 (much less traumatic), median 9.

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Less traumatic than surgical debridement	8.59 (1.18) 9.00 (5.00; 10.00) n=41
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Less traumatic than surgical debridement	
5	1 (2.4%)
6	2 (4.9%)
7	2 (4.9%)
8	12 (29.3%)
9	15 (36.6%)
10	9 (22.0%)

The **secondary endpoints** are the following:

- To document % TBSA and cause of the burn
- To document the % BSA treated with NexoBrid
- To document anatomical localisation treated with NexoBrid
- To document % BSA treated covered with skin graft
- To document time to wound closure.
- To document adverse event related to NexoBrid

Mean TBSA is 12.5 %, with a range of 1-66% TBSA. Majority of burns, 35 (85.4%), are caused by flame, 5 caused by scalding and 1 electric burn.

The mean % BSA debrided with NXB is 3.98%, mostly represented by hands and upper extremities.

%TBSA	12.5 (14.0) 7.0 (1.0; 66.0) n=41
Cause of injury	
Flame	35 (85.4%)
Scalding	5 (12.2%)
Electricity	1 (2.4%)
% BSA treated with NXB	3.98 (2.16) 4.00 (1.00; 10.00) n=41

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Anatomical location	
Both arms + ventral torso	1 (2.4%)
Both feet	1 (2.4%)
Both forearms	1 (2.4%)
Both hands	1 (2.4%)
Left calf	1 (2.4%)
Right foot/calf	1 (2.4%)
Right hand	1 (2.4%)
both hands	3 (7.3%)
both hands/forearms	4 (9.8%)
left arm	3 (7.3%)
left arm/hand	2 (4.9%)
left hand	5 (12.2%)
left hand/forearm	1 (2.4%)
right arm	4 (9.8%)
right arm/hand	1 (2.4%)
right hand	6 (14.6%)
right hand/arm + left hand	1 (2.4%)
right hand/forearm	4 (9.8%)

14 patients (34.1%) were skingrafted on the Nexobrid debrided area. The mean grafted area was 2.43% BSA, with a range of 0.5-5.0% BSA.

Skin graft	14 (34.1%)
Skin Graft % BSA	2.43 (1.40) 2.75 (0.50; 5.00) n=14

Time to wound closure was documented on 27 patients. In average the wound was considered closed 24.6 days after Nexobrid treatment, with a range of 9 – 60 days. The median time to wound closure was 19 days.

Days to wound closure	24.6 (13.2) 19.0 (9.0; 60.0) n=27
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10.2.2 Efficacy conclusions

Primary efficacy endpoint:

Efficacy of debridement was rated very good to excellent (8-10) in 63.4%, and good (5-7) in 29.3% of the cases. The clinical effectiveness (sufficient debridement) was 92.7%, which was in line with efficacy reported in previous studies.

Secondary endpoints:

Mean burnt area TBSA was 12.5 % (ranging from 1 to 66 %). On average 3.98 % (with range from 1 to 10 %) BSA was treated with NXB, mainly upper extremities and hands.

14 patients (34.1%) had a skin graft (STSG) due to full thickness injury on the NXB treated wound. On average 2.43 % (with range from 0.5 to 5 %) BSA was treated with STSG. 27 patients were treated conservatively, allowing spontaneous wound healing. Surgical excision will always lead to surgical coverage of the wound, and NXB reduced this by approximately two thirds in this study, compared to using SOC. This reduction of grafting incidence was similar to data from previous studies. Furthermore the area in need of STSG was reduced by approximately 40% by using Nexobrid instead of SOC (3.98% BSA treated and only 2.43% BSA covered by STSG).

The average time to closure was 24.6 days (ranging from 9 to 60 days), again similar to previous reports.

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11. SAFETY EVALUATION

11.1 Adverse events

11.1.1 Brief summary of adverse events

No adverse events attributed to NXB were observed.

Adverse event related to Nexobrid	0 (0.0%)
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11.2 Deaths, other serious adverse events, and other significant adverse events

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

11.2.1.1 *Serious adverse events and Deaths*

Two deaths were recorded, primary cause of death is reported to be sepsis and multiorgan failure. Both patients had multiple injuries including smoke inhalation and trauma, and without any relation to NexoBrid in the investigator's opinion. Furthermore, one case of pneumonia, due to inhalation injury without causal relation to NXB treatment was documented.

Serious Adverse event reported	3 (7.3%)
Adverse event Term	
pneumonia	1 (33.3%)
sepsis	2 (66.7%)

11.3 Safety conclusions

No adverse events related to NexoBrid treatment were observed in this study, according to the investigators opinion.

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12. DISCUSSION AND OVERALL CONCLUSIONS

A total of 41 patients, 31 males and 10 females, were included in the study from two German Burn centers and analyzed. NexoBrid demonstrated an overall clinical effectiveness (sufficient debridement) rate of 92.7%. Only three patients experienced insufficient debridement (rated 0- 3).

On average 3.98 % (with range from 1 to 10 %) burnt surface area (BSA) was treated with NXB, and the majority on hands and the upper extremities. Only 14 patients (34.1%) of the patients needed a skin graft, which represents a reduction of the need of autologous skin grafting with 66% compared to using SOC. The NXB treatment was considered much easier to perform (8-10) than SOC in 68.2% of the patients, and easier (rated 5-7) in 21.9%. NexoBrid was considered less traumatic (rated 5-10) than surgical excision in all cases, and much less traumatic (rated 8-10) in 87.9%.

In 92.7% of the cases Nexobrid was helpful (rated 5-10) in diagnosing the burn depth.

NexoBrid treatment saved viable tissue and wound bed assessment after selective enzymatic debridement with NexoBrid was enhanced, and provided extra information to decide more accurate if a wound could heal by means of conservative treatment or that it needed coverage with a skin graft. With other words NexoBrid allowed for a more precise burn depth assessment if compared to clinical burn depth assessment.

Time to wound closure was recorded in 27 patients, the average time being 24.6 days (range 9 to 60), in line with previous studies and similar to expected times to wound healing using SOC. No adverse events were reported with a causal relation to Nexobrid.