PASS information

Title	An international, observational retrospective data collection study assessing efficacy of applied risk minimisation measures in burn patients treated with NexoBrid
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Active substance	ACT code D03BA03, concentrate of proteolytic enzymes enriched in bromelain
Medicinal product	NexoBrid
Product reference	
Procedure number	
Marketing authorisation holder(s)	MediWound Germany GmbH Eisenstrasse 5 65428 Rüsselsheim Germany
Joint PASS	No
Research question and objectives	Main objective- The main goal of this study is assessing the effectiveness of the risk minimisation activities and their effect on the incidence rate of identified risks that have shown to be sensitive to these activities (pain, and pyrexia) reported in the first two years from launch of each participating country. This will be investigated by a comparison of the incidence rates of these identified risks reported in a pre-defined time frames from treatment (as is further described in section 9.3) in routine clinical practice in the first two years from launch to those obtained in clinical trials after implementation of risk minimisation activities. Secondary objectives will be evaluated by the following secondary endpoints: **Key secondary endpoints:** The compliance of the physician with the Educational Material instructions for use relates to the risk minimization activities and incidence of wound infection AEs. **Secondary endpoints:** • Overall incidence of reported AEs • Incidence of severe irritation and/or allergic reaction events captured within 96 hrs from start of debridement[1]

[1] Suggested timeframe is based on PK data demonstrating that most of the drug is eliminated from patients' blood at 24 hrs

	• Incidence of cardiopulmonary events captured within 48 hrs from start debridement • Incidence of other wound related complications (related to NexoBrid) captured during patient's hospitalization • Time to complete wound closure • Proportion of NexoBrid patients treated as off-label; facial burns, perineum/genital burns and wounds >15% TBSA treated in one session • Incidence of severe blood loss captured within 24hrs from the debridement procedure (reported as blood transfusions) • Time to hospital discharge.
Countries of study	About 15 representative specialist burn centres in Europe countries in which NexoBrid was launched with at least 160 patients
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2 LIST OF ABBREVIATIONS

AE	Adverse Event
BSA	Body Surface Area
CA	Competent Authority
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
DGD	Debrase Gel Dressing
EU	European Union
FDA	Food and Drug Administration
ICSR	Individual Case Safety Report
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFU	Instructions For Use
ITT	Intent-to-Treat
MAH	Marketing Authorization Holder
PRAC	Pharmacovigilance Risk Assessment Committee
PIL	Patient Information Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SOC	Standard of Care
TBSA	Total Body Surface Area
TTCWC	Time to Complete Wound Closure

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Principal investigator and Coordinating investigators: About 15 sites within countries of market launch of NexoBrid will be recruited for data collection. The final sites number and list will be available after all participating sites will start the study. Listings of principal investigators and coordinating investigators will be kept available if requested by competent authorities. For each participating country a coordinating investigator will be appointed, if requested by the authorities.

4 ABSTRACT

Title: An international, observational retrospective data collection study assessing efficacy of applied risk minimisation measures in burn patients treated with NexoBrid.

MW2013-06-01, version 6, dated 24 April 2017

Rationale and background: NexoBrid is indicated for removal of eschar in adults patients with deep partial and full thickness thermal burns and has been recently (December 2012) approved in Europe via the centralized procedure. The product is presented as sterile lyophilised powder (2g and 5g) and sterile gel (20 g and 50g), that following mixing are applied topically on burn area at patient bed side.

The following identified and potential risks have been included in the Risk Management Plan:
Identified risks: Pain, pyrexia, wound infection, delay in time to complete wound closure.
Potential risks: increased tendency to bleeding, severe irritation, increased mortality in patients with cardiopulmonary diseases and allergic reaction.

Three areas of risks of NexoBrid were identified and clarified during the first two prospective phase II studies: ***pain, pyrexia and wound infection*** for which corrective actions were taken in subsequent phase II and phase III studies. Implementation of known, simple and effective corrective measures,detailed below were associated with improvement of NexoBrid safety profile, mainly pain & pyrexia events:

1. Administration of effective analgesic medications as commonly used for routine major dressing change in burned patients prior to Debrase/NexoBrid treatment to reduce pain,
2. Antibacterial soaking prior to and after NexoBrid treatment, as routinely done in wound care, to reduce pyrexia and wound infections,

The rates of AEs of interest observed in clinical trials without risk minimisation activities (MW 2001-10-03 and MW 2002-04-01) and with risk minimisation activities (MW2004-11-02 and MW2005-10-05) in the NexoBrid group are presented below:

AE of interest	Clinical trials without risk minimsation	Clinical trial with risk minimisation
Pain	23.3% [15.8%;33.0%]	3.6% [1.4%;8.9%]
Pyrexia	34.4% [25.4%;44.7%]	19.1% [12.9%;27.4%]
Wound infection[1]	7.8% [3.8%; 15.2%]	8.2% [4.4%; 14.8%]

As the implementation of the effective corrective measures procedures detailed above into subsequent clinical trials resulted with a significant decrease in the incidence of pain and pyrexia-related AEs, similar plans were implemented in the risk management

[1] The effect of the risk minimization activities could not be established in the clinical trials although the observed rates in the NexoBrid group were similar to those in the control groups. Thus, this endpoint is not appropriate to assess the effectiveness of the risk minisation activities in routine clinical practice

plan. This risk mitigation strategy includes training and educational programme aimed at minimising the identified and potential risks.

Research question and objectives:

Primary objective:

The main goal of this study as described above is assessing the effectiveness of the risk minimisation activities and their effect on the incidence rate of identified risks that have shown to be sensitive to these activities reported in each participating country. This will be investigated by a comparison of the incidence rates of the identified risks pain and pyrexia reported in a pre-defined time frames from treatment (as is further described in section 9.3) in routine clinical practice in the first two years from product launch to those obtained in clinical trials after implementation of risk minimisation activities.
Given the experience from the clinical trials, the incidence rates of pain and pyrexia AEs before risk minimisation activities were relatively high and the effect of reduction by the risk minimisation was well pronounced. Therefore, these health outcomes are considered sensitive to risk minimization activity, thus the primary objective of this study focuses on these risks.

Secondary objectives:

Secondary objectives will be evaluated by the secondary endpoints (EPs) described below. It is distinguished between key secondary endpoints and secondary endpoints. Key secondary endpoints are considered to be more important than secondary endpoints.

Key Secondary EPs:

- The compliance of the physician with the instructions from the Educational Material relate to the risk minimization activities (i.e. whether antibacterial soaking before and after NexoBrid application performed; adequate pain management/administration of analgesia/sedation medication prescribed to the patient before applying NexoBrid and before removing NexoBrid).
- Incidence of wound infection AEs

Secondary EPs:

- Overall incidence of reported AEs
- Incidence of severe irritation and/or allergic reaction events captured within 96 hrs from start of debridement
- Incidence of cardiopulmonary events captured within 48 hrs from start debridement
- Incidence of wound related complications (related to NexoBrid) captured during patient's hospitalization
- Time to complete wound closure
- Proportion of patients treated with NexoBrid off-label; pediatric patients (< 18 years), facial burns, perineum/genital burns and wounds >15% TBSA treated in one session
- Incidence of severe blood loss (reported as blood transfusions) captured during the debridement procedure
- Time to hospital discharge.

Study design: International, retrospective data collection study, using secondary data sources.

Population: At least 160 burn patients who received NexoBrid treatment and Consent for data collection from participating specialized European burn centres.

Variables:
The following variables will be collected during the study on CRFs:

- Values for assessment of pain captured during the debridement procedure (e.g. repeated patient's complaints followed by prescription of pain management medications)
- Values for assessment of pyrexia captured within 48hrs from start of treatment (e.g. temperature above 38.5°C requiring fever relief medications prescribed due to high temperature within 1 hrs from complaint, consecutive measurements of high temperature (above 38.5°C), 4 to 6h apart
- Physician Compliance with Instructions- the number (n) and percentage (%) of wounds that were treated in compliance with instructions will be displayed
- Values for assessment of wound infection captured during the 1st week following debridement (e.g. antibiotics prescribed to a patient captured with positive swabs, positive wound biopsies performed)
- Values for assessment of severe irritation and allergic reaction within 96hrs from start of treatment and cardiopulmonary events captured within 48hrs from start of treatment[1]
- Values for assessment of wound related complications related to NexoBrid captured during hospital stay (e.g. wound reopening, graft loss)
- Values for assessment of time to complete wound closure (e.g. % graft applied on wound area, if performed, % wound epithelialized during follow up) will be collected
- Values for assessment of time to hospital discharge for all patients treated with NexoBrid.
- Values for assessment of blood loss captured within 24hrs from the debridement procedure (e.g. captured by blood transfusions)
- Values for assessment of number of patients where NexoBrid was used as off-label treatment i.e. in paediatric patients (<18 years), on facial burns, perineum/genital burns or wounds >15% TBSA treated in one session.
- Values for assessment of demographic parameters and medical characteristics of the patients population such as age, gender, burn description (locations, % area burned, number of sites), burn etiology, injury date and time, physical examination.

[1] Suggested timeframe is based on PK data demonstrating that most of the drug is eliminated from patients' blood at 24 hrs

- Values for assessment of medical history (including existing co-morbidities), concomitant diseases/conditions, and previous and concomitant medications and therapies.
- Values for assessment of management of NexoBrid application such as area debrided with NexoBrid, number of applications, NexoBrid treatment duration, NexoBrid dosage, debridement outcome.
- Values for assessment of overall debridement performed on each patient such as areas treated with SOC and the way these were treated (e.g. surgical and/or non surgical procedures performed, duration, debridement efficacy, wound management following SOC treatment)
- Values for assessment of post debridement wound management such as any coverages used including area covered and date, wound bed preparation procedures performed for autograft including application time and area covered
- Values for Index score for Tobiasen's abbreviated burn severity index[1] planned to be calculated by the statistician
- Values for assessing overall safety profile of patients by collecting reported AEs including severity and baseline lab tests.

Data sources: Structured electronic case report forms filled-in by investigators based on medical records of patients who received NexoBrid treatment at burn centres and signed on inform consent form.

Study size: About 15 representative specialist burn centres in European countries in which NexoBrid was launched (e.g. Germany, Sweden, Belgium, Spain, Poland and Slovakia) with at least 160 patients.

Data analysis:

All measured variables and derived parameters will be listed individually in listings. Tables using descriptive statistics will be provided for the primary and secondary variables as well as for other variables concerning demographics and baseline characteristics.

Milestones: First data collection (subject to protocol approval by the PRAC and local EC) will be started in Q3 2017. Retrospective data collection is planned for duration of up to 2 years post launch of each participating country and its completion is expected by Q3 2018. Final report of study results will be provided to the respective authorities in Q2 2019.

[1] Clinical useful morbidity score developed by Tobiasen et al. 1982 (See: Tobiasen, J. Hiebert J.M. and Edlich R.F. (1982) . The abbreviated burn severity index. *Ann Emerg Med*. 11(5), 260-262)

5 AMENDMENTS AND UPDATES

Not applicable

6 MILESTONES

Milestone	Planned date*
Start of data collection	Q3 2017
End of data collection	Q3 2018
Registration in the EU PAS register	After approval by CHMP/PRAC
Final report of study results	Q2 2019

* Planned dates are based on protocol approval by the PRAC in Q2 2016.

MediWound Ltd. reserves the right to suspend or prematurely terminate either the data collection in an individual site or the entire study after agreement with the responsible committees (PRAC/CHMP).
The reasons for such decision may include:

1. Failure of the Investigator to comply with the protocol or legal requirements.
2. Poor quality of data records that do not enable proper collection of the data required for the study

   If suspension or premature termination occurs, the terminating party must justify its decision in writing and promptly inform the other parties. If for any reason, the MAH suspends or prematurely terminates the data collection at a single site or the entire study, the responsible IEC must be notified.

7 BACKGROUND AND RATIONALE

7.1 BACKGROUND

In December 2012 NexoBrid received marketing authorization in Europe. It is indicated for removal of eschar in adult patients with deep partial and full thickness thermal burns. Since 1985, 6 prospective clinical studies with Debrase/NexoBrid (concentrate of proteolytic enzymes enriched in bromelain) were conducted by MediWound, Ltd. In addition, a retrospective data collection study was performed. In the clinical development programme, more than 380 patients, were treated with /NexoBrid, of which more than 110 patients were pediatric and more than 270 adults (including 8 elderly patients >65 years of age).

Risk Minimisation in Clinical Trials

Three areas of risks of NexoBrid treatment were identified and clarified during the first two prospective phase II studies (MW 2001-10-03 and MW2002-04-01): ***pain, pyrexia and wound infection*** for which corrective actions were taken in subsequent phase II and phase III studies (MW2005-10-05, MW2004-11-02 and MW2008-09-03 (on-going study, final study data not available, yet)). Implementation of known, simple and effective corrective measures, as detailed below were associated with improvement of NexoBrid safety profile:

1. Administration of effective analgesic medications as commonly used for routine major dressing change in burned patients prior to Debrase/NexoBrid treatment to reduce pain,
2. Antibacterial soaking prior to and after NexoBrid treatment, as routinely done in wound care, to reduce pyrexia and wound infections,

The outcomes of implemented corrective actions are shown below:

Pain

No pain-related SAEs were reported in any of the studies. In studies MW 2001-10-03 and MW 2002-04-01, 21(23.3%) out of 90 NexoBrid patients reported 25 (14.5%) pain-related AEs (out of 173 AEs). In the control group 8 (11.4%) patients (out of 70) reported 9 (7.0%) pain-related AEs (out of 129 AEs).

After implementation of corrective actions (in studies MW2005-10-05 and MW 2004-11-02) the percent of patients reporting pain-related AEs was markedly reduced in NexoBrid group (3.6% vs. 23.3%) with a similar incidence rate to the control group treated with SOC: 4 patients in each group (3.6% in NexoBrid and 4.0% in the control groups). (MediWound, 2012)

Pyrexia

No pyrexia-related SAEs were reported in any of the studies. In studies MW 2001-10-03 and MW 2002-04-01, 32 (35.6%) out of 90 NexoBrid patients reported 38 (22.0%) pyrexia-related AEs (out of 173 AEs). In the control group 13 (18.6%) patients (out of 70) reported 17 (13.2%) pyrexia-related AEs (out of 129 AEs). All AEs, except one in the NexoBrid group, were recovered without sequelae.

After implementation of corrective actions (in studies MW2005-10-05 and MW 2004-11-02) the percent of patients reporting pyrexia-related AEs were almost

halved in the NexoBrid group (35.6% vs. 19.1%) and was similar to the control group. In NexoBrid groups 21 (19.1%) patients out of 110 reported 21(10.1%) pyrexia – related AEs (out of 208 AEs). In control groups 16 (15.8%) patients out of 101 reported 20 (12,8%) pyrexia-related AEs (out of 156 AEs). Except one AE in the NexoBrid group, all AEs were recovered without sequelae. (MediWound, 2012)

Wound infection

In studies MW 2001-10-03 and MW 2002-04-01, no wound infection-related SAE was reported in the NexoBrid group, while in the control group a wound infection-related SAE was reported. In the NexoBrid group 7 (7.8%) out of 90 NexoBrid patients reported 7 (4.0%) wound infection-related AEs (out of 173 AEs). In the control group 4 (5.7%) patients (out of 70) reported 4 (3.1%) wound infection - related AEs (out of 129 AEs). All AEs, except one in the control group, were recovered without sequelae.

After implementation of corrective actions (in studies MW2005-10-05 and MW 2004-11-02) the percent of patients reporting wound infection AEs was similar to previous studies. In the NexoBrid group 9 (8.2%) patients out of 110 reporting 10 (4,8%) wound infection-related AEs (out of 208 AEs). In control groups 8 (7.9%) patients out of 101 reported 9 (5.8%) wound infection AEs (out of 156 AEs). All AEs were recovered without sequelae. No wound infection-related SAE was reported in the NexoBrid group, while in the control group a wound infection-related SAE was reported. (MediWound, 2012).

The comparable results obtained for wound infection in both NexoBrid and control groups before and after implementation, and the absence of drug related AEs suggest that this is the normal incidence rate of wound infections in burn patients and that treatment with NexoBrid is not associated with increased risk to patients.

In addition, in the pivotal study MW 2004-11-02 a small, yet not statistically or clinicaly significant, delay in time to wound closure (TTCWC) was observed between two treatment groups. Analysis of intent-to-treat (ITT) population of time to complete wound closure calculated from injury date (per wound) was 32.8 days in the NexoBrid vs. 29.2 days in the SOC (p=0.1197). No AEs were reported for delayed in time to complete wound closure as the difference is mainly related to the wound care strategy applied by the physician, where an attempt to minimise grafting and allow for spontaneous epithelialisation of the wound areas that still have dermis may prolong time to first autograft (time to autograft: NexoBrid: 14.7 days vs. SOC: 5.9 days) and hence prolong complete wound closure. (MediWound, 2012)

No allergic or hypersensitivity reactions to NexoBrid were reported in clinical trials, nonetheless, based on literature reports, there is a potential risk of developing allergy by patients who have hypersensitivity to pineapples, papains, latex proteins, bee venom or olive tree pollen (due to cross-sensitivity). The contraindication statement in the SmPC is a general one (potential for sensitisation): *The potential of NexoBrid (a protein product) to cause sensitisation should be taken into account when re-exposing patients to bromelain-containing products at a later point in time. The use of NexoBrid in subsequent burn injury is not recommended*.

7.2 RATIONALE

As the burn disease is a multifactor disease involving most if not all body systems and thus associated with many adverse effects, including the identified risks of pain, pyrexia and wound infection, and potential risks of increased tendency to bleeding, severe irritation, and cardiopulmonary disease, making it difficult to distinguish between symptoms and diagnosis related to the underlying disease and the AEs related to study treatment.

It is anticipated that training provided to the health care professionals in each burn center and adherence to the education materials will lead to good implementation of risk minimisation procedures into routine clinical practice and the reduced levels of incidence of both identified and potential risks achieved in the later clinical studies are maintained in daily practice.

And thus, the objective of this observational study is assessing effectiveness of the risk minimisation activities (educational materials and training) and its effect on the incidence rate of identified risks, by achieving comparable incidence rates of identified risks in routine clinical practice to those obtained in clinical trials after implementation of risk minimisation activities.

7.3 RISK MINIMISATION PROCEDURES

The identified and potential risks associated with the use of NexoBrid are mitigated by routine and additional risk minimization measures.
Pain, pyrexia, wound infection and delayed time to complete wound closure are being addressed routinely by the specific precautions and IFU as included in the SmPC.

As was previously discussed and agreed, prior to launch in each Member State, the content of the educational programme is being discussed and approved by the national competent authority. The MAH undertakes a controlled distribution of NexoBrid to ensure that the product is not available for use at a centre until at least one surgeon at the centre has received formal training in the use of NexoBrid. This is in addition to the educational material which all potential users receive. To date the training of the education program is still on going across EU along with the product launch in new centres.
The educational pack provided to potential burn centres comprises the SmPC, PIL and Educational Material.

The training program presents a step by step treatment guide that includes information on the following key elements:

1. Before prescribing NexoBrid
   a. The limitation of the total area than can be treated to 15% TBSA
   b. Precautions associated with the use of NexoBrid, e.g. risk of allergic reaction and of cross reactivity and the contraindication in patients,
2. Before applying NexoBrid
   a. The need for pain management

b. The need for wound cleansing and preparation before treatment with NexoBrid
c. Application of a dressing soaked with an antibacterial solution for two hours before NexoBrid application
d. Protection of surrounding skin areas
e. The method of preparation of NexoBrid and of its application to wound area

3. After applying NexoBrid
   a. The removal of NexoBrid and of dissolved eschar
   b. The wound assessment
   c. Wound management after NexoBrid treatment with:
      i. Application of a dressing soaked with an antibacterial solution for two hours
      ii. Performance of grafting procedures as soon as possible after debridement
4. Monitoring the patients for any occurrence of AEs
5. Full review of the SmPC with focus on warnings and precautionary Measures- the SmPC review addresses the potential risks, precautions associated with NexoBrid use and appropriate use of NexoBrid.

8 RESEACH QUESTIONS AND OBJECTIVES

8.1 STUDY HYPOTHESIS

The following global study hypothesis will be tested to assess the effectiveness of the risk minimisation activities in routine clinical practice:
The incidence rates of pain and pyrexia in patients treated with NexoBrid in routine clinical practice exceed the point estimates of the incidence rates of pain and pyrexia observed in patients treated with NexoBrid in clinical trials after risk minimisation procedures were implemented by a clinically relevant amount.
In order to reject this global null hypothesis the following two null hypotheses have to be rejected simultaneously:

Pain:
The incidence rate of pain in patients treated with NexoBrid in routine clinical practice exceeds the point estimate of the incidence rate of pain observed in patients treated with NexoBrid in clinical trials after risk minimisation procedures were implemented (3.6%) by a clinically relevant amount of 10%.

Pyrexia:
The incidence rate of pyrexia in patients treated with NexoBrid in routine clinical practice exceeds the point estimates of the incidence rate of pyrexia in patients treated with NexoBrid in clinical trials after risk minimisation procedures were implemented (19.1%) by a clinically relevant amount of 10%.

8.2 PRIMARY OBJECTIVE

The main goal of this study is to assess the effectiveness of the risk minimisation activities and their effect on the incidence rate of identified risks that have shown to

be sensitive to these activities in the first two years from product launch in each participating country. This will be investigated by a comparison of the incidence rates of the identified risks pain and pyrexia within pre-defined time frames in routine clinical practice to those obtained in clinical trials after implementation of risk minimisation activities.
Given the experience from the clinical trials, the incidence rates of pain and pyrexia AEs before risk minimisation activities were relatively high and the effect of reduction by the risk minimisation was well pronounced. Therefore, these health outcomes are considered sensitive to risk minimisation activity and the primary objective of this study focuses on these risks.
For the third identified risk, wound infection, the effect of the risk minimization activities could not be established in the clinical trials although the observed rates in the Debrase/NexoBrid Gel Dressing (DGD) group has been similar to those in the control groups. Thus, this endpoint is not appropriate to assess the effectiveness of the risk minisation activities in routine clinical practice. Nevertheless, this risk will be declared as key secondary endpoint to emphasize its clinical relevance and importance.

8.3 SECONDARY OBJECTIVES

Secondary objectives of this study will be evaluated by the secondary endpoints described below. It is distinguished between key secondary endpoints and secondary endpoints. Key secondary endpoints are considered to be more important than secondary endpoints.

Key secondary endpoints:

The first key secondary endpoint is the compliance of the physician with the instructions from the Educational Material relate to the risk minimization activities (i.e.. whether antibacterial soaking before and after NexoBrid application performed; adequate pain management/administration of analgesia/sedation medication prescribed to the patient before applying NexoBrid and before removing NexoBrid). The compliance is not only an indicator for effectiveness of risk minimisation activities but it is also important to assess possible influence of compliance on the primary objectives.

Another key secondary endpoint is the incidence of wound infection AEs. Wound infection is the third identified risk of treatment with NexoBrid, but it did not show to be sensitive to risk minimization activities in the clinical trials. Thus, there is no effect of the risk minimization activities expected and the incidence rate of wound infection is declared as key secondary endpoint instead of primary endpoint.

Secondary endpoints:

- Overall incidence of reported AEs
- Incidence of severe irritation and/or allergic reaction events captured within 96 hrs from start of debridement[1]
- Incidence of cardiopulmonary events captured within 48 hrs from start debridement

[1] Suggested timeframe is based on the elimination time of NexoBrid from patients' blood which is 24 hrs

- Incidence of other wound related complications (related to NexoBrid) captured during patient's hospitalization
- Time to complete wound closure
- Proportion of NexoBrid patients treated off-label; paediatric patients (<18 years), facial burns, perineum/genital burns and wounds >15% TBSA treated in one session
- Incidence of severe blood loss (reported as blood transfusions) captured during the debridement procedure
- Time to hospital discharge for all patients.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is a multi-center, observational, retrospective study collecting data (chart review) on patients treated with NexoBrid in routine clinical practice. Each participating study site has received the training program for implementation of risk minimization procedures within the frame of regular product launch. The training program is similar in all EU countries, approved by national competent authorities, and is following the EU RMP approved by CHMP. As this is an observational study, each patient´s visit schedule and treatment is according to discretion of his/her physician.
All Patients treated with NexoBrid at the designated sites, as further detailed below, and who were discharged from the hospital, will be contacted and be asked to participate in the observational study. Once consent is given, collection of data which is relevant to the treatment as described in the CRFs and in Section 9.3 will be initiated.
Upon each patient´s enrollment into the observational study, data of the patient´s medical records will be entered into an electronic case report forms (eCRFs). Site staff will enter the data into eCRFs.

9.2 SETTING

This is a multi-centre, observational (retrospective chart review) study using secondary data sources in burn patients who received NexoBrid treatment in participating specialist burn centres. At least 160 subjects, as further described in 9.5, will be enrolled from approximately 15 participating burn centres. Sites will be chosen based on the NexoBrid launched plan in the EU countries and will be in accordance with the launched progress in each country. The data will be collected retrospectively from the following countries:

Country	Launch date
Germany	December 2013
Sweden	October 2014
Belgium	October 2014
Spain	November 2014
Poland	November 2014
Slovakia	October 2014

Centres will be chosen in advance, based on the launched date, number of burn centres in each participating country and will be included in the study subject to the number of patients treated since launch date. Centres that will have data on 5-10 patients will be preferred. All patients treated with NexoBrid (and discharged from the hospital) at each chosen site will be approached. This will allow a meaningful number of patients to be enrolled to the study after consent was given. Screening logs will be recorded to include patients approached yet consent was not given. This will be submitted with final CSR.

9.2.1 Study population

This study will include all patients who received NexoBrid treatment according to the hospital routine in participating specialist burn centres which received the training program for implementation of risk minimization procedures within the frame of regular product release. Specific data of participating centres will be collected and presented. These will include burn center size, number of hospitalization per year, admitted population, launch date. The planned number of patients will be at least 160 subjects.

The possibility to participate in this observational data collection shall be offered consecutively to all subjects in whom NexoBrid was used for debridement of burn wounds (***Note:*** *irrespective of their age, wound location or extent*) (***Note****: patients treated in NexoBrid clinical studies will not be included)*. Investigators will contact treated patients, who were discharged from the hospital, by telephone to inform them about the non-interventional study. In countries of which consent should be given in writing, patients will be invited to come to the study site to receive further information and sign on informed consent form. In case of pediatric subjects, the corresponding informed consent form for parents must be signed by a parent or legal representative, if consent was be given in writing. For incapacitated subjects, the informed consent form must be signed by a legal representative of the patient. Minor or incapacitated subjects who are able to read and understand the informed consent document may provide their consent on that form on a separate signature line.

All patients who were offered to take part in the study should be reported on the Subject Screening Log. For patients not taking part in the study, a reason for non-inclusion should be stated (e.g. refused to participate, death, etc.). These screening logs will include patients' gender, age, % TBSA burned.

9.3 VARIABLES

The following variables will be collected during the study on CRFs:

- Values for assessment of pain captured during the debridement procedure (e.g. repeated patient's complaints followed by prescription of pain management medications)
- Values for assessment of pyrexia captured within 48hrs from start of treatment (e.g. temperature above 38.5^0C requiring fever relief medications prescribed due to high temperature within 1 hrs from complaint, consecutive measurements of high temperature (above 38.5^0C), 4 to 6h apart
- Physician Compliance with Instructions- the number (n) and percentage (%) of wounds that were treated in compliance with instructions will be displayed
- Values for assessment of wound infection captured during the 1st week following debridement (e.g. antibiotics prescribed to a patient captured with positive swabs, positive wound biopsies performed)
- Values for assessment of severe irritation and allergic reaction within 96hrs from start of treatment and cardiopulmonary events captured within 48hrs from start of treatment[1]
- Values for assessment of wound related complications related to NexoBrid captured during hospital stay (e.g. wound reopening, graft loss)
- Values for assessment of time to complete wound closure (e.g. % graft applied on wound area, if performed, % wound epithelialized during follow up) will be collected
- Values for assessment of time to hospital discharge for all patients treated with NexoBrid.
- Values for assessment of blood loss captured within 24hrs from the debridement procedure (e.g. captured by blood transfusions)
- Values for assessment of number of patients where NexoBrid was used as off-label treatment i.e. in paediatric patients (<18 years), on facial burns, perineum/genital burns or wounds >15% TBSA treated in one session same comment as above
- Values for assessment of demographic parameters and medical characteristics of the patients population such as age, gender, burn description (locations, % area burned, number of sites), burn etiology, injury date and time, physical examination
- Values for assessment of medical history (including existing co-morbidities), concomitant diseases/conditions, and previous and concomitant medications and therapies
- Values for assessment of management of NexoBrid application such as area debrided with NexoBrid, number of applications, NexoBrid treatment duration, NexoBrid dosage, debridement outcome
- Values for assessment of overall debridement performed on each patient such as areas treated with SOC and the way these were treated (e.g. surgical and/or non

[1] Suggested timeframe is based on PK data demonstrating that most of the drug is eliminated from patients' blood at 24 hrs

surgical procedures performed, duration, debridement efficacy, wound management following SOC treatment)

- Values for assessment of post debridement wound management such as any coverages used including area covered and date, wound bed preparation procedures performed for autograft including application time and area covered
- Values for Index score for Tobiasen's abbreviated burn severity index[1] planned to be calculated by the statistician
- Values for assessing overall safety profile of patients by collecting reported AEs including severity and baseline lab tests.

No data can be collected for purposes of this data collection prior to obtaining of an informed consent. Data collection will include the following specific information, if performed routinely at the participating sites **and if available**:

Status at admission

The following procedures and assessments will be collected, if recorded:

- Basic demographics (age and sex)
- Medical condition (relevant co-morbidities including cardiopulmonary diseases[2], impaired immune system and medication used since injury) and concomitant disease/condition
- Burn etiology
- General burn wound description (location, %TBSA (size), partial or full thickness burns (depth))
- Presence of burn shock
- Malnutrition risk / nutritional status (weight, height)
- Baseline Labs- Haematology and Serum chemistry tests

Hospitalization

The following procedures and assessments will be collected, if recorded, during patient's hospitalization:

- ICU discharge date
- NexoBrid application (time after injury, wound location and duration, debridement efficacy, wound assessment (depth and size) after debridement)
- Antibacterial soaking before and after NexoBrid application, duration
- Adequate pain management/administration of analgesia/sedation medication to the patient before applying resp. before removing NexoBrid including drug name, dosage, start and stop time
- Application of adhesive barrier to protect the surrounding area
- Blood transfusions (during the debridement procedure)

[1] Clinical useful morbidity score developed by Tobiasen et al. 1982 (See: Tobiasen, J. Hiebert J.M. and Edlich R.F. (1982) . The abbreviated burn severity index. *Ann Emerg Med*. 11(5), 260-262)

[2] Cardiopulmonary- History of cardiac disease and/or pulmonary disease such as Ischemic heart disease, Valvular disease, pulmonary hypertension, COPD, restrictive lung disease
Impaired immune system- e.g. autoimmune diseases, AIDS, cancers of the immune system, such as leukemia, immune-complex diseases, such as viral hepatitis, multiple myeloma, Treatment with immunosuppressive drugs

- Pain assessments captured during the debridement procedure
- Wound infection captured within 7 days from start of treatment (confirmed by cultivation examination and local/systemic antibiotics)
- Pyrexia captured during 48hrs from start of treatment
- Wound management- any coverage used post debridement, autograft performed including date and % area applied with Autograft
- Vital signs (Temperature, Blood pressure)
- Skin irritation and/or allergic reaction within 96 hrs from start of treatment and Cardiopulmonary complications reported within 48 hrs from start of treatment
- Assessment of Adverse Events
- Concomitant therapy
    - Analgesics
    - Antibiotics – administered systemically and topically (incl. use of topical antimicrobial agents)
    - Infusion therapy
    - Adverse Event related
- Weekly follow-up assessments (assessment of % wound area epithelialized and/or closed by graft)

Hospital Discharge

The following procedures and assessments will be collected, if recorded:

- Physical examination and weight
- Assessment of wound closure (% of wound area epithelialized and/or closed by graft)
- Adverse events

Wound Closure

The following procedures and assessments will be collected, if recorded:

- Assessment of wound closure (% of wound area epithelialized and/or closed by graft)
- Concomitant therapy incl. non-pharmacological procedures
- Adverse Events

9.4 DATA SOURCES

All patients meeting the below mentioned **inclusion criteria** shall be included into the data collection:

1. Patients who were treated with NexoBrid
2. Signed written informed consent approving data collection according to ethics committee requirements

Existing data before signature of informed consent starting from injury and data collected during treatment until wound closure as documented in the medical charts of the patients will be used.
In case of discharge of the patient prior to wound closure it could occur that the patient will be examined elsewhere. The site will be asked to contact the respective treating

physician to follow up on wound closure results and possible AEs/SAEs to avoid missing data.

9.5 STUDY SIZE

The incidence rates of pain, pyrexia and wound infection AEs in the routine clinical practice with implementation of risk minimisation activities shall be compared with the results of the previously conducted clinical trials MW2005-10-05 and MW 2004-11-02.
Each primary endpoint, i.e. incidence rates of pain and pyrexia AEs, will be tested using a one-tailed non-inferiority test at the significance level of 2.5%. Since the two primary endpoints are of equal importance, they are considered as co-primary endpoints. Only if both primary null hypotheses have been rejected, the key secondary endpoint 'incidence rate of wound infection AEs' will be tested using a one-tailed non-inferiority test at significance level 2.5%. As this corresponds to a combination of co-primary endpoints and hierarchical testing strategy, no multiple testing problem shall evolve.

The sample size calculation has to achieve a power of 80% for the simultaneous rejection of the two primary null hypotheses and is not powered for the key secondary endpoint. The steps used to design the study with adequate statistical power are described in the SAP, section 2.7.

With p being the assumed incidence rate of an adverse event of interest and p_0 being the incidence rate assumed under the null hypothesis, the sample size n needed to achieve a desired power β can be simulated using the following power formula:

$$\beta = P(X \geq \lceil np_0 + z_\alpha \sqrt{np_0(1-p_0)} \rceil_+ | n, p)$$

where X denotes a random variable that is binomial distributed with parameter n, p ($X \sim$ binomial (n,p)), z_α denotes the upper αth quantile of the standard normal distribution and $[x]_+$ denotes the smallest integer greater than or equal to x (Krishnamoorthy and Peng, 2007).
The corresponding type I error rate is obtained by replacing p with p_0, i.e.

$$\beta = P(X \geq \lceil np_0 + z_\alpha \sqrt{np_0(1-p_0)} \rceil_+ | n, p_0)$$

(Krisnamoorthy, K. and Peng, J. Some Properties of the Exact and Score Methods for Binomial Proportion and Sample Size Calculation. *Communications in Statistics—Simulation and Computation*® **36**, 1171–1186, 2007)

The above equations were implemented in SAS 9.4 in order to simulate the sample size needed for the non-interventional study by use of the assumed rates of adverse events and corresponding non-inferiority margins described in section 2.7.1 of the SAP. The SAS macro can be found in the appendix of the SAP.
A minimum sample size of 153 subjects satisfies the significance level α of 2.5% and achieves a power of 80% for the simultaneous rejection of the three primary null hypotheses. Table 1 describes the results of the simulation in more detail:

Table 1- Power and type I error rate of the score test for the assumed rates of AEs of interest

AE of interest	Assumed rate of AE	Sample size	Power for rejection of H_0	Type I error rate
Pain	3.6%	153	99.62%	1.96%
Pyrexia	19.1%	153	81.18%	2.25%
Wound infection	8.2%	153	72.68%	1.94%

The power β for the simultaneous rejection of the three primary null hypotheses results from the product of the power of each statistical test, i.e. according to Table 1:

$$\beta = 99.62\% \cdot 81.18\% = 80.87\%$$

Summary:

Overall a minimum sample size of 153 subjects is required for rejection of the global null hypothesis with a power above 80%. In order to have a slight buffer regarding the power a minimum sample size of **160** patients will be included in this trial.

9.6 DATA MANAGEMENT

For data collection an electronic CRF will be used to ensure expedited data processing. No data will be directly entered into the e-CRF without source documentation.
The CRF is an integral part of the study and subsequent reports. The electronic Case Report Form provided by MediWound Ltd. must be used to capture all study data recorded in the subject's medical record. The eCRF must be kept current to reflect subject status during the course of the study. Only a subject identification number will be used to identify the subject. The investigator must keep a separate log of subject names and medical record numbers (or other personal identifiers).
The protocol will use an Internet-Based Remote Data Entry System, primarily to collect clinical trial data at the investigational sites. The system will comply with 21 CFR Part 11 and ICH E6. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. Paper source documents are to be retained to enable a reconstruction and evaluation of the trial. No original observations will be entered directly into the computerized system. Source documents defined as primary source of documentation like the hospital patient files including the patient notes, anaesthesia reports, referral letters to GPs, lab reports and all other medical data belonging to study patients are considered source data. Data collected on medical history will include relevant co-morbidities including cardiopulmonary diseases. General burn wound description will include partial or full thickness burns. Data on procedures and assessments regarding NexoBrid application will include wound location, extent and depth. Data on adequate pain management and administration of analgesia and sedation medication to the patient before applying respectively before removing NexoBrid and data on application of a sterile paraffin ointment adhesive barrier to protect the surrounding area will be collected. In addition data on wound depth as assessed after NexoBrid treatment will be provided. Further on, in case of grafting, data on the time between debridement and grafting will be collected as for data on the grafting procedure (area applied, location) and any additional data available on

coverage applied. If patients were debrided by standard of care procedures as well, this information will be recorded as well.

All data listings and tables will be generated using SAS® Version 9.3 or higher.

9.7 DATA ANALYSIS

The statistical methods foreseen for the primary and secondary analysis as at the time of study planning are roughly described here. A more detailed description will be provided in the SAP. Any changes in the planned statistical methods will be documented in the CSR.

All measured variables and derived parameters will be listed individually in listings. Tables using descriptive statistics will be provided for the primary and secondary variables as well as other variables concerning demographics and baseline characteristics.
Primary analysis will be performed on the safety evaluation set.
Each primary endpoint, i.e incidence rates of pain and pyrexia AEs, will be tested using a one-tailed non-inferiority test at the significance level of 2.5%. Since the two primary endpoints are of equal importance, they are considered as co-primary endpoints. Only if both primary null hypotheses have been rejected, the key secondary endpoint 'incidence rate of wound infection AEs' will be tested using a one-tailed non-inferiority test at significance level 2.5%. As this corresponds to a combination of co-primary endpoints and hierarchical testing strategy, no multiple testing problem shall evolve.
The secondary objectives will be analysed using descriptive statistics. Categorical variables will be displayed using summary tables which will provide sample size, absolute and relative frequencies. Continuous variables will be displayed by sample size, mean, standard deviation, median, minimum and maximum. Where appropriate, 95% confidence interval will be calculated.

Other variables that will be displayed in tables are the demographics, baseline characteristics (physical examination, burn characteristics, NexoBrid treatment information, etc.), medical history, concomitant diseases, previous and concomitant medications, concomitant therapies and NexoBrid Pain Management.
Medications will be displayed coded by ATC (Anatomic therapeutic Chemical) Classification using third and fourth level categories. Concomitant therapies and NexoBrid Pain Management as recorded in the patient's medical chart will be coded by WHO classification. Concomitant therapy will be collected starting from injury until wound closure.

The statistical analysis will be based on the safety evaluation set (SES) which consist of all subjects who receive NexoBrid at least once and consent for data collection. No other populations will be defined for this study.

Subgroup analyses are based on the subgroups listed below:

Criteria for subgroup	Categorisation
Country	Each country where patients have been enrolled
Burn etiology	As recorded in the eCRF
Use of NexoBrid	Patients with vs. without study treatment of facial, perineal and/or genital burns
Age and sex	<18 years; 18-40; >41 separate for male and female
Medical history 1	Patients With vs. without impaired immune system
Medical history 2	No occurrence vs. occurrence of relevant allergy (i.e. patients with history of allergy to pineapple or papain)
Medical history 3	Presence vs. Absence of cardiopulmonary disease(s)
Treatment	NexoBrid vs. NexoBrid and SOC (surgical) vs. NexoBrid and SOC (non-surgical)
Compliance (overall)	Patients treated in compliance with educational material vs patients not treated in compliance with educational material as recorded in the eCRF
Compliance by relevant risk minimisation activity	Compliance with the risk minimisation activity implemented for the current identified risk if recorded in eCRF.
Burn severity 1	%TBSA (≤ 5% / > 5%, ≤ 10% // > 10%, ≤ 15% / > 15%)
Burn severity 2	Patients with only second degree burns vs patients with mixed second & third degree burns
Number of wounds treated	1, 2-3, >4

For the primary variables, each subgroup analysis comprises only descriptive statistics such as determination of the observed incidence rates of pain, pyrexia and wound infection. If applicable, the corresponding two-sided 95% score confidence interval will be provided. The results and the number of subjects per subgroup will be illustrated in a forest plot together with the corresponding values of the primary analysis for comparison reasons.

In case of the secondary endpoints, subgroup analyses will be limited to the most relevant subgroups. The analysis by country will be always provided.

All subgroup analyses have a supportive and/or exploratory role and will not be part of the confirmatory analysis strategy.

No drop-outs are expected since the study is conducted retrospective.

9.7.1 Risk Factor Analysis

Risk factor analysis will be done using logistic regression under the assumption of the logit model. Dependent variables include the primary variables, independent variables include potential risk factors and, if applicable, corresponding confounders. Based on the results of the regression, odds ratios are presented with the corresponding 95% likelihood-ratio confidence interval for each risk factor. In case of significant influence of confounders or risk factors, odds ratios will be calculated with and without adjustment. It is planned to investigate the following univariate models:

Dependent variable (DV) (only one DV per model. The analysis will be repeated for each DV listed)	Independent variables (IV)	
	Potential risk factor(s)	Potential confounder
AE (pain), AE (pyrexia), AE (wound infection)	Non-compliance (overall and partial compliance, i.e. risk minimization activities implemented to limit the occurrence of the DV.)	-
AE (pain), AE (pyrexia), AE (wound infection)	%TBSA	-
AE (pain), AE (pyrexia), AE (wound infection)	Age	-
AE (pain), AE (pyrexia), AE (wound infection)	Sex	-
AE (pain), AE (pyrexia), AE (wound infection)	Study treatment of facial, perineal and/or genital burns	
AE (pain), AE (pyrexia), AE (wound infection)	Cardiopulmonary Events	Age
AE (wound infection)	Impaired immune system	Age
AE (pyrexia)	AE (wound infection)	%TBSA
AE (pain), AE (pyrexia), AE (wound infection)	Tobiasen's abbreviated burn severity index	

Subsequent to the univariate risk factor analysis, it is planned to perform multivariable analyses building a regression model by the purposeful selection algorithm using the settings recommended by Bursac et al[1].

Furthermore, it is planned to provide stratified respective descriptive analyses for patients with and without risk factors and occurrence of endpoints in form of respective tables.

In order to assess the comparability between the populations in this retrospective chart view and the clinical studies, descriptive statistics are provided for the risk factors for both, the retrospective chart view and the clinical studies, if available. By means of these descriptive statistics the comparability of the populations will be discussed in the final study report with regard to the results of the risk factor analysis.

9.8 QUALITY CONTROL

Quality control includes verification and quality control of all activities undertaken before, during and after the data collection. These operational techniques and activities will be performed according to the applicable ISO standards and SOPs of MediWound Ltd (and/or CRO SOPs).

9.8.1 Monitoring and Quality Assurance

Data entry into the eCRFs will be performed by local study coordinators in each of the participating sites. Training on the system and required data to be captured will be performed by the Sponsor prior to the initiation of study collection. Data entry will be controlled by automatic logic checks on consistency, defined before initiation of the study. Furthermore, data reported on the eCRFs will be compared with medical records of corresponding patients. This will be done by CRAs (CRO representatives authorized by MediWound Ltd.). At each study centre, source data verification will be done in an extent of 100% for the first documented patient. Special attention will be invested in monitoring ICF review and signing off process, verify that data protection was kept and study requirements were understood. Additional monitoring will be performed on following patients and will be based on pre-defined risks which affect study conduct and primary objective and per site's enrollment rate. The following parameters trigger additional monitoring visits:

- Site enrolled more than 10 patients (risk: impact of number of patients on study population is quite large)
- eCRF data not documented within 14 days after ICF signed (risk: study oversight cannot be ensured)
- Number of data queries per patient higher than 5 (risk of low data quality)

A documented remote monitoring visit will be done on a monthly basis at each site which has started data entry into eCRF. Based on the remote monitoring visits, the sponsor will trigger centralized onsite Monitoring visit.
Co-monitoring and internal pre planned audit might be performed by MediWound to assure proper conduct of the study at the sites (assuring all patients are being contacted, screening logs are being filled, etc).
Auditors/inspectors have the right to inspect MediWound Ltd., CRO and study site(s)

[1] Bursac, Z. Gauss, C. H., Williams, D. K. and Hosmer D. W. (2008). Purposeful selection of variables in logistic regression, Source Code for Biology and Medicine. 3, 17.

at any time during or after completion of the clinical trial and will have access to source documents, including subject's medical records. By participating in this study, Investigators agree to this requirement.

9.9 LIMITATIONS OF THE RESEARCH METHODS

It is recognized that control of biases in an observational trial design is generally more difficult than in controlled randomized trials. With observational research, the main limitation relates to the quality of the data sources to be used (such as medical records of patients). On the other hand, quality of documentation in the burn centers tends to be relatively high. It is also expected that patients' records may lack some of the data being collected in the CRFs.

It should be noted as a limitation of the study that rejection of the null hypothesis for the primary endpoint pyrexia does not imply that a pyrexia incidence rate larger than the lower 95% confidence interval from the clinical trials without risk minimization can be excluded. Therefore, the conclusion on the efficacy of risk minimization for pyrexia based on the hypothesis is associated with uncertainty. However, a trial with a NI margin such that rejection of the null hypothesis implies non-overlapping confidence intervals would require >350 patients which is not feasible.

Collecting data retrospectively, especially for parameters that are being reported in routine practice that might result from the disease itself rather the medication, may results with many missing values and unclear definitions of specific parameters. Study coordinators entering data into the eCRFs will be instructed in advance, before study initiation, for specific parameters and guidelines that will support reporting of specific events such as pain and pyrexia.

Approximately 30% of the launch sites in each chosen countries will be approached to participate in the study. As it is estimated that consent rates will be of less than 50% of the patients that are being approached in the study, centres that treated reasonable number of patients with NexoBrid will be approached in order to allow at least 5-10 patients to consent for data collection. By approaching centres that treated a reasonable number of patients (at least 15 patients per center), the true affect of the training program could be investigated as these centres were able to implement the treatment path into their routine practice.

Including centres from different countries in Western and Eastern Europe that might have different standard of Care treatment as well and the way each site implemented NexoBrid in its routine practice may introduce a large variability in the data collected. Each center routine and involved staff (surgeons, anaesthesiologist, etc) will affect the way NexoBrid patients are being treated. Data of routine standard of care practice will be collected for participating sites as well as standard of care treatments on patients treated with combination of NexoBrid and standard of care.
The education material and training are very similar in all participating sites. Nevertheless some variations in the implementation may be expected in order to align the treatment procedures with the centres' standard practices. Moreover, as the center will gain more experience there might be changes in the treatment procedures overtime.

10 PROTECTION OF HUMAN SUBJECTS

This is a post-authorization, observational data collection where the indication for use of NexoBrid is done solely in discretion of the attending physician, without being influenced by this protocol. Burn wound management of each patient will be performed according to routine clinical practice of each participating specialist burn centre. No additional procedures, beyond routine clinical practice are requested therefore participation in this observational study is not associated with any additional risks to study participants.

10.1 DATA PROTECTION

Patient medical information obtained during this observational data collection will be handled as strictly confidential and disclosure to third parties, other than those mentioned in this Protocol is prohibited. MediWound Ltd. and all its delegates will affirm and uphold the principle of patient's right for protection against the invasion of privacy. In order to guarantee this principle, all data will be pseudonymized and identified only by patient`s number throughout the entire data collection and during all analyses.

Data generated by this observational data collection will be available for MediWound Ltd. or its delegated representatives, representatives of national and international health authorities as well as the IEC. A Subject Identification Log with name and code of each patient will be kept and updated by the Investigator, only.

10.2 INFORMED CONSENT

Upon patients' consent to participate in the study, patients must be explicitly informed that no study procedure will be performed with the patients, and that the study focuses mainly on retrospective data collection of the past NexoBrid treatment and the routine burn wound management. Only if the patients agree that these standard of care data are recorded and evaluated, the patient would eligible. The participation of patients in this retrospective data collection is voluntary. Finally, patients have to be informed that their records may be accessed by competent authorities and authorized MediWound Ltd and/or CRO representatives in the extent permitted by applicable national law(s) and regulations. By consenting the subject will authorize such access.

Inform consent procedure will be performed in accordance with the local regulatory requirements for non interventional retrospective data collection. In countries of which consent must be given in writing, patients must get sufficient time to read the informed consent form and to ask additional questions. These questions shall be answered by the Investigator during a personal meeting.

In case of adult subjects being not able to provide an informed consent an impartial witness shall be involved into the process and the informed consent form shall be signed by the impartial witness. As soon as the health status of the patient will allow it, an informed consent must be obtained from the patient.

In case of pediatric subjects the corresponding informed consent form for parents must be signed by the parents or legal representative. Minor subjects who are able to read and understand the informed consent document (parent's informed consent form) may provide assent on that form on a separate signature line.

For incapacitated subjects the informed consent form must be signed by a legal representative of the patient. Subjects who are able to read and understand the informed consent document may provide their consent on that form on a separate signature line.

10.3 ETHICS AND REGULATORY REQUIREMENTS

The study is a non-interventional, observational collection of pseudonymized data of patients who received NexoBrid according to the routine practice of each participating site. No additional procedures, beyond routine clinical practice, are requested by the Study Protocol. Participation in this data collection does not present any additional risks or benefits for patients.

10.3.1 Regulatory requirements

This observational data collection will be conducted in accordance with applicable laws and regulations of corresponding participating countries and with the ethical principles having their origin in the Declaration of Helsinki.

10.3.2 Independent Ethics Committee

The data collection will not begin until the required favorable opinion from the responsible IEC(s) has been obtained. This document must be dated and shall clearly identify the Study Protocol including its title and code of the study, amendments (if any), the informed consent form and any potential recruiting materials.

During the trial protocol amendments and revised informed consent forms (if any) will be sent to the IEC for review.

If applicable, reports and reviews of the study and its progress will be submitted to the IEC(s) at intervals stipulated in their guidelines. At the end of the data collection, the IEC(s) will be notified about the trial completion.

10.3.3 Regulatory approval

This post-authorization, observational data collection shall be reviewed and approved by the PRAC prior to study commencement. In countries, where an approval from a regulatory authority is required by local laws or regulations, the study will be submitted to the authority(ies) and initiated only after obtaining of the approval.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ REACTIONS

Adverse Events will be coded and presented in coding dictionary MedDRA in its latest version, as applicable.

All adverse events found in this retrospective study will be collected as part of the data collection procedures described in this protocol, and summarized by presenting the number and percentage of subjects having any adverse events, having an

adverse event in each body system and having each individual adverse event. Information will further be categorized by severity/intensity or relationship to study medication.

For studies with secondary data collection, expedited reporting of suspected adverse reactions in the form of Individual Case Safety Report (ICSRs) is not required, as per the EU GVP Module VI. Reports of adverse events/reactions will be summarized as part of interim safety analysis and final study report.

All AEs (both serious and non-serious) will be entered by investigator to eCRF and its causal relationship to studied medicinal product will be assessed using causality scale:

- **Not related**;
    - Not Related: The event is clearly related to other factors such as a patient's clinical state, therapeutic interventions or concomitant medications.
    - Remotely Related: The event was most likely produced by other factors such as a patient's clinical state, therapeutic interventions or concomitant medications and does not follow a known response pattern to the drug.
    - Not Feasible
- **Related;**
    - Possibly Related: The event has a reasonable temporal relationship to drug administration and follows a known response pattern to the drug. However, a potential alternate etiology may be responsible for the event. The effect of drug withdrawal is unclear. Rechallenge information is unclear or lacking.
    - Probably Related: The event follows a reasonable temporal sequence from the time of drug administration and follows a known response pattern to the drug and cannot be reasonably explained by other factors. There is a reasonable response to withdrawal of the drug. Rechallenge information is not available or advisable.
    - Related: The event follows a temporal sequence from the time of drug administration and follows a known response pattern to the drug and either occurs immediately following drug administration, or improves on stopping the drug, or reappears on repeat exposure.

AEs assessed as possible, probably or related will be addressed as Adverse Drug Reaction (AEs related to study arm).

Any AE (both serious and non-serious) will be shared with global pharmacovigilance department by the data management on every 6 months in the form of interim safety analysis and in the final study report.

AE/SAEs will be extracted from the medical documentation, if occurred in the period between the period of hospital admission and up to the end date. End date is defined as wound closure or hospital discharge, the latest between the two. EU QPPV should be involved in the revision process of the study protocol, should be informed about any urgent safety restriction detected during the study conduct and should be informed about the results of the interim and final study reports.

All AEs (both serious and non-serious) will be discussed in PSUR and RMP.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of this observational, retrospective data collection will be reported in a single Final Study Report.

Synopsis of study report will be annexed to the RMP. Study results will be used to adjust the safety specification (Part II-SV) and the pharmacovigilance plan (Part III) of the Risk Management Plan. In addition, the final study results will be periodically and critically discussed in Sections 7 and 8 of the Periodic Safety Update Report and in the EU Regional Appendix “Reporting of Results From Post-Authorisation Safety Studies”.

Based on the results of the study, academic publication in medical journals focusing on clinical management of burn patients is envisaged.

13 REFERENCES

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ANNEX 1. List of stand-alone documents

ANNEX 2. ENCePP checklist for study protocols

ANNEX 3. Additional information

Company Signature and Approval Page

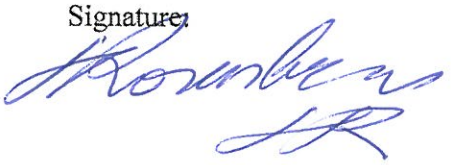
An international, retrospective, observational study assessing efficacy of applied risk minimisation measures in burn patients treated with NexoBrid.

We hereby declare that this Study Protocol was prepared scientifically accurately and in full compliance with the current regulatory guidelines.

With our signatures, we agree to conduct this study in accordance with the Study Protocol, applicable local laws and regulatory requirements of corresponding participating countries and with the ethical principles having their origin in the Declaration of Helsinki.

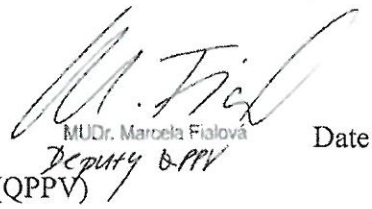
Moreover, we will keep all information obtained in this study confidential unless otherwise agreed in writing.

For MediWound Ltd., this Study Protocol has been approved by:

Prof. Lior Rosenberg
Chief Medical Officer
MediWound Ltd.
Signature: 
Date: 30/4/2017

Keren David Zarbiv
Director Clinical Affairs
Mediwound Ltd.
Signature: Keren David
Date: 27 Apr 17

Nimrod Leuw
Director of QA/QC
MediWound Ltd.
Signature: 
Date: 30.04.2017

Jan Petracek, MD
Qualified Person for Pharmacovigilance (QPPV)
European Pharminvent Services s.r.o.
Signature: 

Date: 27-APR-2017