Clinical Study Report (CSR)

1 TITLE PAGE

Study Title:	An international, observational retrospective, data-collection study assessing efficacy of applied risk-minimisation measures in burn patients treated with NexoBrid®
Study Code:	MW2013-06-01
EU PAS Register® Number:	EUPAS18751
Medicinal Product:	Concentrate of proteolytic enzymes enriched in bromelain (ACT code D03BA03)
Indication:	NexoBrid® is indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns
Study Design:	International, retrospective, post-authorisation, data-collection study using secondary data sources
Study Dates:	January 2018 to January 2019 (start and end of data collection)
Report Date:	12-Sep-2019

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Representative Sponsor:

Prof. Lior Rosenberg
Chief Medical Officer
MediWound Ltd.

16 Sep. 2019 [Date] [Signature]

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2 STUDY SYNOPSIS

Name of Sponsor:	MediWound Ltd.
Name of Finished Product:	NexoBrid®
Name of Active Ingredient:	Concentrate of proteolytic enzymes enriched in bromelain
Title of Study:	An international, observational, retrospective data-collection study assessing efficacy of applied risk-minimisation measures in burn patients treated with NexoBrid®
Study Centres:	Burn centres in Western and Eastern Europe: Belgium (1 site), Germany (4 sites), Poland (4 sites), Slovakia (1 site), Spain (3 sites), and Sweden (1 site)
Publication (Reference):	None.
Study Period:	January 2018 to January 2019 (start and end of data collection)
Phase of Development:	Post-authorisation safety study (PASS)

Objectives:

Primary:

Effectiveness of the risk-minimisation measures based on the incidence rate of pain and pyrexia associated with NexoBrid® treatment reported in the first two years from product launch in each participating country in routine clinical practice.

Secondary:

Descriptive analysis of all secondary endpoints (see Section 9.7.1) with focus on the key secondary endpoints "incidence of wound infection adverse events" and "physician compliance with educational materials".

Methodology:

International, retrospective, post-authorisation, data-collection study using secondary data sources.

Fifteen burn centres in Western and Eastern Europe participated in the observational study. All participating study sites received the training program for implementation of risk-minimisation measures within the frame of regular product launch.

The incidence rates of pain, pyrexia, and wound infection in the routine clinical practice with implementation of risk-minimisation measures were compared with the results of the previously conducted clinical trials.

Burn-wound management of each patient was performed according to routine clinical practice of each participating specialist or burn centre, and the indication for use of NexoBrid® was in accordance with the approved SmPC (without being influenced by this protocol) and with the medical training that was performed by the sponsor at all burn centres before study initiation.

All patients enrolled into the study were treated with NexoBrid® for at least one burn wound. Some patients were treated also with SoC procedures for other wounds.

Number of Patients:

164 patients were considered for the statistical analysis.

Main Criteria for Inclusion:

- Burn patients treated with NexoBrid® and discharged from hospital.
- Signed written informed consent approving data collection according to ethics committee requirements.

Test Product, Dose and Mode of Administration:

Concentrate of proteolytic enzymes enriched in bromelain:
ATC code D03BA03, trade name NexoBrid®.

Dose and administration according to summary of product characteristics / leaflet.

Duration of Treatment Observation:

Available data from hospital admission (due to burn) until wound closure or hospital discharge, whichever is the latest date.

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Reference Therapy, Dose and Mode of Administration, Batch Number:

N/A

Main Criteria for Evaluation

Primary Endpoints:
- Incidence rate of pain during the treatment procedure.
- Incidence rate of pyrexia within 48 hours from start of treatment.

Key-Secondary Endpoints:
- Incidence of wound infection during the 1st week following debridement.
- Physician compliance with educational material instructions.

Additional Secondary Endpoints:
- Overall incidence of reported adverse events.
- Incidence of severe irritation and/or allergic reaction events captured within 96 hours from start of debridement.
- Incidence of cardiopulmonary events captured within 48 hours from start debridement.
- Incidence of other wound-related complications (related to NexoBrid®) captured during patient's hospitalisation.
- Time to complete wound closure.
- Proportion of NexoBrid® patients treated as off-label (paediatric patients, facial/perineal/genital burns, wounds >15 %TBSA in one session, repeated application in more than one session).
- Incidence of severe blood loss captured within 24 hours from the debridement procedure (reported as blood transfusions).
- Time to hospital discharge.

Statistical Methods:

It was tested whether the incidence rates of pain and pyrexia in patients with NexoBrid® in routine clinical practice (after risk-minimisation measures were implemented, and reported within pre-defined time frames from treatment) exceed the point estimates of the incidence rates of pain and pyrexia observed in patients treated with NexoBrid® in clinical trials by a clinically-relevant amount of 10% (absolute).

Non-inferiority applies, when both null hypotheses regarding pain and pyrexia are rejected simultaneously. Two-sided, 95%-score-confidence intervals were calculated for all incidence rates.

All other statistical analyses including analyses of key-secondary endpoints, risk factors, and sub-groups were explorative. The below results provide relative frequencies (%) of categorical data and mean values (arithmetic mean ± standard deviation [median]) of numerical data.

The retrospective data collection resulted in a high percentage of missing values. All data were analysed as recorded, and no imputations were done, unless explicitly mentioned.

Results - Baseline:

Patient Characteristics:

Most of the patients were Caucasian (87.8% patients), belonged to the Non-Hispanic / Non-Latino ethnicity (70.1% patients), were male (74.4% patients), and had no malnutrition risk (76.2% patients). Mean age was 42.3 ± 14.6 years, mean body height 173.8 ± 9.7 cm, body weight 79.7 ± 18.2 kg, and mean BMI 26.42 ± 4.94 kg/m^2.

Previous medication or non-pharmacological procedures were reported in 89/164 patients (54.3%). Average blood pressure was 129.6 ± 21.5 mmHg systolic and 75.6 ± 13.2 mmHg diastolic, pulse rate 83.7 ± 16.4 beats/minutes, and body temperature 36.57 ± 0.79 °C.

Medical History and Concomitant Diseases/Medication/Procedures:

A medical history for any cardiopulmonary disease was confirmed in 35/164 patients (21.3%), any impaired immune system disease in 7/164 patients (4.3%), and any allergy to pineapple or papain in no patient (0.0%).

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Concomitant diseases ongoing at hospital admission were reported in 100/164 patients (61.0%). The most frequent MedDRA System Organ Classes (SOCs) with incidence above 10% were vascular disorders in 41/164 patients (25.0%), psychiatric disorders in 34/164 patients (20.7%), metabolism and nutrition disorders in 29/164 patients (17.7%), and injury/poisoning and procedural complications in 26/164 patients (15.9%).

All (100%) patients were prescribed concomitant medications or underwent non-pharmacological procedures after hospital admission, which were most frequently analgesics in 163/164 patients (99.4%), blood substitutes and perfusion solutions in 101/164 patients (61.6% patients), anaesthetics in 99/164 patients (60.4%), antiinflammatory and antirheumatic products in 97/164 patients (59.1%), all other therapeutic products in 83/164 patients (50.6%), psycholeptics in 79/164 patients (48.2%), antibacterials for systemic use in 71/164 patients (43.3%), drugs for acid-related disorders in 57/164 patients (34.8%), all other non-therapeutic products in 50/164 patients (30.5%), and antithrombotic agents in 39/164 patients (23.8%).

The mean Tobiasen's Abbreviated Burn Severity Index was 4.8 ± 1.7 points.

Wound Characteristics:

The statistical evaluation based upon 164 subjects, whose wounds were treated either with NexoBrid® alone (89/164 patients, 54.3%) or with NexoBrid® and standard-of-care (SoC) procedures (75/164 patients, 45.7%). Overall there were 532 wounds, 313 wounds (59%) were treated with NexoBrid. SoC procedures were applied on 219 wounds (219/532 wounds, 41%).

On average, each patient had 3.2 ± 2.5 (median=2.0) treated wounds [range from 1 to 15], which represented a mean total body surface area (TBSA) of 12.71% ± 14.40 (median=6.75%). The average affected TBSA per wound was 4.10% ± 5.47 (median = 2.5%).

The body areas mostly affected (> 20% attributions) were the right hand (87/164 patients, 53.0%), left hand (72/164 patients, 43.9%), lower right arm (63/164 patients, 38.4%), upper right arm (47/164 patients, 28.7%), face (43/164 patients, 26.2%), upper left arm (38/164 patients, 23.2%), left thigh (33/164 patients, 20.1%), and right thigh (33/164 patients, 20.1%).

Most frequent causes of burn were fire/flame (106/164 patients, 64.6%) and scald (37/164 patients, 22.6%). Before admission, 22/164 patients (13.4%) suffered from inhalation injury and 21/164 patients (12.8%) developed a burn shock.

Wound severity was classified as full thickness for 22.7% wounds, superficial partial thickness for 15.0% wounds, mixed wound for 10.3% wounds, and deep partial thickness for 7.7% wounds. For all other wounds, there was no available data of wound severity.

Wound Management With NexoBrid®:

The average time from burn injury to treatment with NexoBrid® was 2.6 ± 1.3 days (n= 164), on average there were 1.9 ± 1.2 wounds per patient (range from 1 to 8) treated with NexoBrid®, with an average %TBSA of 3.66 ± 3.66 per wound. An average dose of 5.34 ± 5.84 g NexoBrid® per wound was applied for a mean duration of 204.3 ± 87.7 minutes. Treatment with NexoBrid® resulted in an average of 93.9% ± 15.7 (median of 100%) removal of eschar from the wound (data available for 107/313 wounds).

NexoBrid® was prepared (mixture of NexoBrid powder and gel) 15 minutes or less prior to use for 119/313 wounds (38.0%), an adhesive barrier was applied for 181/313 wounds (57.8%). An antibacterial soaking was applied before NexoBrid® application and following removal for 165/313 wounds (52.7%) and 181/313 wounds (57.8%), respectively. Pain was pharmacologically managed before NexoBrid® application and before removal for 294/313 wounds (93.9%) and 248/313 wounds (79.2%). High percentages of missing data were present for these analyses.

Wound Management With SoC Procedures:

Overall, 219 wounds were treated with SoC procedures, on average 1.3 wounds per patient (range from 0 to 12) were treated with SoC procedures. The average TBSA per wound was 4.6% ± 6.98.
The types of procedures were surgical for 121/219 wounds (55.3%), non-surgical for 85/219 wounds (38.8%), and combined surgical plus non-surgical procedures for 13/219 wounds (5.9%). The SoC

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procedures resulted in an average of 97.2% (median of 100%) removal of eschar from the wound (data available for 70/219 wounds).

Coverage After Debridement:

Initial coverage was recorded for 292/313 wounds (93.3%) treated with NexoBrid® after a median time of 1.0 day from NexoBrid® removal. The initial coverages mostly applied to wounds treated with NexoBrid® were Suprathel® 102/313 (32.6%), autograft 36/313 (11.5%), Mepitel® 33/313 (10.5%), and allograft 29/313 (9.3%).

For wounds treated with NexoBrid®, the wound was eventually closed by an autograft for 140/313 wounds (44.7%) and graft take was recorded for 130/140 autografted wounds (92.9%).

For wounds treated with SoC procedures, 60/313 wounds (27.4%) were closed by an autograft and graft take was recorded for 56/60 autografted wounds (93.3%).

Results - Data Evaluation:

Primary Endpoints:

Pain incidence is defined as "at least 2 pain events during the debridement procedure, from start of treatment until end of soaking period, 2 hours post-NexoBrid® removal with subsequent pain medication".

The pain incidence rate of 0.6% lies below the given non-inferiority limit of 13.6% ($p<0.0001$).

Pyrexia incidence is defined as "temperature >38.5 °C within 48 hours from start of NexoBrid® treatment requiring fever relief medications prescribed due to high temperature within 1 hour from complaint, consecutive measurements of high temperature (>38.5 °C), 4 to 6 hours apart". The pyrexia incidence rate of 3.7% also lies below the given non-inferiority limit of 29.1% ($p<0.0001$).

Both null-hypotheses were rejected simultaneously, which indicates that the primary study objective was achieved at a significance level of $p<0.025$. Thus, it can be concluded that the applied risk-minimisation measures are effective.

Key-Secondary Endpoints:

Wound infection is defined as "prescription of antibiotics during the first week following debridement with NexoBrid® to a patient captured with positive swabs and/or positive wound biopsies performed".

The wound-infection incidence rate of 7.3% lies below the given non-inferiority limit of 15.2% ($p<0.0051$) providing evidence that the rate did not exceed the incidence rates observed in previously conducted clinical trials before implementation of risk-minimisation measures.

Total compliance (definition see Section 11.2.2) with NexoBrid® educational material was recorded in 79.9% patients [95%-CI: 72.9; 85.7] patients, based on available study data. The observed rate is consistent with the predefined desired rate of 80%.

The compliance rates for each criterion (each required procedure from the educational material) were 93.9% for pain managed before applying NexoBrid®, 79.2% for pain managed before removing NexoBrid®, 52.7% for antibacterial soaking applied before NexoBrid®, and 57.8% for antibacterial soaking applied after NexoBrid®.

Risk-Factor Analyses:

Univariate risk-factor analyses identified burn %TBSA ($p < 0.0001$), Tobiasen's Abbreviated Burn Severity Index ($p < 0.0001$), and off-label treatment ($p = 0.0003$) as potential risk factors for wound infection, but a statistically relevant influence of the variables on the incidence of wound infection was not confirmed in the final multivariate logistic regression model. The p value and the estimate for off-label treatment ($p = 0.0931$) suggests that off-label treatment may be associated with higher wound infections.

Additional Secondary Endpoints:

Among NexoBrid-treated patients, severe irritations were observed in no patient (0.0%), allergic reactions in 1/164 patient (0.6%), cardiopulmonary events in 7/164 patients (4.3%) mostly patients above 40 years old, wound-related complications in 2/164 patients (1.2%), severe blood loss (reported as blood transfusions

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captured during the treatment procedure). in 8/164 patients (4.9%), and off-label treatment of NexoBrid® in 32/164 patients (19.5%).

Off-Label application of NexoBrid® was due to treatment of facial/perineal/genital burns (8.5% patients), application at wounds representing >15 %TBSA in one session (6.1% patients), repeated application in more than one session (5.5% patients), and treatment of children (2.4% patients).

All treated patients were discharged from hospital after a mean time of 24.9 ± 24.6 (median 17.5) days.

The median time to complete wound closure was 42.0 days at the patient level (closure date of patient's last-closed wound) and 39.0 days on the wound level (date of wound closure), regardless of the treatment modalities (NexoBrid or SoC). Assessment of wound closure was done in many cases after hospital discharge, so earlier wound closures could not be captured in real time, but only during the next follow-up visit, and the frequency of follow-up visits is not standardised between sites or countries.

<u>All Adverse Events (Overview):</u>

In total, 582 AEs in 119/164 patients (72.6%) were recorded, including 68 AEs in 33/164 patients (20.1%), which started before initiation of NexoBrid® treatment, and 514 AEs in 119/164 patients (72.6%), which started after initiation of NexoBrid® treatment. No recorded AE was fatal.

Severity was assessed as mild for 219 AEs, moderate for 268 AEs, and severe for 86 AEs, and unknown for 9 AEs. The highest incidences of severe AEs were observed for "general disorders and administrative site conditions" (36 AEs) and "infections and infestations" (10 AEs).

For relationship to treatment for 65 AEs in 47/164 (28.7%) patients, the investigators assumed a relationship of at least possible to the NexoBrid® application. Related AEs most frequently observed were attributed to "general disorders and administration site conditions" (49 AEs, of which 35 AEs were pain and 11 AEs were pyrexia).

The seriousness of 97 SAEs was documented in 35/164 (21.3%) patients. SAEs most frequently observed were attributed to "infections and infestations" (22 SAEs), "general disorders and administration site conditions" (21 SAEs, of which 16 SAEs were impaired healing), and "injury, poisoning and procedural complications" (13 SAEs). For 5 SAEs in 3/164 (1.8%) patients, the investigators defined a relationship of at least possible to the NexoBrid® application.

<u>Adverse Events With Onset After NexoBrid® Application:</u>

Overall, 514 AEs in 119/164 patients (72.6%) comply with the above condition. The AEs most frequently observed were attributed to "general disorders and administration site conditions" (231 AEs, of which 130 AEs were pain, 66 AEs were pyrexia, 28 AEs were impaired healing), "infections and infestations" (72 AEs, of which 15 AEs were wound infection, 12 AEs were pneumonia, "skin and subcutaneous tissue disorders" (29 AEs, of which 20 AEs were pruritus), "injury/poisoning/procedural complications" (28 AEs, of which 14 AEs were graft loss), "gastrointestinal disorders" (26 AEs, of which 14 AEs were nausea), and "psychiatric disorders" (25 AEs, of which 10 AEs were delirium).

<u>Adverse Events Within 72 Hours After NexoBrid® Application:</u>

In total, 217 AEs in 100/164 patients (61.0%) comply with the above condition. The AEs most frequently observed were attributed to "general disorders and administration site conditions" (85 AEs, of which 54 AEs were pain, 23 AEs were pyrexia), "infections and infestations" (25 AEs, of which11 AEs were pneumonia), "psychiatric disorders" (21 AEs), "gastrointestinal disorders" (18 AEs, of which 11 AEs were nausea), and "injury, poisoning and procedural complications" (10 AEs).

<u>Related Adverse Events Within 72 Hours After NexoBrid® Application:</u>

52 AEs in 42/164 patients (25.8%) comply with the above condition. The AEs most frequently observed were attributed to "general disorders and administration site conditions" in 37/164 patients (22.6%) for 40 AEs, i.e. pain (30 AEs) and pyrexia (10 AEs).

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Related Serious Adverse Events Within 72 Hours After NexoBrid® Application:

A relationship to the NexoBrid® application was assessed as related for 2 SAEs (pain) in 2/164 patients (1.2%).

Vital Signs:

All median values of vital signs decreased from hospital admission to discharge (absolute changes): systolic/diastolic blood pressure by -6.0/-3.5 mmHg, pulse rate by -4.0 beats per minutes, and body temperature by -0.05 °C.

Conclusion:

The main goal of this study was to assess the effectiveness of the risk-minimisation measures based on the incidence rate of pain and pyrexia (primary key endpoints) in burn patients treated with NexoBrid® reported in the first two years from product launch in each participating country in routine clinical practice.

The incidence rates of both primary efficacy variables were below their pre-defined non-inferiority limits (both at $p < 0.0001$) indicating that the incidence rates of pain and pyrexia in the study did not significantly exceed the incidence rates in prior clinical trials and proving that the applied risk-minimisation measures are efficient.

The incidence rate of the key-efficacy variable wound infection was below its pre-defined non-inferiority limit ($p = 0.0051$), which provides evidence that the incidence of wound infections in the study did not exceed the appropriate incidence rate in prior clinical trials.

Physicians were in total compliance with the educational material in 131/164 patients (79.9%) [95%-CI: 72.9; 85.7]. The observed rate is consistent with the predefined desired rate of 80% based on available study data. Total compliance was assessed to have occurred when antibacterial soaking was applied to all wounds before and after NexoBrid® application and pain was adequately controlled before NexoBrid® application and before NexoBrid® removal. Comparing compliance rates for each criterion separately, it was found that the partial compliance rates differed greatly. Higher compliance rates were observed for pain management before application / removal of NexoBrid (93.9% / 79.2%, respectively) versus lower compliance rates for applying antibacterial soaking before / after application of NexoBrid® (52.7% / 57.8%, respectively). Nevertheless, higher percentages of missing data were found for antibacterial soaking and therefore the difference in compliance rates may be due to missing data and not entirely due to actual incompliance.

For the secondary variables assessed, events of severe irritation were not recorded in any patient. Events of allergy and wound-related complications were recorded in 1 and 2 patients, respectively. Overall, the reported rates of cardiopulmonary and severe blood loss events were well below the rates reported in the literature for burn patients (3,4,6,7,10,11,13).

Data was collected in the study retrospectively and was based on chart reviews. This design, as discussed in the study protocol, has many limitations. These limitations resulted, as expected, in higher percentages of missing data in comparison with prospective, well-controlled clinical studies, which was handled with additional sensitivity analyses.

Furthermore, it was anticipated in the protocol that retrospectively collected data, especially for parameters that are being reported in routine practice and might result from the disease condition itself rather than from the use of NexoBrid® (e.g. adverse events), may be difficult to interpret. This concern was addressed by defining relevant windows and guidelines for adverse events reporting (i.e. specific timeframes during and after treatment) and specific causality assessment. In addition, while in controlled clinical studies, patients are debrided only per their randomisation arm (NexoBrid® or SoC), in this retrospective, data-collection study, patients were treated with mixed modalities, resulting in uncertainties regarding the interpretation of the relatedness of an event to the NexoBrid® treatment.

The AE profile observed in this study was comparable to the profile reported in the Summary of Product Characteristics (SmPC). However, as anticipated due to the study design limitations, a higher number of AEs were reported as compared with the observed rate in clinical studies; in this study, 3.5 events were reported on average per patient, while in MW2004-11-02, 1.7 events were reported on average per patient. 514 AEs were found in 119/164 patients (72.6%), which started after the first NexoBrid® application.

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The post-treatment AEs that were most frequently assessed as related to NexoBrid® treatment were pain and pyrexia. Pain is a well-known entity in deep partial thickness and full-thickness burn patients appearing during the burn treatment and healing period (1,14,16). According to the data collected in this study, only one patient suffered from pain during the NexoBrid® treatment (repeated patient's complaints followed by prescription of pain management medications). The majority of pain AEs reported in the first 72 hours were post-NexoBrid® treatment and not procedural pain.

The events reported as pain AEs after NexoBrid® treatment did not comply with a consistent definition as usually done in controlled trials or as it is clearly defined for the primary endpoint in this study, and it was based on retrospective assessment of the patient's records a few years after the patient was discharged from the hospital. Most of the pain AEs that were assessed as related to NexoBrid® treatment did not consist of the minimal defined criteria to be included as cases for the primary endpoint of pain AEs (at least 2 pain events during the debridement procedure, from start of treatment until end of soaking period, 2 hours post-NexoBrid® removal with subsequent pain medication).

NexoBrid® educational material does not refer to pain management post treatment. The latter is done according to the site's standard practice for pain management. Indeed, investigation of the data revealed that most of the pain AEs (25/30 pain AEs, 83.3%) reported after NexoBrid® treatment were from 4/14 sites (2 sites in Germany, 1 site in Belgium, and 1 site in Spain) that consisted of 48.8% of all patients enrolled into the study. Each of these 4 sites reported 5 to 8 pain AEs in 21.4% to 57.1% of patients at each site, while in all other 10 sites, the frequency of AEs of pain in 72 hours post treatment ranged between 0 to 2 pain events per site.

Pyrexia is a well-known phenomenon in burn patients. The burn patient is catabolic, with a very high basal metabolic rate (BMR), and often has elevated body temperature. The rate of AEs of pyrexia assessed as related (6.1%) after implementation of risk-minimisation measures (use of effective analgesic medications prior to NexoBrid® treatment and prior to removal of NexoBrid®, and antibacterial soaking before and after NexoBrid® treatment) is well below the observed rate of 19.1% [range from 12.9% to 27.4%], reported for NexoBrid® in clinical trials.

No wound infection was reported as an AE related to NexoBrid®.

Overall, the training program for implementation of risk-minimisation measures was found to be effective, with comparable incidence rates of reported pain and pyrexia events. For key-secondary variables, incidence of wound infection and physicians' compliance with educational materials, the results further confirm the conclusion that the training program is effective. For all data collected for the secondary variables, no safety concerns were raised, and the overall incidence rates were below the reported ones in the literature (for the variables that incidence rates from literature is available for comparison).

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3.1 In-Text Tables

3.2 In-Text Figures

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

In-Text Table 1: Abbreviations and Terms

Term	Abbreviation	Definition
Acquired Immune Deficiency Syndrome	AIDS	-
Acute Respiratory Distress Syndrome	ARDS	-
Adverse Event	AE	-
Alkaline Phosphatase	AP	-
Anatomical Therapeutic Chemical (WHO-DDE)	ATC	Classification system grouping substances with respect to their inherent properties. Levels 1 to 4 are implemented in WHO-DDE.
Basal Metabolic Rate	BMR	-
Beats per Minutes	BPM	-
Blood Pressure Systolic / Diastolic	RR sys/dia	-
Body Mass Index	BMI	-
Carbon Monoxide	CO	-
Case Report Form	CRF	-
Chronic Obstructive Pulmonary Disease	COPD	-
Clinical Data Management System	CDMS	-
Clinical Database	CDB	-
Clinical Research Associate	CRA	-
Clinical Research Organisation	CRO	-
Committee for Medicinal Products for Human Use	CHMP	Committee of the European Medicines Agency involved in the centralised procedure for the authorisations of medicines in the EU.
Confidence Interval	CI	-
C-Reactive Protein	CRP	-
Data Cleaning Plan	DCP	-
Data Review Meeting	DRM	-
Ear / Nose / Throat	ENT	-
Electronic Case-Report Form	eCRF	-
European Union Electronic register of Post-Authorisation Studies	EU PAS Register	-
Good Pharmacovigilance Practices	GVP	-
Haematocrit	Hct	-
Haemoglobin	Hb	-
Identification Number	ID <no.>	-
Independent Ethics Committee	IEC	Independent body responsible to review clinical investigations to protect the rights, safety, and well-being of subjects participating in a clinical investigation.
Informed Consent Form	ICF	-
Intensive Care Unit	ICU	-
Marketing Authorisation Holder	MAH	Company, firm, or non-profit organisation that has been granted a marketing authorisation.
Mean Corpuscular Haemoglobin Concentration	MCHC	-
Mean Corpuscular Haemoglobin	MCH	-
Mean Corpuscular Volume	MCV	-
Medical Dictionary for Regulatory Activities	MedDRA	International, medical terminology dictionary.
Non-inferior	NI	-
Packed Red Blood Cells	PRBC	-

Term	Abbreviation	Definition
Patient Information Leaflet	PIL	Patient-friendly version of the SmPC, which is included in the pack with a medicine.
Pharmacokinetic	PK	-
Pharmacovigilance Risk Assessment Committee	PRAC	European Medicines Agency's committee responsible for assessing and monitoring the safety of human medicines.
Post-Authorisation Safety Study	PASS	Study carried out after a medicine has been authorised to obtain further information on a medicine's safety, or to measure the effectiveness of risk-management measures.
Preferred Term (MedDRA)	PT	Distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic.
Qualified Person Pharmacovigilance	QPPV	-
Red Blood Count	RBC	-
Risk Management Plan	RMP	-
Safety-Evaluation Set	SES	Data set of all subjects, who were enrolled in the PASS and had no major protocol deviations.
Serious Adverse Event	SAE	-
Serum Glutamic-Oxaloacetic Transaminase	SGOT	-
Serum Glutamic-Pyruvate Transaminase	SGPT	-
Source Data Verification	SDV	-
Standard Deviation	SD	-
Standard of Care	SoC	-
Statistical Analysis Plan	SAP	-
Statistical Analysis Software System	SAS	-
Summary of Product Characteristics	SmPC	Legally approved document as part of the marketing authorisation; basis of information for healthcare professional on how to use a medicine.
System Organ Class (MedDRA)	SOC	Group of related high-level group terms based upon aetiology, manifestation site, purpose, product issues, and social circumstances.
Tables, Figures, and Listings	TFL	Statistical output package consisting of all summary tables, raw data listings, and figures.
Total Body Surface Area	TBSA	-
Unknown	UNK	-
World Health Organisation Drug Dictionary Enhanced	WHO-DDE	International dictionary for coding of medicinal products.

5 ETHICS AND REGULATORY REQUIREMENTS

5.1 Ethics and Regulatory Requirements

This study was conducted in accordance with the ethical principles having their origin in the Declaration of Helsinki and with applicable laws and regulations of the participating countries.

Prior to start of the data collection, the responsible independent ethics committees (IEC) were asked for favourable opinions, and they were provided with all study protocol amendments for review and notified, as stipulated in their guidelines.

The study protocol and SAP were reviewed and approved by the Pharmacovigilance Risk Assessment Committee (PRAC) prior to study commencement. In countries, where an approval from a regulatory authority was required by local laws or regulations, the study was submitted to the local authorities.

All required legal study approvals and favourable ethics opinions were obtained before starting patient data screening and collection.

5.2 Patient Safety

The study is non-interventional. Participation in this study was not associated with any additional risks to study participants.

Burn-wound management of each patient was performed according to routine clinical practice of each participating specialist or burn centre, and the indication for use of NexoBrid® should have been in accordance with the approved SmPC (without being influenced by this protocol) and with the medical training for implementation of risk-minimisation measures that was performed by the sponsor at all burn centres before study initiation.

The protocol did not request any additional procedures beyond routine clinical practice.

5.3 Patient Informed Consent

All potential study patients, treated with NexoBrid® at the participating study sites during the first 2 years from NexoBrid launch and discharged from the hospital, were contacted and asked to participate in the study.

The informed consent procedure was performed in accordance with the local regulatory requirements for non-interventional, retrospective data collections. In countries where consent must be given in writing, patients should have been given enough time to read the informed consent form and to ask additional questions. Consent process was documented in each patient's study specific records.

In case of paediatric subjects, the informed consent form for parents was signed by the parents or legal representative. Minor subjects, who could read and understand an informed consent, signed a separate assent form designated for children, according to the child’s age (under or over 14 years old).

For incapacitated subjects, the informed consent form was signed by the patient's legal representative. Subjects, who could read and understand the informed consent document, could provide their consent on that form on a separate signature line.

Upon consent to participate, the patients were explicitly informed about the following topics:

- no additional procedures were planned to be performed,
- the study is a retrospective data collection of the past NexoBrid® treatment and the routine burn-wound management,
- the study data is recorded and evaluated,
- the patient's medical records may be accessed by members of competent authorities or authorised representatives of the sponsor / contract research organisation (CRO) in the extent permitted by applicable national laws and regulations,
- the participation in the study is voluntary.

Once written/oral (according to IEC approval in each site) consent was given, a patient was enrolled in the study, and the retrospective data collection could be initiated by the study site staff.

5.4 Data Privacy

Patient medical information obtained during this observational data collection is handled as strictly confidential, and disclosure to third parties other than those mentioned in the study protocol was prohibited.

All collected study data was entered in an electronic case-report form (eCRF). The design of the eCRF ensured that all entered data was pseudonymised and could be identified only by patient's number throughout the entire data collection and during all statistical analyses.

The collected study data is available for the sponsor 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 are maintained by the investigator only.

6 STUDY ADMINISTRATIVE STRUCTURE

6.1 Study Sites

Centres were chosen in West and East European countries based on the launch date of NexoBrid®, number of burn centres in each country, and the number of patients treated in the first two years from launch date. Around one third of the launch sites in each chosen country were approached, preferably sites with data on at least 5 patients in the first two years from product launch.

The patients' consent rate was estimated to be less than 50% of approached patients.

For each participating country, a coordinating investigator was appointed, if requested by the authorities.

For the list of study sites, please refer to Section 9.9.7.3.

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7 INTRODUCTION

Since 1985, 467 study subjects (adults and paediatric subjects) have been exposed to NexoBrid® within the global clinical development program, under rigorous evaluations of 8 clinical studies conducted globally. In addition, since NexoBrid® has been launched in Europe in 2012, more than 4500 subjects have been treated with the marketed product, and NexoBrid® has become a SoC in many EU burn centres (5,9).

The product consists of a sterile lyophilised powder and a sterile gel that following reconstitution is applied topically on the burn areas for 4 hours.

Pain, pyrexia, and wound infection were identified as risks by MediWound during early clinical development. There were four corrective measures that were implemented in later clinical studies - effective analgesic medications prior to NexoBrid® treatment and prior to removal of NexoBrid®, antibacterial soaking before and after NexoBrid® treatment - and these resulted in a significant decrease in the incidence rates, which were comparable to SoC.

The rates of AEs of interest observed in the early clinical trials without risk-minimisation measures (MW2001-10-03 and MW2002-04-01) and in the late trials with risk-minimisation measures (MW2004-11-02 and MW2005-10-05) in the NexoBrid® group are presented below and compared to the rates in the SoC group in the late clinical trials:

In-Text Table 2: AE of Interest Observed in the Early and Late Clinical Trials: Rate, 95%-Score-Confidence Interval

AE of Interest	Clinical Trials Without Risk Minimisation		Clinical Trials With Risk Minimisation	
	NexoBrid® Treatment	SoC Treatment	NexoBrid® Treatment	SoC Treatment
Pain	23.3% [15.8%; 33.0%]	11.4%	3.6% [1.4%;8.9%]	4.0%
Pyrexia	34.4% [25.4%;44.7%]	18.6%	19.1% [12.9%;27.4%]	15.8%
Wound infection[1]	7.8% [3.8%; 15.2%]	5.7%	8.2% [4.4%; 14.8%]	7.9%

Source: SAP, Section 2.7.1

Similar corrective procedures were implemented in the risk-management plan for NexoBrid®, and an "educational pack" for health-care professionals was distributed to all physicians using NexoBrid in clinical practice. The educational pack consists of the summary of product characteristics (SmPC), the patient information leaflet (PIL), educational materials, and an in-person training programme. The educational material and the training program are very similar in all EU countries.

The current observational study assessed the effectiveness of the risk-minimisation measures based on the incidence rate of identified risks in routine clinical practice, primarily focussing on pain and pyrexia (primary endpoints) and on the physicians' compliance with the educational material instructions and the incidence of wound infection during the 1st week following debridement (key-secondary endpoints).

The aim of the risk-minimisation measures is to achieve comparable incidence rates in routine clinical practice to those obtained in clinical trials after implementation of the risk-minimisation measures.

For further background information with respect to the study treatment, the study design (including its inherent limitations), and the risk-minimisation measures, please refer to the study protocol 04-Jan-2018, sections 7.1, 7.2, 7.3, and 9.9 (list of basic study documents in Appendix 16).

1 The effect of the risk-minimisation measures could not be established in the later clinical trials because infection rates were similar in early and late studies. Thus, this endpoint is not appropriate to assess the effectiveness of the risk-minimisation measures in routine clinical practice. Nevertheless, NexoBrid® was not associated with a higher incidence of infections and the observed rates in the NexoBrid® group were similar to those in the control groups.

8 STUDY OBJECTIVES

Primary Objectives:

The main goal of this study was to assess the effectiveness of the risk-minimisation measures based on the incidence rate of pain (during the debridement procedure with NexoBrid®) and pyrexia (within 48 hours from start of NexoBrid® treatment) reported in routine clinical practice, during the first two years following product launch in each participating country in routine clinical practice.

Pain and pyrexia were identified as sensitive to the risk-minimisation measures, as the incidence rates of pain and pyrexia AEs in clinical studies before risk-minimisation measures were relatively high and the effect of reduction by the risk-minimisation measures was unequivocally pronounced.

The incidence rates of pain and pyrexia (primary endpoints) were to be investigated in routine clinical practice of NexoBrid use in the first two years from product launch and compared to those obtained in clinical trials after implementation of risk-minimisation measures.

Secondary Objectives:

Secondary objectives were evaluated based on pre-defined secondary endpoints.

The study design distinguishes between key-secondary endpoints and other secondary endpoints. Key-secondary endpoints were "compliance of the physician with the educational material instructions" and "incidence of wound infection during the 1st week following debridement".

The primary, key-secondary, and other secondary endpoints are defined in section 9.7.1.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design

The study was a multi-centre, observational, retrospective, study-data collection (patient's medical chart review) on patients treated with NexoBrid® in routine clinical practice.

The incidence rates of pain, pyrexia, and wound infection in routine clinical practice were compared with the results of the previously conducted clinical trials MW2005-10-05 and MW2004-11-02 following the implementation of risk-minimisation measures.

Fifteen burn centres in Western and Eastern Europe were asked to participate in the observational study and were contracted. All participating study sites received the training program for implementation of risk-minimisation measures within the frame of regular product launch.

All required legal study approvals and favourable ethics opinions were obtained before patient screening and data collection.

The investigators contacted their potential study patients by telephone to inform them about the study. Patients willing to participate were either invited to come to the study site to receive further information and to sign an informed consent form (ICF) or received the ICF via mail, and the signed informed consent form was received from the patient by correspondence. The ethics committees in two sites in Spain (site 502 in Barcelona and site 504 in Zaragoza) allowed obtaining oral consent without written consent from the patients to participate in the study. The oral consent process for these patients was documented by the investigator.

Once consent was given, the data collection could be initiated.

All study data was entered by the site personnel in an eCRF for clinical data management (plausibility checks, query management, data reconciliation) and final statistical analysis. This clinical study report refers to the final statistical output.

9.2 Study Design Rationale

NexoBrid® has been approved for removal of eschar in adult patients with deep partial and full-thickness thermal burns in Europe since December 2012. The product consists of a sterile lyophilised powder and a sterile gel that following reconstitution is applied topically on the burn areas for 4 hours after which wound management procedures commence according to standard practice applicable in the burn centre.

In prospective phase II and phase III studies, three areas of risks (pain, pyrexia, wound infection) were identified and corrective measures (preventive analgesia as routinely practiced before dressing changes in burn patients prior to NexoBrid® treatment and before removing NexoBrid®, and antibacterial soaking prior to and after NexoBrid® treatment) were successfully implemented and significantly decreased the risk-incidence rates.

Given the experience from the clinical trials, the incidence rates of pain and pyrexia AEs before risk-minimisation measures were relatively high and the effect of reduction by the risk-minimisation measures was clearly pronounced. Therefore, these health outcomes are considered sensitive to risk-minimisation measures and the primary objective of this study focuses on these risks.

The effect of the risk-minimisation measures on incidence of infection could not be established in the later clinical trials, because infection rates were similar in early and late studies and were comparable to SoC. Thus, this endpoint is not appropriate to use to assess the effectiveness of the risk-minimisation measures in routine clinical practice. Nevertheless, NexoBrid® was not associated with a higher incidence of infections, and the observed rates in the NexoBrid® group were like those in the control groups. Wound infection was declared as key-secondary endpoint to emphasise its clinical relevance and importance.

Appropriate corrective procedures were implemented in the risk-management plan, and an "educational pack" for healthcare professionals (SmPC, PIL, educational material, training programme) was distributed to healthcare professionals. It was anticipated that training provided and adherence to the educational material instructions would reduce the incidence of risks of pain and pyrexia in daily practice.

The current observational study evaluates the incidences of identified risks to assess the effectiveness of the risk-minimisation measures in routine clinical practice.

For further background information with respect to the study treatment and the study design including its limitations please refer to the study protocol 04-Jan-2018, sections 7.1, 7.2, and 9.9 (list of basic study documents in Appendix 16).

9.3 Risk-Minimisation Measures

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

1. Before prescribing NexoBrid®:
   - Limit the total area that can be treated to 15% total body surface area (TBSA).
   - Be aware of the 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®:
   - Provide pain management medication.
   - Perform wound cleansing and preparation before treatment with NexoBrid®.
   - Apply a dressing soaked with an antibacterial solution for two hours before NexoBrid® application.
   - Protect the surrounding skin areas.
   - Prepare NexoBrid® and apply to the wound area according to the instruction.
3. After applying NexoBrid®:
   - Provide appropriate pain management before removal of NexoBrid.
   - Remove NexoBrid® and dissolved eschar.
   - Assess the Wound.
   - Provide wound management after NexoBrid® treatment with
     - application of a dressing soaked with an antibacterial solution for two hours,
     - performance of grafting procedures as soon as possible after debridement for wounds with areas of full thickness and deep burn.
4. Patient monitoring for any occurrence of AE.
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®.

For more details, please refer to the data management plan 21-Aug-2017 (list of basic study documents in Appendix 16).

9.4 Study Procedures

The study is an observational, retrospective, data collection from individual, in-patient records.

9.4.1 Patient Informed Consent

All potential study patients, treated with NexoBrid® at the participating study sites during the first 2 years from NexoBrid® launch and discharged from the hospital, were contacted and asked to participate in the study.

Pre-requisite for a data collection was that an informed consent of the concerned subject (study patient) should be on file before start.

For further details, please refer to section 5.3.

9.4.2 Data Collection

Existing data before informed consent, between the period of hospital admission and up to the end date (end date was defined as wound closure or hospital discharge, the latest of the two) as documented in the medical charts of the patients was used.

The following data (by categories) were collected and documented in the eCRF, if performed routinely at the participating sites and if available in the medical records.

In-Text Table 3: Data Collection by eCRF Module

Module	Study Stage / Patient Hospitalisation Stage			
Study	**Screening**	**Enrolment**	**Treatment**	**Termination**
Hospital	**-**	**Admission**	**Intensive Unit Care**	**Discharge**
Informed consent	x			
Eligibility criteria	x			
Administrative data		x	x	x
Demographics		x		
Previous diseases / conditions		x		
Previous medication / procedures		x		
Burn aetiology		x		
Co-Morbidities		x		
Laboratory assessments		x		
Wound assessment at admission		x		
Physical examinations		x		x
Vital signs		x	x	x
Concomitant diseases / conditions		x	x	x
Concomitant medication / procedures		x	x	x
Adverse events		x	x	x
Wound treatment (debridement, pain assessment during debridement, NexoBrid® application, wound assessment after debridement, coverage)			x	
Blood transfusions ≤ 24 h after debridement			x	
Pyrexia assessments ≤ 48 h after debridement			x	
Co-Morbidities ≤ 96 h after NexoBrid® application			x	
Wound culture / biopsy ≤ 7 d after debridement			x	
Wound assessments			x	

Source: eCRF Mock-Up 3.0

The following sub-sections provide an overview of all eCRF items by module:

9.4.2.1 Administrative Data

Study / Screening:

- Date of start of eCRF documentation.
- Informed consent (date, signed [yes/no], by whom [patient, legal guardians, legal representative], oral consent [yes/no]).
- Eligibility criteria (confirmation of treatment and hospital discharge, written informed consent, no participation in a NexoBrid® study before).

Hospital:

- Date and time of hospital admission.
- Date of intensive care unit (IUC) admission.
- Date of ICU discharge.
- Date and time of hospital discharge.

9.4.2.2 Demographics & Medical History

Demographics:

- Age.
- Gender (male, female).
- Race (White and 5 other categories).
- Ethnicity (Non-Hispanic or Latino, Hispanic or Latino).

Previous Medications / Procedures:

Previous medications and non-pharmacological therapies from injury until the day before first treatment with NexoBrid® were documented.

- Name of medication / procedure.
- Indication.
- Start date and time.
- Single dose.
- Unit.
- Frequency.
- Route.
- Ongoing at discharge (yes, no: stop date and time).

Burn Aetiology:

- Date and time of injury.
- Burn aetiology (7 categories).
- Inhalation injury (no, yes).
- Burn shock (no, yes).

9.4.2.3 Laboratory Assessment at Admission

- Haematology (date of blood sampling, 22 parameters).
- Serum chemistry (date of blood sampling, 21 parameters).

9.4.2.4 Wound Assessment at Admission

Overall Status:

- Total number of wounds.
- %TBSA based on all wounds.

Status by wound:

- Wound number.
- Anatomical location (13 categories).
- %TBSA.
- Depth, thickness (superficial partial, full, deep partial).

9.4.2.5 Physical Examination

Physical examination data from hospital admission and discharge was collected.

- Date of examination.
- Assessment for 10 body systems (normal, abnormal, not done) + other to be specified.

9.4.2.6 Vital Signs

At Admission:

- Height.
- Weight.
- Body-mass index (BMI).
- Malnutrition risk.

During Hospitalisation / Intensive Care:

- Body temperature.
- Blood pressure.
- Pulse.

At Discharge:

- Weight.

9.4.2.7 Medical History and Concomitant Diseases / Conditions

- Name of disease / condition.
- Start date.
- Ongoing at discharge (yes, no: stop date).

9.4.2.8 Co-Morbidities

Specific co-morbidities ("medical conditions") were documented in the eCRF. Examples were given for the three disease categories of interest:

- Impairments of the immune system:
  - Autoimmune diseases.
  - Acquired-immune-deficiency syndrome (AIDS).
  - Cancers of the immune system such as leukaemia.
  - Immune-complex diseases such as viral hepatitis.
  - Multiple myeloma.
  - Treatment with immunosuppressive drugs.
- Any allergy to pineapple or papain.
- Cardiopulmonary diseases:
  - Ischemic heart disease.
  - Valvular disease.
  - Pulmonary hypertension.
  - Chronic-obstructive-pulmonary disease (COPD).
  - Restrictive lung disease.

9.4.2.9 Concomitant Mediation / Therapies

Medication which was administered during hospitalisation was documented, namely adverse event and medical history related medication (if ongoing during hospital admission), analgesics, antibiotics including antimicrobial agents administered systemically and topically, infusion therapy, and non-pharmacological procedures related to wound recovery (concomitant therapies related to burn recovery or medical history; if ongoing during hospital admission, starting from injury until wound closure).

- Name of medication / therapy.
- Start date.
- Ongoing at discharge (yes, no: stop date).

9.4.2.10 Adverse Event

- Any AE reported (no, yes).
- Description.
- Start date and time.
- Severity (mild, moderate, severe).
- Relationship to NexoBrid® application (related, probably, possibly, remotely, not applicable, not feasible).
- Action taken with NexoBrid® (dose change, dose reduction, dose increase, interrupted, withdrawn, not applicable, unknown).
- Other action taken (none, concomitant therapy, hospitalisation, other action).
- Outcome (recovered/resolved, recovering/resolving, not recovered/resolved, recovered/resolved with sequelae, fatal, unknown).
- Seriousness (no, yes: death, life-threatening, hospitalisation, disability/incapacity, congenital abnormality/birth defect, medically significant).
- Stop date.

9.4.2.11 Wound Treatment

Data was collected from all patients' wounds, those who were treated with NexoBrid® and those with SoC treatment.

Debridement:

- Timing of debridement (start date and time, completion time).
- Eschar removed (%).
- Procedure (NexoBrid®, SoC surgical, SoC non-surgical, SoC mix-surgical & non-surgical).
- Number of NexoBrid® applications (one or two).

Pain Assessment During Debridement:

- Assessment (no, yes).
- Date and time of assessment.
- Pain scale used (numeric / visual analogue scale, other to be specified).
- Pain score.
- Pain assessment (mild, moderate, severe).
- Complaints related to pain (no, yes).
- Pain medication administered (no, yes).

Wound Assessment After Debridement:

- Changes in the assessment after debridement (no, yes: [see below]).
- %TBSA.
- Depth, thickness (superficial partial %TBSA, full %TBSA, deep partial %TBSA).

NexoBrid® Application:

- Dose of application.
- NexoBrid® mixed within 15 minutes prior to use (no, yes).
- Adhesive barrier to protect surrounding area (no, yes).
- Antibacterial soaking before NexoBrid® application (no, yes: duration).
- Pain management before NexoBrid® application (no, yes).
- Antibacterial soaking after removing NexoBrid® (no, yes).
- Pain management before removing NexoBrid® (no, yes).

Coverage:

- Date of coverage.
- Type of coverage:
  - autograft (no, yes: wound bed preparation, area covered),
  - 9 other given types (no, yes).

9.4.2.12 Blood Transfusion

- Blood transfusion performed within 24 hours from start of debridement (no, yes).
- Date of blood transfusion.
- Product (packed RBC, whole blood, FFP, platelets, cryoprecipitate, other to specify).
- Number of units.
- Volume per unit.
- Blood units given in relation to specific procedure (no, yes: NexoBrid®, surgical, non-surgical, other to specify).

9.4.2.13 Pyrexia Assessment

The study protocol provided criteria for a high body temperature:
temperature above 38.5 °C requiring fever relief medications prescribed due to high temperature within one hour from complaint, consecutive measurements of body temperatures of above 38.5 °C, 4 to 6 hours apart)

- Assessment within 48 hours from start of debridement (no, yes).
- Date and time of assessment.
- Body temperature.
- Pyrexia assessment (normal, abnormal not clinically significant, abnormal clinically significant).

9.4.2.14 Co-Morbidities

- Cardiopulmonary complications within 48 hours from start of treatment (no, yes).
- Severe irritations within 96 hours from start of treatment (no, yes).
- Allergic reactions within 96 hours from start of treatment (no, yes).

9.4.2.15 Wound Culture / Biopsy

Culture:

- Culture performed within 7 days after start of debridement (no, yes).
- Date and time of biopsy.
- Result (negative, positive: specification of bacteria).
- Assessment (normal, abnormal not clinically significant, abnormal clinically significant).

Biopsy:

- Biopsy performed within 7 days after start of debridement (no, yes).
- Date and time of biopsy.
- Result (positive, negative).
- Assessment (normal, abnormal not clinically significant, abnormal clinically significant).

9.4.2.16 Wound Assessment After NexoBrid® Application / Wound Closure

- Assessment performed until wound closure (no, yes).
- Date of assessment.
- Wound area epithelialised or closed by graft.
- Wound closed (no, yes).
- Wound closed by graft (no, yes).
- Did the graft take (no, yes).

9.5 Study Population

Patients who received NexoBrid® treatment according to the hospital routine in participating specialist-burn centres were enrolled into the study.

Patients treated in NexoBrid® clinical studies were not included.

9.5.1 Subject Recruitment

The option to participate in the study was offered consecutively (patients were contacted in the same order as they were treated, from the first treated patient to the latest) to all subjects treated with NexoBrid® for debridement of burn wounds in the time frame of two years from launch at each participating site (irrespective of their age, wound location, or extent; patients treated in NexoBrid® clinical studies were not included).

Investigators contacted NexoBrid®-treated patients, who were discharged from the hospital, by telephone to inform them about the non-interventional, retrospective study. In sites for which consent should be given in writing, patients were invited to either come to the study site to receive further information and to sign an informed consent form, or the informed consent form was sent by mail to be signed and returned to the site. In sites for which consent could be obtained orally (as pre-approved by local ECs) without written consent, the oral consent process for these patients was documented by the investigator.

All patients who were offered the opportunity to take part in the study were reported on a subject screening log. For patients not taking part in the study, a reason for non-inclusion was stated.

In case of discharge of the patient prior to wound closure, it could have occurred that the patient was examined elsewhere. In such a case, the site should have contacted the respective treating physician to follow up on wound closure results and possible adverse events to avoid missing data, if documentation of these was available (photos, written documentation) for the study records.

9.5.2 Inclusion Criteria

Patients eligible for retrospective data collection should fulfil the following criteria:

1. Patients treated with NexoBrid®.
2. Signed written informed consent or oral consent approving data collection according to ethics-committee requirements.

9.5.3 Exclusion Criteria

1. Patients treated in NexoBrid® clinical studies.

9.5.4 Subject Information & Informed Consent

See section 5.3.

9.6 Treatment

Concentrate of proteolytic enzymes enriched in bromelain:
ATC code D03BA03, trade name NexoBrid®.

Administration according to SmPC / leaflet.

9.7 Variables for Assessment

9.7.1 Primary Variables

- Incidence rate of pain during the treatment procedure (repeated patient's complains with subsequent pain medication).
- Incidence rate of pyrexia within 48 hours from start of treatment (temperature above 38.5ºC requiring fever relief medications prescribed due to high temperature within 1 hour from complaint or consecutive measurements of high temperature (above 38.5ºC), 4 to 6h apart).

9.7.2 Key-Secondary Variables

- Compliance of the physician with the educational material instructions.
  (The physician's compliance refers to the criteria, whether antibacterial soaking before and after NexoBrid® application was performed and an adequate pain management/administration of analgesia/sedation medication was prescribed to the patient before applying and removing NexoBrid®.)
- Incidence of wound infection during the 1st week following debridement (prescription of antibiotics during the first week following debridement with NexoBrid® to a patient captured with positive swabs and/or positive wound biopsies performed).

9.7.3 Secondary Variables

- Overall incidence of reported AE.
- Incidence of severe irritation and/or allergic reaction events captured within 96 hours from start of treatment (suggested timeframe is based on PK data demonstrating that most of the drug is eliminated from patients' blood at 24 hours).
- Incidence of cardiopulmonary events captured within 48 hours from start of treatment.
- Incidence of other wound-related complications (related to NexoBrid®) captured during patient's hospitalisation.
- Time to complete wound closure.
- Proportion of NexoBrid® patients treated off-label (facial burns, perineum/genital burns, wounds >15 %TBSA treated in one session).
- Incidence of severe blood loss captured during the treatment procedure (reported as blood transfusions).
- Time to hospital discharge.

9.7.4 Safety Variables

Adverse events were identified in the medical documentation, if they occurred in the period between hospital admission and up to wound closure or hospital discharge, the latest between the two (end date).

All identified adverse events were categorised by seriousness, severity, and causality based on the definitions below.

AEs were assessed retrospectively, at the time of data collection for the study and not in due time.

AE Definition:

An AE is any untoward medical occurrence in a patient or clinical-investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated (defined by a reasonable possibility that the event may have been caused by the investigational drug) with the use of a medicinal (investigational) product, irrespective of the relationship with the medicinal (investigational) product.

AE Seriousness Definitions:

A SAE is an event that is
- Fatal,
- Life-threatening,
- Results in persistent or significant disability/incapacity,
- Requires or prolongs inpatient hospitalisation,
- Is a congenital anomaly or birth defect, or
- Is a medically important event.

AE Severity Definitions:

A mild AE is one that the symptoms are barely noticeable to a patient. It does not influence performance or prevents a patient from carrying on with normal life activities.

A moderate AE is one that the symptoms make a patient uncomfortable and causes some impairment to normal life activities. Treatment for symptoms may be required.

A severe AE is one that the symptoms cause severe discomfort to a patient and severely limits the patient's normal daily activities. Treatment for symptoms is given.

AE Causality Definitions:

AE is not related, if one of the following assessments apply:
- 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, or
- not feasible.

AE is related (= adverse drug reaction), if one of the following assessments apply:
- 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 aetiology may be responsible for the event. The effect of drug withdrawal is unclear. Re-challenge 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. Re-challenge information is not available or advisable.
- (definitely) 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.

9.8 Quality Assurance

9.8.1 Project Management

The sponsor's vendor CATO Europe GmbH was contracted to oversee, coordinate, and assess the study.

The sponsor had 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). Potential reasons for premature study termination could have been failure of the investigator to comply with the study protocol or legal requirements or poor quality of data records that do not enable proper collection of the data required for the study.
If suspension or premature termination would have occurred, the terminating party should have justified its decision in writing and promptly informed the other parties. If for any reason, the marketing authorisation holder (MAH) would have suspended or prematurely terminated the data collection at a single site or the entire study, the responsible IEC should have been notified.

No suspension or premature termination occurred during this study.

9.8.2 Clinical Monitoring

The sponsor's vendor CATO Europe GmbH was contracted for clinical monitoring, which comprised on-site source data verification and remote monitoring.

All site staff was trained on the eCRF and the data-collection requirements prior to the initiation of study data collection.

During on-site monitoring visits, the eCRF data was compared with medical records of corresponding patients by clinical research associates (CRA) at each study site (= source data verification).

On-site clinical monitoring with source data verification (SDV) was performed in an extent of 100% for the first documented patient at each site and for all signed ICFs. Monthly remote monitoring was performed for each active study site, which had entered data into the eCRF. Depending on the results of remote monitoring, on pre-defined risks, and on the enrolment rate, additional on-site monitoring visits could be performed at the study sites including targeted SDV. Co-monitoring visits were not performed by the sponsor.

The following parameters triggered additional on-site 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).

9.8.3 On-Site Procedures

Each participating study site had to receive the training program for implementation of risk-minimisation measures within the frame of regular product launch. The training program was similar in all EU countries, approved by national competent authorities, and followed the EU RMP approved by the CHMP.

In addition, all site study personnel entering data into the eCRF were instructed before study initiation about specific parameters and guidelines supporting reporting of specific events such as pain and pyrexia.

No data should have been directly entered in the eCRF without source documentation, excluding retrospective assessment of seriousness, severity, and causality of AE. Source documents were defined as primary source of documentation belonging to the study patients.

9.8.4 Data Management

The sponsor's vendor X-act Cologne Clinical Research GmbH was contracted for clinical-data management and provision of the clinical data management system (CDMS).

The vendor prepared a data management plan (DMP) describing all data management activities. For more details, please refer to the data management plan 21-Aug-2017 (list of basic study documents in Appendix 0).

All study data was entered and hosted in a fully validated CDMS via a web-based, eCRF user interface. The CDMS included automatic logic checks (online checks) on data consistency and an audit trail.

The vendor had to check the study data in the CDMS for validity according to the data specifications and grammatical correctness (off-line checks) as scheduled. Off-line checks were programmed in the Statistical Analysis System (SAS®) Version 9.3 or higher, and feedback to the study sites in case of questions was to be provided via queries in the eCRF. Data management has also checked, whether manually posted queries as well as queries triggered by edit checks within the eCRF were resolved correctly.

Quality checks of the clinical database (CDB) were divided in two types: the complete quality check was a 100% check of the study-specific critical data to ensure that this data was free of errors. The sample quality check was defined as the check of non-critical data of at least 10% of the treated subjects of a randomly drawn sample of subjects.

The quality check of the CDB was performed in reasonable batches. Data of the following modules were considered critical: demographics, informed consent, aetiology of burn, burn wound description, assessment 48/96 hours from start of treatment with NexoBrid®, pain assessment, pyrexia assessment, blood transfusion, burn description per wound, treatment, wound assessment after debridement, wound biopsy, wound culture, wound closure, adverse events.

The vendor prepared a data-clarification plan (DCP) describing all checks by data management. For more details, please refer to the DCP 2.0, 14-May-2018.

Coding of AE data, medical histories, and diagnoses were done with MedDRA 21.0, coding of previous and concomitant medications with WHO-DDE March 2017.

9.8.5 Biostatistics

The sponsor's vendor X-act Cologne Clinical Research GmbH was contracted to analyse the data.

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

All variables and derived parameters were individually compiled in data listings. Summary tables with descriptive and inferential statistics are provided for the primary and secondary variables as well as for other variables concerning demographics and baseline characteristics.

Planned quality checks of the statistical analysis included source code review and double programming of the primary efficacy endpoints.

Before database lock, a data review meeting was performed to make a final decision about the subject population or outcome allocation and whether an update of the planned analysis was required. Please refer to the SAP for more details.

All details of the planned analyses are provided in the statistical analysis plan (SAP) 22-May-2018 (list of basic study documents in Appendix 0), in the mock tables/figures/listings (TFL), and the minutes of the data review meeting (DRM) held on 10-Jan-2019. Database lock was performed on 23-Jan-2019.

Further details see section 9.9.

9.8.6 Pharmacovigilance

The sponsor's EU Qualified Person Pharmacovigilance (QPPV) was involved in the revision process of the study protocol and in the results of the statistical analyses.

No SAE was to be reported to the sponsor's pharmacovigilance department. Instead, the vendor sent an AE listing with identified SAEs to the sponsor's pharmacovigilance department twice, on 29-Jun-2018 and on 02-Nov-2018. The final AE listing was provided with all study listings after data entry was complete.

9.8.7 Audits

No internal audits were performed by the sponsor.

9.9 Statistical Methods and Determinations

9.9.1 Study Hypothesis

The following hypothesis was tested to assess the effectiveness of the risk-minimisation measures 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 measures were implemented by a clinically relevant amount.

To reject the null hypothesis, the following two null hypotheses had to be rejected simultaneously:

1. Pain: the incidence rate of pain (repeated patient's complaints followed by prescription of pain management medications) 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 measures were implemented (3.6%) by a clinically relevant amount of 10%.
2. Pyrexia: the incidence rate of pyrexia (temperature above 38.5 ºC requiring fever relief medications prescribed due to high temperature within 1 hr from complaint or consecutive measurements of high temperature (above 38.5 ºC), 4 to 6 hrs apart 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 measures were implemented (19.1%) by a clinically relevant amount of 10%.

9.9.2 Sample Size Calculation

The incidence rates of pain, pyrexia (primary endpoints), and wound infection AE (key-secondary endpoint) in the routine clinical practice after implementation of risk-minimisation measures were to be compared with the results of the previously conducted clinical trials MW2005-10-05 and MW2004-11-02.

Each primary endpoint was 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 were considered as co-primary endpoints. Only if both primary null hypotheses was rejected, the key-secondary endpoint would 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, there was no multiple-testing problem.

The sample-size calculation must 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 following.

9.9.2.1 Assumed Rates of Adverse Events and Non-Inferiority Margins

Rate of AE:

The reported AE rates in the MW2005-10-05 and MW2004-11-02 study with risk-minimisation measures were 3.6% for pain, 19.1% for pyrexia, and 8.2% for wound infection in the NexoBrid® group. The rates for the routine clinical practice were assumed to be equal with 3.6% for pain, 19.1% for pyrexia, and 8.2% for wound infection.

Non-Inferiority Margins:

The assumed non-inferiority margin was 10% for pain, 10% for pyrexia, and 7% for wound infection.

In-Text Table 4 displays the rates and corresponding 95%-score-confidence intervals of AE of interest observed in the NexoBrid® group of the clinical trials without (study type A: MW2001-10-03, MW2002-04-01) and with (study type B: MW2004-11-02, MW2005-10-05) risk-minimisation measures as well as the non-inferiority margins assumed in the current study:

In-Text Table 4: AE of Interest: Rate, 95%-Score-Confidence Interval, Assumed Non-Inferior Margin

AE of Interest	95%-Score-Confidence Interval: study type A	95%-Score-Confidence Interval: study type B	Assumed Non-Inferiority Margin
Pain	23.3% [15.8%;33.0%]	3.6% [1.4%;8.9%]	10%NI-margin
Pyrexia	34.4% [25.4%;44.7%]	19.1% [12.9%;27.4%]	10%NI-margin
Wound Infection	7.8% [3.8%; 15.2%]	8.2% [4.4%; 14.8%]	7%NI-margin

Source: SAP, Section 2.7.1

The assumed non-inferiority margins considered that the study population treated in burn centres will likely be more heterogeneous than in the clinical trials (no inclusion/exclusion criteria, other than the use of NexoBrid®). The non-inferior (NI) margins were set for the incidence rates of pain and pyrexia after corrective measures (type B).

Furthermore, the non-inferiority margin of 10% for pain ensured that, in case of rejection of the null hypothesis, the resulting 95%-confidence interval of the observed rate of adverse events did not include the lower bound of the 95%-confidence interval for the observed rate in the clinical trials without risk-minimisation measures.

In case of pyrexia, a non-inferiority margin of 10% ensured that, if the null hypothesis is rejected, the observed rate is part of the 95%-confidence interval of the rate observed in clinical trials without risk-minimisation measures. Although the confidence limits of both rates may overlap, the non-inferiority margin of 10% was chosen, since a trial with a non-inferior margin such that rejection of the null hypothesis implies non-overlapping confidence intervals would require >350 patients, which was too large.

In case of wound infection, the non-inferiority margin of 7% ensured that, if the null hypothesis is rejected, the 95%-confidence interval of the observed rate does not exceed the upper limit of the 95%-confidence interval for the rate of wound infection observed in clinical trials without risk-minimisation measures.

In conclusion, the rates of AE of interest were assumed to be equal to the rates observed in clinical trials without risk-minimisation measures, and the assumed non-inferiority margin is 10% for pain, 10% for pyrexia, and 7% for wound infection. These margins were chosen to consider that the study population might be more heterogeneous than in clinical trials and thus the rate of observed AE might be higher. Nevertheless, the non-inferiority margins established for pain and pyrexia are clinically non-meaningful ranges compared to the observed rate in clinical trials without risk-minimisation measures. In case of wound infection, since there was no difference between the rates recorded for NexoBrid® patients compared to the rates in SoC patients, this is not considered as an identified risk associated particularly with NexoBrid®, but with the severe burn condition, and thus the risk-minimisation measures are not expected to reduce the incidence rates of wound infections. Thus the sum of the assumed rate of adverse events and the non-inferiority margin corresponds to the upper limit of the 95%-confidence interval for the rate observed in clinical trials without risk-minimisation measures.

9.9.2.2 Power and Type-I-Error Rate of the Score Test

The sample size calculation was based on the score test, which corresponds to an asymptotic binomial test with variance calculated under the null hypothesis.

With p being the assumed incidence rate of an AE 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 could be simulated using the following power formula:

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

where X denotes a random variable that is binomial distributed with parameter n, p (X ~ binomial (n,p)), z_α denotes the upper α^{th} quantile of the standard normal distribution and $[x]_+$ denotes the smallest integer greater than or equal to x (8).

The corresponding type-I-error rate was obtained by replacing p with p_0, i.e

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

In case of a non-inferiority test, both equations were adapted by incorporating the non-inferiority margin δ. This was done by replacement of p_0 with $p - \delta$.

9.9.2.3 Determination of Sample Size

The equations in section 9.9.2.2 were implemented using SAS 9.4 as described in the SAP 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 9.9.2.1. The SAS macro can be found in the SAP, appendix B.

A minimum sample size of 153 subjects satisfied the significance level α of 2.5% and achieved a power of 80% for the simultaneous rejection of the two primary null hypotheses. In-Text Table 5 describes the results of the simulation in more detail:

In-Text Table 5: AE of Interest: Rate, Sample Size, Power for Rejection, Type-I-Error Rate

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%

Source: SAP, Section 2.7.3

The power β for the simultaneous rejection of the two primary null hypotheses results from the product of the power of each statistical test: 99.62% x 81.18% = 80.87%.

A minimum sample size of 153 subjects satisfied the significance level α of 2.5% and achieved a power of 80% for the simultaneous rejection of the two primary null hypotheses. To have a slight buffer regarding the power, a minimum sample size of 160 patients was to be included in this trial.

9.9.3 Definition of Analysis Populations

The statistical analysis is based on the safety-evaluation set (SES), which consists of all subjects who were enrolled in the study sequentially (informed consent provided) and received NexoBrid® at least once.

No other population was defined for this study.

9.9.4 Statistical Analysis

Data is presented using standard descriptive statistics. Summaries (N, mean, standard deviation, median, minimum, and maximum) were calculated for continuous variables and absolute and percent frequencies (n, %) were calculated for discrete variables.

9.9.4.1 Evaluation of Primary Variables

The analysis of the primary variables was performed on the safety evaluation set.

The incidence rate p of reported pain and pyrexia within the specified period was calculated for the analysis of the primary endpoints. Pain incidence is defined as "at least 2 pain events during the debridement procedure, from start of treatment until end of soaking period, 2 hours post-NexoBrid® removal with subsequent pain medication", Pyrexia incidence is defined as "temperature >38.5 °C within 48 hours from start of NexoBrid® treatment requiring fever relief medications prescribed due to high temperature within 1 hour from complaint, consecutive measurements of high temperature (>38.5 °C), 4 to 6 hours apart". These incidence rates were each tested using a one-tailed, non-inferiority score test at significance level α =2.5%.

The following hypotheses were tested:
- pain: H_0: $p - 0.036 > 0.10$ vs. H_a: $p - 0.036 \leq 0.10$,
- pyrexia: H_0: $p - 0.191 > 0.10$ vs. H_a: $p - 0.191 \leq 0.10$.

Additionally, two-sided 95%-score-confidence intervals were presented for all incidence rates.

Values for the assessment of pain and pyrexia were further analysed in a descriptive and, if meaningful, in an exploratory way.

Score Test:

In general, the hypothesis of a one-sided score test with non-inferiority margin δ can be expressed as
- H_0: $p - p_0 > \delta$ vs. H_a: $p - p_0 \leq \delta$,

where p is the rate of an event and p_0 is a specified value of p.

To test the null hypothesis that the rate p does not exceed the rate p_0 by the margin δ, it was necessary to calculate the test statistic. For a binomial distributed random variable X, which corresponds to the number of subjects with an AE of interest in a total number of subjects n, the test statistic of the score test was given by

$$Z(X, n, p_0 + \delta) = \frac{X - n(p_0 + \delta)}{\sqrt{np_0(1 - (p_0 + \delta))}} = \frac{\hat{p} - (p_0 + \delta)}{\sqrt{(p_0 + \delta)(1 - p_0 - \delta)/n}}$$

where the estimated incidence rate $\hat{p}$ results from $\hat{p} = X\backslash n$.

If the absolute value of the test statistic |Z(X, n, p0 - δ)| was equal to or exceeds the upper α^{th} quantile z_α of the standard normal distribution, the null hypothesis was to be rejected. In case of this study, the critical value z_α is 1.96.

Score-Confidence Interval:

The score-confidence interval is a confidence interval that is consistent with the test decision of the score test, as it is obtained by inverting the score-test statistics.

With the same definitions as in section "score test", the (1-α)-score interval was given by

$$\left(\frac{\hat{p} + \frac{z^2_{\alpha/2}}{2n}}{1 + \frac{z^2_{\alpha/2}}{n}}\right) \pm \frac{\frac{z_{\alpha/2}}{\sqrt{n}}\sqrt{\hat{p}(1-\hat{p}) + z^2_{\alpha/2}/(4n)}}{1 + \frac{z^2_{\alpha/2}}{n}}$$

Supportive Analysis:

Sensitivity analyses were conducted to assess robustness of the results, i.e. best-case analyses with subjects treated in compliance with the educational materials and worst-case analyses based on an incidence rate for which each "possible" AE of interest is regarded as a definite AE of interest.

9.9.4.2 Evaluation of Secondary Variables

The analysis of the secondary variables was performed on the safety-evaluation set (SES).

Physician Compliance with Instructions:

Compliance with the instructions from the educational materials was documented when the answer to below questions was each 'Yes':

- antibacterial soaking applied before NexoBrid® application?
- pain management before applying NexoBrid®?
- antibacterial soaking applied following NexoBrid® removal?
- pain management before removing NexoBrid®?

The number (n) and percentage (%) of wounds that were treated in compliance with the instructions are displayed. Moreover, the number (n) and percentage (%) of patients treated in compliance with instructions are presented.

Besides the assessment of these values for the whole study population, a by-country consideration, and, if applicable, a by-site consideration of the compliance and non-compliance is provided.

Non-compliance was concluded, if the physician violated any key element of the training programme recorded in the eCRF. As stated in the RMP (version 3.1, 14-May-2014), a threshold-rate level of 80% of wounds and patients respectively treated in compliance with the instructions will indicate success. For the observed rate of compliance, the score-confidence interval is provided as an exploratory evaluation whether it was consistent with the predefined desired rate of compliance of 80%.

Furthermore, partial compliance was to be analysed on patient level. In case of partial compliance, the analysis was to be repeated for the compliance with each element of the risk-minimisation measures recorded in the eCRF to identify the non-violation frequency of each risk-minimisation measures.

Since it was expected to have missing data for the compliance, a best- and worst-case analysis was performed, where missing data was replaced by compliance and non-compliance, respectively.

The number and percentage of non-compliance was tabulated together with corresponding reasons.

Incidence of Wound Infection AE:

The incidence rate p of reported wound infection AE within the specified period of the 1st week following treatment was calculated. If each of the null hypotheses of the co-primary endpoints will be rejected, the following hypotheses should be tested using a one-tailed, non-inferiority score test at significance level $\alpha = 2.5\%$.

- H_0: $p - 0.082 > 0.07$ vs. H_a: $p - 0.082 \leq 0.07$.

Additionally, a two-sided, 95%-score-confidence interval was to be presented.

If the study failed its primary objective, only descriptive statistics were to be presented for this key-secondary endpoint to avoid a multiple-testing problem.

Supportive Analysis (Wound Infection Only):

Sensitivity analyses were conducted to assess robustness of the results, i.e. best-case analyses with subjects treated in compliance with the educational materials and worst-case analyses based on an incidence rate for which each "possible" AE of interest is regarded as a definite AE of interest.

Assessment of Severe Irritation, Allergic Reaction, and Cardiopulmonary Event:

The assessments of severe irritation and allergic reaction were captured within 96 hours from start of treatment. Cardiopulmonary events were captured within 48 hours from start of treatment.

The data were displayed using descriptive statistics. Furthermore, incidence rates are presented.

In addition, results are presented by
- country,
- number of wounds treated,
- age, and
- gender.

Assessment of Wound-Related Complications:

Wound-related complications were captured during hospital stay and were presented in a descriptive way.

They were identified in the data-review meeting based on all adverse events.

In addition, results are presented by
- country,
- burn severity,
- number of wounds treated,
- use of NexoBrid® (i.e., treatment vs. no treatment of facial, perineal, or genital burns with NexoBrid®),
- age, and
- gender.

Time to Complete Wound Closure:

Time to complete wound closure and related variables are displayed per patient and by treatment (all, NexoBrid®, SoC) as well as per wound using descriptive summary statistics.

Additionally, a Kaplan-Meier curve is presented to display the distribution of time to complete wound closure, and the estimator for the median time to complete wound closure is presented.

On wound level, time to complete wound closure was calculated from injury date to wound closure confirmation date. On patient level, time to complete wound closure was calculated from injury date to wound-closure-confirmation date of the last wound.

If applicable, time to complete wound closure was analysed separately per wound with autografts and without autografts.

In addition, results are presented by
- country,
- age, and
- gender.

Off-Label Treatment:

Number and percentage of subjects where NexoBrid® was used as off-label treatment are presented separately for
- paediatric patients <18 years of age,
- facial burns, perineal burns, and genital burns,
- NexoBrid® application at wounds representing >15 %TBSA in one session,
- repeated NexoBrid® application in more than one session.

Furthermore, the results are displayed by country.

Time to Hospital Discharge:

Time to hospital discharge and related variables are displayed using descriptive statistics.

Additionally, a Kaplan-Meier curve is presented to display the distribution of time to hospital discharge, and the estimator for the median time to hospital discharge is presented. Time to hospital discharge starts at the admission date.

In addition, results are presented by
- country and
- site.

Assessment of Severe Blood Loss:

Values for the assessment of severe blood loss, indicated by the total volume per patient of reported blood transfusions for packed red-blood cells and whole blood, are displayed using descriptive statistics.

Incidence of severe blood loss is provided for the time of 24 hours from the treatment procedure.

In addition, results are presented by
- country,
- age, and
- gender.

9.9.4.3 Evaluation of Safety Variables

Evaluation of AE:

Incidences of AEs are presented on system-organ-class level and preferred-term level.

All AEs are summarised by presenting the number and percentage of subjects having any AE and the number of AEs.

AEs are further categorised by severity as well as by relationship to NexoBrid®. Relationship was assessed for AE occurring overall as well as within 72 hours from start of treatment. If the start date of an AE was missing, the AE was evaluated as AE within 72 hours (worst-case approach).

Listings and tables are provided for:
- AE leading to discontinuation of treatment,
- AE classified serious, and
- AE leading to death.

Physical Examination:

For each body system, a frequency table is provided with the number of normal or abnormal findings.

The table is split by time point (status at admission, hospital discharge).

Vital Signs:

Blood pressure, pulse, body temperature, and weight are listed.

The first and the last recorded values during hospitalisation are displayed in a summary table together with the absolute change.

Laboratory Parameters:

Haematology and serum chemistry tests should be recorded only for baseline assessments at admission to hospital.

All laboratory values are listed.

For each laboratory parameter, a summary table is presented with descriptive statistics. Where necessary, conversions to the units shown in the eCRF are made.

9.9.4.4 Evaluation of Other Variables

Prior- and Concomitant Medications:

Prior and concomitant medications are displayed by Anatomic-Therapeutic-Chemical (ATC) Classification using second- and fourth-level categories.

Management of NexoBrid®:

The area debrided with NexoBrid®, the number of applications, the duration of NexoBrid® treatment, the NexoBrid® dosage, and the debridement outcome are presented using standard descriptive statistics.

Debridement with Standard-of-Care (SoC):

The number (n) and percentage (%) of wounds treated with SoC are displayed separately by surgical and non-surgical procedure.

Other values related to SoC treatment (areas treated, duration of first treatment, debridement efficacy, and wound management following SoC treatment) are summarised using descriptive statistics.

Post-Debridement Wound Management:

Date of procedure and area of
- coverages used and
- wound-bed preparation for autograft

are presented in a descriptive way.

Evaluation of Tobiasen's Abbreviated Burn Severity Index:

The data needed for Tobiasen's Abbreviated Burn Severity Index were captured in the eCRF.

The index score was calculated as follows with a minimum of 2 points (best value) and a maximum of 18 points (worst value):

In-Text Table 6: Definition of Tobiasen's Abbreviated Burn Severity Index

Parameter	Finding	Points
Gender	Female	1
	Male	0
Age (years)	0-20	1
	21-40	2
	41-60	3
	61-80	4
	81-100	5
Inhalation injury	Yes	1
	No	0
Presence of full-thickness burn	Yes	1
	No	0
TBSA burn (%)	1-10	1
	11-20	2
	21-30	3
	31-40	4
	41-50	5
	51-60	6
	61-70	7
	71-80	8
	81-90	9
	91-100	10

Source: SAP, Section 7.5.4

The analysis includes standard descriptive statistics.

9.9.5 Risk Factor Analyses

Risk factor analyses were done using logistic regression under the assumption of the logit model.

Dependent variables include the primary variables and one key-secondary variable; 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 were calculated with and without adjustment.

It was planned to investigate the following univariate models:

In-Text Table 7: Univariate Models

Dependent Variable (DV) *	Independent Variables (IV)	
(AE)	**Potential Risk Factors**	**Potential Confounder**
Pain Pyrexia Wound infection	Non-compliance (overall and partial compliance, i.e. risk-minimisation measures implemented to limit the occurrence of the DV)	-
	Percentage of TBSA	-
	Age	-
	Gender	-
	Off-label use of NexoBrid® (this factor is defined in the study protocol. Off-label use includes NexoBrid® treatment of facial/perineal/genital burn, which was defined in the SAP.)	-
	Cardiopulmonary events (within 96 hours from start of treatment)	Age
	Tobiasen's abbreviated Burn Severity Index	-
Wound infection	Impaired immune system	Age
Pyrexia	AE (wound infection)	Percentage of TBSA

Source: SAP, Section 7.3.3

* Only one DV per model. The analysis was to be repeated for each DV listed.

After the univariate risk-factor analysis, it was planned to perform multivariate analyses building a regression model by the purposeful-selection algorithm using the settings recommended by Bursac et. al. (2).

Furthermore, it was planned to provide stratified respective descriptive analyses concerning occurrence of endpoints for patients with and without risk factors.

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 the retrospective chart view and the clinical study MW2004-11-12 (representing other clinical studies as well), if available.

9.9.6 Analysis of Subgroups

For the primary endpoint and the key secondary endpoint "incidence rate of wound infection AE", each subgroup listed in In-Text Table 8 were analysed.

In-Text Table 8: Subgroup Analyses Criteria

Criterion	Categorisation
Country	Each country, where patients were enrolled.
Burn aetiology	As recorded in the eCRF (up to 7 categories).
Use of NexoBrid®	Patients with vs. without study treatment of facial, perineal, or genital burns.
Age and gender	<18 years; 18-40 years; >41 years; separately for male and female (i.e., 6 subgroups).
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 diseases.
Treatment	NexoBrid® vs. NexoBrid® and SoC (surgical) vs. NexoBrid® and SoC (non-surgical).
Compliance (overall)	Patients treated in compliance with the educational materials vs. patients not treated in compliance with the educational materials as recorded in the eCRF.
Burn severity 1	%TBSA (≤ 5% / > 5%, ≤ 10% / > 10%, ≤ 15% / > 15%).
Burn severity 2	Patients with only second-degree burns (i.e., deep partial thickness > 0% and full thickness = 0%) vs. patients with mixed second- & third-degree burns (i.e., deep partial thickness > 0% and full thickness > 0%).
Number of wounds treated with NexoBrid®	1, 2-3, ≥4.

Source: SAP, Section 4.2

The analyses comprise only appropriate descriptive statistics such as determination of the observed incidence rates separated for each subgroup. That means, for example, the incidence of endpoints is provided in separate descriptive tables for the group of patients treated with and without compliance to risk-minimisation measures. If applicable, the corresponding two-sided 95%-score-confidence interval is provided.

The results and the number of subjects per subgroup are 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 are limited to the most relevant subgroups. The analyses by country are provided.

9.9.7 Data Handling

9.9.7.1 Handling of Missing Data

All data of the subjects was used as available. Missing data was not replaced as they are not assumed to be missing because of their value, but because of a missing assessment, measurement, or documentation. Thus, missing values were assumed to be missing completely at random.

For categorical variables, number of missing values was incorporated into the corresponding tables and is displayed as missing. Percentages should be based on all subjects of the SES.

In case of the primary variables and the key secondary endpoint wound infection, the incidence rates were determined as in clinical trials, i.e. no imputation, to increase the comparability of the observed incidence rates with those from the clinical trials. Furthermore, it was expected to be difficult to assess whether an AE of interest was missing or did not occur, as this, in contrast to adverse events reported in prospective clinical trials, is usually not documented. However, if it was unclear whether an AE occurred, it was declared as 'possible adverse event' in the statistical evaluation. Criteria for detection of possible AE of interest are listed in In-Text Table 9.

In-Text Table 9: Possible AE of Interest: Criteria for Detection

Possible AE of Interest	Criteria
Pain	Any event of pain assessed in the eCRF module "pain assessment".
Pyrexia	Any event of pyrexia with temperature > 38.5 ºC, recorded in the eCRF module ▪ "Pyrexia Assessment" or ▪ "Vital Signs".
Wound infection	Any hint for wound infection, e.g. ▪ an antibiotic recorded in the eCRF module "previous and concomitant medication" that was given within 1 week after debridement, ▪ a positive wound culture as assessed in the eCRF module "wound culture", or ▪ a positive wound biopsy as assessed in the eCRF module "wound biopsy".

Source: SAP, Section 5.1

Overall, as per above-described suggestion, no imputation was to be done.

9.9.7.2 Handling of Multiple Comparisons and Multiple Primary Variables

For the analysis of the primary safety variables, no alpha adjustment was required since they were handled as co-primary endpoints.

The key-secondary endpoint "incidence of wound infection AE" was tested in a deductive sense, if both primary null hypotheses were rejected. This corresponds to a hierarchical testing strategy.

None of the other endpoints/variables were tested in a deductive sense, so that no multiple-testing problems should evolve.

9.9.7.3 Rules for Data Derivations

Time to Wound Closure:

The time was calculated from date of injury to date of wound-closure confirmation:
- patient level: time [days] = date of wound-closure confirmation (last wound) – date of injury + 1
- wound level: time [days] = date of wound-closure confirmation – date of injury + 1.

Time to Hospital Discharge:

The time was to be calculated from date of admission to date of hospital discharge:
- time [days] = date of hospital discharge – date of hospital admission + 1.

Day to Month Conversion:

1 month = 30.4375 days.

Baseline Value:

The baseline value of a variable was defined as the last available measurement of this variable before the first treatment with NexoBrid®.

NexoBrid® Launch Date and Study Reporting Period by Country:

In-Text Table 10 contains all data referring to the time period of two years after launch date of NexoBrid® in European countries:

In-Text Table 10: NexoBrid® Launch Date, Study-Data-Collection Limit

Country	Site	Launch Date	Patient-Data-Collection Limit
Belgium	101 (Gent, Monstrey)	07-Nov-2014	November 2016
Germany	201 (Berlin, Hartmann)	12-Nov-2013	November 2015
	202 (Cologne, Schulz)	12-Dec-2013	December 2015
	203 (Ludwigshafen, Cordts)	28-Nov-2013	November 2015
	204 (Tübingen, Held)	13-Dec-2013	December 2015
Poland	301 (Krakow, Chrapusta)	29-Apr-2015	April 2017
	302 (Gryfice, Urban)	15-Dec-2014	December 2016
	303 (Łęczna, Korzeniowski)	25-Feb-2015	February 2017
	304 (Poznan, Slowinski)	04-Feb-2015	February 2017
Slovakia	401 (Bratislava, Koller)	19-Nov-2014	November 2016
	402 (Košice, Lengyel)	07-Oct-2014	October 2016
Spain	502 (Barcelona, Serracanta)	24-Nov-2014	November 2016
	503 (Madrid, Martinez)	25-Nov-2014	November 2016
	504 (Zaragoza, Monclus)	27-Feb-2015	February 2017
Sweden	602 (Uppsala, Huss)	19-Sep-2014	September 2016

Source: SAP, Section 5.5

9.9.7.4 Handling of Protocol Deviations

Protocol deviations were captured by the CRAs.

Protocol deviations are a divergence from the protocol. In an observational data-collection study, these may include, but are not limited to the following:
- Deviations observed in ICF collection (e.g. wrong version signed, newest approved version not signed, signed after data collection started).
- Data collection although patient withdrew consent.
- Confidential data such as personal identifiers reported in the eCRF.
- Inclusion criteria not met.

The sponsor provided a list of protocol deviations including their meaningful categorisation to data management.

Protocol deviations were presented in a frequency table.

9.10 Changes in the Conduct of the Study or Planned Analyses

9.10.1 Changes in the Study Conduct

Study Protocol 5.0 to 6.0:

After approval of study protocol 5.0, dated 28-Feb-2016, by the PRAC and before patient enrolment, the MAH initiated an internal review process and revised the protocol to version 6.0, dated 24-Apr-2017.

The changes from study protocol 5.0 to 6.0 were formal revisions and modifications of the following topics:
- Addition of the EU PAS Register® number,
- Addition of abbreviations being used in protocol,
- Romania was replaced with Slovakia,
- Precision of study population (patients treated in NexoBrid® clinical studies will not be included),
- Clarification that expedited reporting was not required (ref.: GVP Module VI),
- Clarification was implemented in the revised protocol stating collection, recording, reporting of AEs and sharing with global pharmacovigilance department on 6-monthly basis. (ref.: GVP Module VI),
- Definition of AE causality was adapted to the definition in NexoBrid® clinical studies.

The MAH considered the changes in the study protocol to be minor and not fulfilling the criteria for a substantial amendment in the sense of GVP Module VIII (GVP VIII.B.2).

Study Protocol 6.0 to 6.1:

Due to changes triggered by the development and implementation of the eCRF, the MAH amended study protocol 6.1, dated 27-Jun-2017.

The change from study protocol 6.0 to 6.1 included only a change to the study timelines (one year earlier).

Study Protocol 6.1 to 7.0:

Due to needed updates in study timelines and additional clarification regarding data collection, the MAH amended the protocol to version 7.0, dated 19-Dec-2017.

The changes from study protocol 6.1 to 7.0 were formal revisions and modifications of the following topics:
- timelines updated due to delays,
- modification of screening log to ensure data privacy (gender, age, and %TBSA burned not included anymore),
- clarification that all concomitant medication during patient hospitalisation should be compiled,
- clarification that non-pharmacological procedures relate to wound recovery,
- clarification of timeframe for data collection,
- clarification that source documentation was not expected for AE assessments,
- definitions of AE, SAE, and AE intensity were added.

9.10.2 Changes to Planned Analyses

The participants of the data review meeting (DRM) decided to skip the statistical analysis of the laboratory parameters, as in many cases the unit recorded in the eCRF does not match with its value. Laboratory parameters were recorded only at baseline, when data was available. The eCRF raw data is included in the laboratory data listings, which display the reported values and units and the corresponding data after conversion to standard units (reference: DRM meeting minutes) (list of basic study documents in Appendix 16).

Missing data regarding seriousness of AE was imputed to serious by default, which was done for one AE of unknown seriousness that was included in the SAE table as a ”worst case“.

According to the SAP, time to complete wound closure was also calculated from injury date to wound-closure-confirmation date of the last wound to allow comparison to study MW2004-11-02. In MW2004-11-02, data was collected prospectively included standardized definition of complete wound closure. This standardization was not implemented in this protocol as it is not feasible to be followed due to the retrospective nature of data collection hence, this comparison will not be performed.

10 STUDY SUBJECTS AND WOUNDS

10.1 Disposition of Subjects

Overall Enrolment / Safety-Evaluation Set:

Between 04-Jun-2015 and 30-May-2017, 399 screened subjects in 6 European countries, as defined in the study protocol, were offered the opportunity to take part in the study. 231/399 subjects (57.9%) did not participate (= screening failures), and 168/399 subjects (42.1%) provided written or oral informed consent form (= enrolled study patients).
The reasons for screening failure were subjects' unattainability before enrolment (n = 148), ineligibility for enrolment (n = 37), patient's death before enrolment (n = 27), patients' refusal to participate (n = 23).

Further 3 subjects signed the informed consent form, but were not treated with NexoBrid® and therefore also considered as "screening failures" (see Summary Table 1: screening failures entered into the database; TOC Summary Tables & Figures in Section 14).

165 subjects were treated with NexoBrid®, 89 subjects with NexoBrid® alone and 76 subjects with NexoBrid® plus SoC.

One subject (no. 402001) was treated far outside the 2-years window from product launch at the site, which was classified as a major protocol deviation (see DRM minutes). Therefore, this patient was also considered as "screening failure" (not "dropout" due to the retrospective data collection) and the patient's data was excluded from statistical analysis (see Summary Table 2.2: patient included by mistake, Raw Data Listing 2; TOC Summary Tables & Figures in Section 14).

By consequence, the safety-evaluation set (SES) comprises 164 study patients.

All enrolment data is provided in Summary Table 1 and 2.2; TOC Summary Tables & Figures in Section 14.

Enrolment by Country & Site:

14 Sites in Belgium, Germany, Poland, Slovakia, Spain, and Sweden participated in the non-interventional study. The number of enrolled patients varied among the sites from 1 patient to 33 patients.

In-Text Table 11: Enrolment per country and site (n = 164)

Country	Site - Principal Investigator	Number of Subjects (%)
Belgium	101 - Monstrey	12 (7.3)
Germany	201 - Hartmann	16 (9.8)
	202 - Schulz	33 (20.1)
	203 - Cordts	7 (4.3)
	204 - Held	3 (1.8)
Poland	301 - Chrapusta	15 (9.1)
	302 - Piorun	2 (1.2)
	303 - Korzeniowski	15 (9.1)
	304 - Slowinski	1 (0.6)
Slovakia	402 - Lengyel	2 (1.2)
Spain	502 - Serracanta	28 (17.1)
	503 - Martinez	8 (4.9)
	504 - Monclus	15 (9.1)
Sweden	602 - Huss	7 (4.3)

Source: Summary Table 2.1.

10.2 Protocol Deviations

During the data review meeting (DRM), which took place before database lock on 10-Jan-2019, potential protocol deviations were discussed, and actual protocol deviations identified and categorised as minor or major (reference: DRM meeting minutes, approved on 23-Jan-2019).

Ten of 165 treated patients (6.1%) had one protocol deviation each.

Patient enrolment was allowed if treatment with NexoBrid® started within the first two years from product launch in the respective site (see study protocol, section "primary objective"). Up to 6 months deviation in this timeframe for inclusion was considered a minor protocol deviation and patients could be included.

The local cut-off date was exceeded in 5 patients by less than 6 months (minor protocol deviations) and in 1 patient (no. 402001) by far more than 6 months (major protocol deviation).

In 4 patients, the executed informed consent form was formally incorrect (minor protocol deviations).

In-Text Table 12: Protocol Deviations (treated patients, n = 165)

Patient ID	Protocol deviation			
	Detection by	Category	Description	Assessment by Data Review Board Members
402001	remote	eligibility	Patient treated far outside the 2-years window from national product launch.	major
201007	on-site	ICF	Investigator's signature was not dated by himself.	minor
204001	on-site	ICF	ICF not signed by investigator, copy not provided to patient.	minor
204002	on-site	ICF	ICF not signed by investigator, copy not provided to patient.	minor
502024	central monitoring	eligibility	Patient treated outside the 2-years window from national product launch.	minor
502025	central monitoring	eligibility	Patient treated outside the 2-years window from national product launch.	minor
502026	central monitoring	eligibility	Patient treated outside the 2-years window from national product launch.	minor
502027	central monitoring	eligibility	Patient treated outside the 2-years window from national product launch.	minor
502028	central monitoring	eligibility	Patient treated outside the 2-years window from national product launch.	minor
602007	on-site	ICF	Unapproved ICF version 1.0 signed.	minor

Source: Summary Table 2.1, 13 (minor protocol deviations), and Raw Data Listing 4.

10.3 Subjects and Wounds Baseline Characteristics

The following layout principles for the display of statistical results apply:

n = number of patients with available data, m = number of wounds with available data,
[x - y] = range, [x; y] = 95%-confidence interval,
AM = arithmetic mean, SD = standard deviation, M = median.

x/y (z% = relative frequency based on y), or
(x/y, z%), or
AM ± SD [M].

10.3.1 Demographics

Most study patients were Caucasian (144/164 patients, 87.8%) and belonged to the Non-Hispanic / Non-Latino ethnicity (115/164 patients, 70.1%), were male (122/164 patients, 74.4%), and had no malnutrition risk (as defined by the investigator) (125/164 patients, 76.2%).

In-Text Table 13 below summarises all numerical demographic characteristics.

In-Text Table 13: Demographic numerical characteristics

Characteristic	Arithm. Mean ± SD	Median	Minimum	Maximum	n
Age [y]	42.3 ± 14.6	42.00	5	85	164
Body Height [cm]	173.8 ± 9.7	175.00	120	194	130
Body Weight [kg]	79.7 ± 18.2	80.00	20	120	143
Body Mass Index [kg/m^2]	26.42 ± 4.94	25.80	13.9	39.2	129

Source: Summary Table 3.

All demographic data is presented in Summary Table 3; TOC Summary Tables & Figures in Section 14.

10.3.2 Previous Disease & Conditions

Any previous diseases were documented in 10/164 patients (6.1%), which belong to the system organ classes vascular disorders (4 patients), gastrointestinal disorders (2 patients), infections and infestations (2 patients), injury/poisoning and procedural complications (2 patients), cardiac disorders (1 patient), and general disorders and administration site conditions (1 patient).

A medical history for any cardiopulmonary disease was confirmed in 35/164 patients (21.3%), any impaired immune system disease (as defined by the investigator) in 7/164 patients (4.3%), and any allergy to pineapple or papain in no patient (0.0%).

More results are available in Summary Table 4.1 and 5; TOC Summary Tables & Figures in Section 14.

10.3.3 Previous Medication & Non-Pharmacological Procedures

89/164 patients (54.3%) reported any previous medication or non-pharmacological procedures at study enrolment.

The most frequent (> 20% attributions) medications and non-pharmacological procedures were analgesics (46/164 patients, 28.0%) and blood substitutes and perfusion solutions (45/164 patients, 27.4%).

More results are available in Summary Table 8; TOC Summary Tables & Figures in Section 14.

10.3.4 Physical Examination at Study Enrolment

Data of physical examination was available in 153/164 patients (93.3%) at hospital admission. At that stage, 92/164 patients (56.1%) had at least one abnormal finding.

The body systems most frequently (>10% attributions) assessed abnormal were skin (75/164 patients, 45.7%), extremities/back (29/164 patients, 17.7%), and head/neck (24/164 patients, 14.6%).

More results are available in Summary Table 39; TOC Summary Tables & Figures in Section 14.

10.3.5 Vital Signs

The initially recorded parameters were at hospital admission:

In-Text Table 14: Vital signs at hospital admission

Characteristic	Arithm. Mean ± SD	Median	Minimum	Maximum	n
Systolic Blood Pressure [mmHg]	129.6 ± 21.5	130.0	75	192	163
Diastolic Blood Pressure [mmHg]	75.6 ± 13.2	76.0	41	112	163
Pulse Rate [beats/minutes]	83.7 ± 16.4	81.00	49	135	162
Body Temperature [°C]	36.57 ± 0.79	36.60	33.0	39.2	160
Body Weight [kg]	79.7 ± 18.2	80.0	20	120	144

Source: Summary Table 40.

10.3.6 Wound Status

By Patient:

On average, the study patients had 3.2 ± 2.5 [2.0] Burn wounds [1 - 15], treated either with NexoBrid or SoC procedures, which represented a mean total body surface area (TBSA) of 12.71 ± 14.40 [6.75] %.

The body areas mostly affected (> 20% attributions) were the right hand (87/164 patients, 53.0%), left hand (72/164 patients, 43.9%), lower right arm (63/164 patients, 38.4%), upper right arm (47/164 patients, 28.7%), face (43/164 patients, 26.2%), upper left arm (38/164 patients, 23.2%), left thigh (33/164 patients, 20.1%), and right thigh (33/164 patients, 20.1%).

Most frequent causes of burn were fire/flame (106/164 patients, 64.6%) and scald (37/164 patients, 22.6%). Before admission, 22/164 patients (13.4%) suffered from inhalation injury and 21/164 patients (12.8%) developed a burn shock.

By Wound:

The mean affected TBSA by wound was 4.10 ± 5.47 [2.50] % (data available: m = 345/532) for all wounds, 3.66 ± 3.66 [2.00] % (m = 185) for wounds treated with NexoBrid®, and 4.62 ± 6.98 [3.00] % (m = 160) for wounds treated with SoC procedures.

Data for wound depth was available for m = 297/532 burn wounds (55.8%). 121/532 wounds (22.7%) were recorded as full thickness, 80/532 wounds (15.0%) were recorded as superficial partial thickness, 55/532 wounds (10.3%) were recorded as mixed depth, and 41/532 wounds (7.7%) were recorded as deep partial thickness. Data for wound depth was missing for 44.2% of all wounds.

10.3.7 Tobiasen's Abbreviated Burn Severity Index

The index for burn severity is composed by gender, age, inhalation injury, presence of full-thickness burn, and burned (affected) TBSA. The detailed criteria for the index are given in In-Text Table 6.

The average score at study enrolment was 4.8 ± 1.7 [5.0] points (n = 152), ranging from a minimum of 2 points to a maximum of 11 points.

More results are available in Summary Table 7; TOC Summary Tables & Figures in Section 14.

10.4 Concomitant Diseases & Conditions

The data in this section apply for any concomitant diseases and medical conditions reported at the time of hospital admission.

100/164 patients (61.0%) records had any concomitant disease at study enrolment.

The most frequent (> 10% attributions) MedDRA SOCs were vascular disorders (41/164 patients, 25.0%), psychiatric disorders (34/164 patients, 20.7%), metabolism and nutrition disorders (29/164 patients, 17.7%), and injury / poisoning and procedural complications (26/164 patients, 15.9%).

More results are available in Summary Table 6; TOC Summary Tables & Figures in Section 14.

10.5 Concomitant Medication & Non-Pharmacological Procedures

The figures in this section apply for any concomitant medication and non-pharmacological procedures that were administered during patient hospitalisation, i.e. from hospital admission to hospital discharge.

164/164 patients (100%) had any concomitant medication and non-pharmacological procedures during study time period.

The most frequent (> 20% attributions) medications and non-pharmacological procedures were analgesics (163/164 patients, 99.4%), blood substitutes and perfusion solutions (101/164 patients, 61.6%), anaesthetics (99/164 patients, 60.4%), antiinflammatory and antirheumatic products (97/164 patients, 59.1%), all other therapeutic products (83/164 patients, 50.6%), psycholeptics (79/164 patients, 48.2%), antibacterials for systemic use (71/164 patients, 43.3%), drugs for acid-related disorders (57/164 patients, 34.8%), all other non-therapeutic products (50/164 patients, 30.5%), antithrombotic agents (39/164 patients, 23.8%).

Data regarding concomitant infusion therapies are reported in Raw Data Listing 9; TOC Raw Data Listings in Section 15.

More results are available in Summary Table 9 (all medication/procedures), 10 (analgesics), and 11 (antibiotics); TOC Summary Tables & Figures in Section 14.

10.6 Extent of NexoBrid® Exposure

The wounds of patients of the safety-evaluation set (SES: 164/164 patients, 100%) were either exclusively treated with NexoBrid® in 89/164 patients (54.3%) or with either NexoBrid® or SoC procedures in 75/164 patients (45.7%).

On average, 1.9 ± 1.2 [2.0] wounds per patient [1 - 8] were treated with NexoBrid®, and 1.3 ± 2.0 [0.0] wounds per patient [0 - 12] were treated with SoC procedures.

Reference: Summary Table 1[2], 14.1; TOC Summary Tables & Figures in Section 14.

10.7 Debridement With NexoBrid®

References: Summary Table 4.2, 4.3, 14.1, 14.2, 16; TOC Summary Tables & Figures in Section 14.

Debridement:

Overall, 313/532 (58.8%) wounds were treated with NexoBrid® at a mean dose of 5.34 ± 5.84 [4.00] g per wound (m = 74) for on average 204.3 ± 87.7 [241.0] min (m = 178), after 2.6 ± 1.3 [2.0] days from burn.

On average, 93.9 ± 15.7 [100] % (m = 107/313) of eschar by wound was removed after debridement.

Coverage:

A coverage was recorded for 292/313 wounds (93.3%) after a mean time from NexoBrid® removal of 1.8 ± 1.1 [1.0] days (m = 290). Data for 18/313 wounds (5.8%) for coverage application was not available. The initial coverages mostly applied were Suprathel® 102/313 (32.6%), autograft 36/313 (11.5%), Mepitel® 33/313 (10.5%), and allograft 29/313 (9.3%).

For wounds treated with NexoBrid®, the wound was eventually closed by an autograft for 140/313 wounds (44.7%) and graft take was recorded for 130/140 autografted wounds (92.9%). The mean % area covered by autograft was 86.92 ± 22.39 [100] % (m = 24) after a mean time from NexoBrid® removal of 1.9 ± 1.2 [2.0] days (m = 36).

Risk-Minimisation Measures:

NexoBrid® was mixed up to 15 minutes prior to use for 119/313 wounds (38.0%). For 61% of patients, data regarding time of mixture is missing.

An adhesive barrier was applied for 181/313 wounds (57.8%). For 41% of patients, data regarding adhesive barrier application is missing.

Antibacterial soaking was applied before NexoBrid® application for 165/313 wounds (52.7%) at a mean duration of 142.3 ± 99.6 [120.0] minutes (m = 65), and after NexoBrid® removal for 181/313 wounds (57.8%) at a mean duration of 156.7 ± 115.6 [120.0] min (m = 100). For 35% of patients, data regarding antibacterial soaking prior to NexoBrid® application is missing and for 29.1% of patients, data is missing for antibacterial soaking after NexoBrid® removal.

Pain was pharmacologically managed before NexoBrid® application for 294/313 wounds (93.9%) and before NexoBrid® removal for 248/313 wounds (79.2%). For 4.2% of patients, data regarding pain management prior to NexoBrid® application is missing and for 11.2% of patients, data is missing for pain management prior to NexoBrid® removal.

See Section 11.2.2 for the evaluation of the physicians' compliance rates.

[2] The data of patient no. 402001 treated with NexoBrid® plus SoC procedures is considered in Table 1, although the dataset was excluded from the SES at the DRM due to a major protocol deviation. For further details, please refer to Section 10.2.

10.8 Debridement With SoC Procedures

Overall, 219/532 (41.2%) wounds were treated with SoC procedures, which were surgical for 121/219 wounds (55.3%), non-surgical for 85/219 wounds (38.8%), and combined surgical plus non-surgical procedures for 13/219 wounds (5.9%). The mean duration of surgical debridement procedures, including combined surgical plus non-surgical SoC procedures, was 78.6 ± 59.7 [56.0] min (m = 62).

On average, 97.2 ± 14.1 [100] % (m = 70) of eschar by wound was removed after debridement.

References: Summary Table 15.1, 15.2; TOC Summary Tables & Figures in Section 14.

11 DATA EVALUATION

The following layout principles for the display of statistical results apply:

n = number of patients, m = number of wounds,
[x - y] = range, [x; y] = 95%-confidence interval,
AM = arithmetic mean, SD = standard deviation, M = median.

x/y (z% = relative frequency based on y), or
(x/y, z%), or
AM ± SD [M].

11.1 Primary Endpoints

11.1.1 Incidence of Pain

References: Summary Table 17.1 (pain incidence), 17.2.1 to 17.2.15 and 29.2 (subgroup analyses); TOC Summary Tables & Figures in Section 14.

According to the SAP, pain incidence is defined as "at least 2 pain events during the debridement procedure, from start of treatment until end of soaking period, 2 hours post-NexoBrid® removal with subsequent pain medication".

Analysis as Documented (no Imputation of Missing Data):

1/164 patients (0.6%) suffered from pain during NexoBrid® application.

The null hypothesis "pain incidence rate in routine clinical practice exceeds the estimated incidence rate observed in patients after implementation of risk-minimisation measures of 3.6% by a clinically relevant amount of 10%" could be rejected (p<0.0001).
The 95%-confidence interval [0.11; 3.37] for the incidence rate lies below the given non-inferiority limit of 13.6%.

The single patient who suffered from pain during NexoBrid® treatment had a single, full-thickness scald wound at the left hand representing 0.4 %TBSA. He was male, between 18 and 40 years old (35 years old), hospitalised in Germany, and without a history or presence of co-morbidities.

The wound was treated with NexoBrid® in full compliance with the educational materials.

Worst-Case Scenario (Imputation of Missing Data):

This scenario includes also "possible" pain events, which are defined as any pain documented in the medical records and recorded in the eCRF module "pain assessment" that occurred within 2 hours after NexoBrid® removal.

Based on these data, 29/164 patients (17.7%) suffered from pain during NexoBrid® application.

The null hypothesis (see above) could not be rejected (p=0.0636).

The 95%-confidence interval [12.60; 24.24] for the incidence rate slightly overlaps the given non-inferiority limit of 13.6%.

Sensitivity Analysis (no Imputation of Missing Data):

In a sensitivity analysis only the 131 patients were considered with eligible data and who were treated in compliance with the educational materials.

Of these patients, 1/131 patients (0.8%) suffered from pain during NexoBrid® application.

The 95%-confidence interval [0.13; 4.20] for the incidence rate lies below the given non-inferiority limit of 13.6% (p<0.0001).

11.1.2 Incidence of Pyrexia

References: Summary Table 18.1 (pyrexia incidence), 18.2.1 to 18.2.15 and 29.2 (subgroup analyses); TOC Summary Tables & Figures in Section 14.

According to the SAP, pyrexia incidence is defined as "temperature >38.5 °C within 48 hours from start of NexoBrid® treatment requiring fever relief medications prescribed due to high temperature within 1 hour from complaint, consecutive measurements of high temperature (>38.5 °C), 4 to 6 hours apart".

Pyrexia is a well-known phenomenon in burn patients. The burn patient is catabolic, with a very high basal metabolic rate (BMR), and often has elevated body temperature.

Analysis as Documented (no Imputation of Missing Data):

Pyrexia (>38.5 °C) within 48 hours from start of NexoBrid® treatment was observed in 6/164 patients (3.7%).

The null hypothesis "pyrexia incidence rate in routine clinical practice exceeds the estimated incidence rate observed in patients after implementation of risk-minimisation measures of 19.1% by a clinically relevant amount of 10%" could be rejected (p<0.0001).
The 95%-confidence interval [1.69; 7.75] for the incidence rate lies below the given non-inferiority limit of 29.1%.

Two patients were between 18 and 40 years old and 4 patients above 40 years old. They were hospitalised in Belgium (2 patients), Germany (2 patients), and Spain (2 patients). A history of cardiopulmonary diseases was recorded in 3 patients.

Three patients with pyrexia had one single wound, 2 patients 2 or 3 wounds, and 1 patient more than 3 wounds treated with NexoBrid®. The degree of burn was documented in 1 patient only, which was deep partial thickness.

The burns were caused by fire/flame (4 patients), scald (1 patient), and a contact with a hot object (1 patient). None of the wounds were in the facial / perineal / genital body region.

The burn wounds affected less than 5 %TBSA (2 patients), >5% to 10 %TBSA (1 patient), >10% to 15 %TBSA (1 patient), or >15 %TBSA (2 patients).
All of the patient's wounds were treated with NexoBrid® only (4 patients) or NexoBrid® plus surgical SoC procedures (2 patients).
Treatment with NexoBrid® was in full compliance with the educational materials in 4 of 6 patients with observed pyrexia.

Worst-Case Scenario (Imputation of Missing Data):

This scenario includes also "possible" pyrexia events, which are defined as any body temperature recorded in the eCRF modules "pyrexia assessment" or "vital signs" that lies above 38.5 °C, regardless whether fever-relief medications were prescribed or whether there were additional consecutive pyrexia measurements.

Based on these data, pyrexia within 48 hours from start of NexoBrid® treatment was observed in 23/164 patients (14.0%).

The null hypothesis (see above) could be rejected (p<0.0001).

The 95%-confidence interval [9.53; 20.17] for the incidence rate lies below the given non-inferiority limit of 29.1%.

Sensitivity Analysis (no Imputation of Missing Data):

In a sensitivity analysis only the 131 patients were considered with eligible data and who were treated in compliance with the educational materials.

Of these patients, 4/131 patients (3.1%) had pyrexia within 48 hours from start of NexoBrid® treatment.

The 95%-confidence interval [1.19; 7.59] for the incidence rate lies below the given non-inferiority limit of 29.1% (p<0.0001).

11.2 Key-Secondary Endpoints

11.2.1 Incidence of Wound Infections

References: Summary Table 19.1 (wound-infection incidence), 19.2.1 to 19.2.15 and 29.2 (subgroup analyses); TOC Summary Tables & Figures in Section 14.

According to the SAP, wound infection is defined as "prescription of antibiotics during the first week following debridement with NexoBrid® to a patient captured with positive swabs and/or positive wound biopsies performed".

Analysis as Documented (no Imputation of Missing Data):

Wound infection within 1 week from start of debridement was observed in 12/164 patients (7.3%). The 95%-confidence interval [4.23; 12.35] lies below the given non-inferiority limit of 15.2% (p<0.0051).

Three (3) male patients were between 18 and 40 years old, 6 male and 2 female patients above 40 years old, and one male patient was below 18 years old. They were hospitalised in Poland (4 patients), Sweden (4 patients), Germany (3 patients), and Slovakia (1 patient). 1 patient had a medical history of an impaired immune system and cardiopulmonary diseases were present in 3 patients.

Four (4) patients with wound infections had one single wound, 6 patients 2 or 3 wounds, and 2 patients more than 3 wounds. The depth of the burn was classified in 9 patients, namely deep partial thickness (1 patient), mixed wound (6 patients), and full thickness (2 patients).
The burns were caused by fire/flame (11 patients) and electricity (1 patient). 2/12 wounds were in the facial/perineal/genital body region.

Two (2) patients were treated with NexoBrid® (5 wounds) and 10 patients with NexoBrid® (28 wounds) plus SoC procedures (45 wounds). All AEs in those patients, including AEs of wound infection, were assessed retrospectively by the sites as not related to NexoBrid®, except in two patients in whom AE of pyrexia was reported as related to NexoBrid®.

The total burn wounds affected >5% to 10 %TBSA (1 patient) and >15 %TBSA (11 patients).
The patients' wounds were treated with NexoBrid® only (2 patients), NexoBrid® plus surgical SoC procedures (6 patients), NexoBrid® plus non-surgical SoC procedures (1 patient), or NexoBrid® plus surgical and non-surgical SoC procedures (3 patients).
Treatment with NexoBrid® was in full compliance with the educational materials in 9/12 patients and antibacterial soaking was applied before and after NexoBrid® application in 10/12 patients.

Wound infection in burn patients is one of the more common infections known in burn patients, and is reported in the literature with an incidence of > 30%. The incidence of wound infection found in this study is less than expected according to the literature in burn patients (2,6,9,11) and as expected more prominent in patients with large burns (>15 %TBSA).

Worst-Case Scenario (Imputation of Missing Data):

This scenario includes also "possible" wound infections, which are defined as any hint for wound infection, i.e., an antibiotic recorded in the eCRF module "previous and concomitant medication" that was given within 1 week after debridement, a positive wound culture as assessed in the eCRF module "wound culture", or a positive wound biopsy as assessed in the eCRF module "wound biopsy". This is different from the definition of wound infection for the main analysis, in which an event of infection was recorded if antibiotics were prescribed to a patient after a positive swab or biopsy was captured (and not any of the events separately).

Based on these data, wound infection within 1 week from start of debridement was observed in 51/164 patients (31.1%).

The 95%-confidence interval [24.51; 38.55] lies above the given non-inferiority limit of 15.2%.

Sensitivity Analysis (no Imputation of Missing Data):

In a sensitivity analysis only the 131 patients were considered with eligible data and who were treated in compliance with the educational materials.

Of these patients, 9/131 patients (6.9%) had a wound infection within 1 week from start of debridement.

The 95%-confidence interval [3.66; 12.54] lies below the given non-inferiority limit of 15.2% (p=0.0076).

11.2.2 Physician Compliance with Educational Materials

Compliance rates regarding the NexoBrid® treatment were calculated based on the total number of patients treated with NexoBrid®.

Total compliance meant that for all wounds an antibacterial soaking was applied before and after NexoBrid® application and pain was adequately managed before NexoBrid® application and before NexoBrid® removal.

11.2.2.1 Patient Level

If a wound had two consecutive applications, the worst compliance result was used to assess compliance per wound (= data imputation).

Partial and Total Compliance:

For evaluation of compliance, data was considered, when eCRF entries were available for all wounds by patient, otherwise the compliance data was classified as "missing".

Based on this requirement, the compliance rates were the following:

In-Text Table 15: Physician Compliance With Educational Material

Compliance Criterion	Yes [n = 164]	No [n = 164]	Missing Data [n = 164]
Antibacterial soaking before NexoBrid® application	92 (56.1%)	18 (11.0%)	54 (32.9%)
Pain management before NexoBrid® application	154 (93.9%)	3 (1.8%)	7 (4.3%)
Antibacterial soaking after NexoBrid® removal	105 (64.0%)	21 (12.8%)	38 (23.2%)
Pain management before NexoBrid® removal	130 (79.3%)	17 (10.4%)	17 (10.4%)
Total compliance	131 (79.9%)	30 (18.3%)	3 (1.8%)
Total compliance (best-case scenario *)	134 (81.7%)	30 (18.3%)	-
Total compliance (worst-case scenario **)	72 (43.9%)	92 (56.1%)	-

Source: Summary Table 20.1.

*) Best case: compliance assumed for all missing data.
**) Worst case: non-compliance assumed for all missing data.

The observed total compliance rate of 79.9% [95%-CI: 72.9%; 85.7%] is consistent with the predefined desired rate of compliance of 80% based on available study data.

For assessment of total compliance, only recorded data (yes/no) was considered. Missing values were not considered for the calculation.

Subgroup Analyses:

Sub-group analyses are provided by country and site.

Total compliance rates by country were in Belgium 12/12 patients (100%) [73.5; 100], in Germany 58/59 patients (98.3%) [90.9; 100], in Poland 31/33 patients (93.9%) [79.8; 99.3], in Slovakia 0/2 patients (0%), in Spain 25/51 patients (49.0%) [34.8; 63.4], and in Sweden 5/7 patients (71.4%) [29.0; 96.3].

Reference: Summary Table 20.2, 20.3; TOC Summary Tables & Figures in Section 14.

11.2.2.2 Wound Level

Partial and Total Compliance:

The partial compliance rates were the following: pain management before applying NexoBrid® in 294/313 wounds (93.9%), antibacterial soaking applied before NexoBrid® in 165/313 wounds (52.7%), pain management before removing NexoBrid® in 248/313 wounds (79.2%), and antibacterial soaking applied after NexoBrid® in 181/313 wounds (57.8%).

Total compliance per wound rates was recorded in 247/313 wounds (78.9%) [95%-CI: 74.0%; 83.3%) based on available data without imputation of missing data, in 255/313 wounds (81.5%) [76.7%; 85.6%) in the best-case analysis (compliance assumed for all missing values), and 136/313 wounds (43.5%) [37.9%; 49.1%) in the worst-case analysis (non-compliance assumed for all missing values).
On the wound level, the total compliance rate lies slightly below the desired rate of 80%, and its 95%-confidence interval overlaps a range of below and of above the 80%-threshold.

Reference: Summary Table 20.4; TOC Summary Tables & Figures in Section 14.

Subgroup Analyses:

Sub-group analyses are provided by country and site.

Total compliance rates by country were in Belgium in 22/22 wounds (100%) [95%-CI: 84.6%; 100%], in Germany in 112/117 wounds (95.7%) [90.3%; 98.6%], in Poland in 58/60 wounds (96.7%) [88.5%; 99.6%], in Slovakia in 0/4 wounds (0%), in Spain in 44/94 wounds (46.8%) [36.4%; 57.4%], and in Sweden in 11/16 wounds (68.8%) [41.3%; 89.0%].

Reference: Summary Table 20.5, 20.6; TOC Summary Tables & Figures in Section 14.

11.3 Subgroup Analyses

Sub-group analyses are provided by country, burn aetiology, use of NexoBrid®, gender and age, three co-morbidities, type of wound treatment, compliance with educational material, three cut-off levels for affected TBSA by patient, burn degree, number of wounds treated with NexoBrid®, and compliance with antibacterial soaking.

Further sub-group analyses are provided in Summary Table 29.2 by compliance with NexoBrid® treatment (yes vs. no), TBSA (low vs. high), age (young vs. old), gender (male vs. female), NexoBrid® use (off-label vs. regular), cardiopulmonary complications (yes vs. no), stable immune disease (yes vs. no), wound infection (yes vs. no), and Tobiasen's Abbreviated Burn Severity Index (low vs. high).

11.4 Risk-Factor Analyses

11.4.1 Univariate Risk-Factor Analyses

Pain (yes, no), pyrexia (yes, no), and wound infection (yes, no) as dependent variables were analysed against pre-defined, potential risk factors as independent factors (see In-Text Table 7).

The potential risk factors were total compliance, partial compliance, affected TBSA by patient, age, gender, off-label treatment, cardiopulmonary events, impaired immune system (wound infection only), wound infection (pyrexia only), and Tobiasen's Abbreviated Burn Severity Index.

The analysis revealed a potential influence of the affected TBSA ($p < 0.0001$), of Tobiasen's Abbreviated Burn Severity Index ($p < 0.0001$), and of an off-label treatment ($p = 0.0003$) on the wound infection rate. Compliance and partial compliance with educational material were not identified as risk factors for wound infection ($p > 0.25$). This is in line with the data in In-Text Table 2 showing same incidence rates of infection before and after risk-minimisation measures applied and no difference between NexoBrid® and SoC treatment.

Reference: Summary Table 29.1.1, 29.1.2, 29.1.3; TOC Summary Tables & Figures in Section 14.

11.4.2 Multivariate Risk-Factor Analyses

It was planned to include those factors in a multivariate logistic regression model which were identified in the univariate logistic regression model as potential risk factors with $p>0.25$.

Regarding pain and pyrexia, no factors qualified for a multivariate risk analysis. Regarding wound infection, TBSA, off-label treatment, and Tobiasen's Abbreviated Burn Severity Index were included in the multivariate model using the purposeful selection algorithm using the settings recommended by Bursac et. al. (2).

In summary, no statistically relevant influence parameter (covariate) remained in the final multivariate logistic regression model. The p-values for the influence of the variable on the occurrence of wound infection were p = 0.1288 for TBSA, p = 0.6474 for Tobiasen's Abbreviated Burn Severity Index, and p = 0.0931 for off-label treatment. The p value (see before) and the estimate (see Summary Table 29.3.3) for off-label treatment suggests that off-label treatment may be associated with higher wound infections.

Reference: Summary Table 29.3.1, 29.3.2, 29.3.3; TOC Summary Tables & Figures in Section 14.

11.5 Additional Secondary Endpoints

Incidences were calculated based on the total number of patients or wounds treated with NexoBrid®.

11.5.1 Incidence of Severe Irritations

Severe Irritations were observed in 0/164 patients (0.0%) [0.00; 2.29].

Reference: Summary Table 21.1; TOC Summary Tables & Figures in Section 14.

11.5.2 Incidence of Allergic Reactions

Any allergic reaction within 96 hours from start of first wound treatment occurred in 1/164 patient (0.6%) [0.11; 3.37]: urticaria (MedDRA Preferred Term).

Patient 303014 (Poland):

A 38-years-old male. The patient suffered from depression and malnutrition at background. Laboratory values outside normal ranges at baseline were observed for SGOT, SGPT, CRP, MCV, and Leukocytes.

Burn affected 1 wound with full & superficial partial thickness, representing 3.5 %TBSA. On 28-Apr-2015, from 18:00 to 20:30 o'clock, 1 g NexoBrid® was applied in compliance with the educational materials in one session. On 29-Apr-2015, brushing and autograft was applied for 100% coverage of the wound.

The patient received metamizole (28-Apr-2015 18:40-ongoing) and tramadol (28-Apr-2015 18:40-19:00) during treatment with NexoBrid®.

Onset of the urticaria AE was on 28-Apr-2015 at 20:30 o'clock (two and a half hours after start of NexoBrid® treatment). The AE was assessed as possibly related and mild in intensity. NexoBrid® treatment was interrupted, 100 mg hydrocortisone i.v. administered once, and 1 mg i.v. clemastin given for 11:20 hours. The AE recovered on the same day (28-Apr-2015, stop time unknown).

Reference: Summary Table 22.1, 22.2.1, 22.2.2, 22.2.3, 22.2.4, and Raw Data Listings; TOC Summary Tables & Figures in Section 14, TOC Raw Data Listings in Section 15.

11.5.3 Incidence of Cardiopulmonary Events

Cardiopulmonary events, which occurred 48 hours from start of first treatment with NexoBrid®, were recorded in 7/164 patients (4.3%) [2.08; 8.55].

The 5 males and 2 females were between 18 and 40 years old (1 patient) or older than 40 years (6 patients). They were enrolled in Germany (4 patients), and Spain (3 patients).

Two (2) patients had one single wound, 4 patients had 2 to 3 wounds, and 1 patient had more than 3 wounds. The wounds were treated with NexoBrid® alone (4 patients) or with NexoBrid® plus SoC procedures (3 patients).

Cardiopulmonary AEs reported in those patients included the following: ventricular extrasystoles, supraventricular tachycardia, atrial fibrillation, each in one patient. According to the literature, arrhythmias are reported in burn patients, occurring in approximately 30% of burned patients (4,10).

The other cardiopulmonary events reported included the following preferred terms: respiratory failure and pneumonia (in one patient), pneumonia and pleural effusion (in one patient who suffered electrical burn), iatrogenic pneumothorax, pulmonary oedema, respiratory tract infection, pleural effusion (in one patient), pulmonary oedema, respiratory tract infection, and hypotension (each in one patient). Pneumonia is a known complication in burn patients reported in 10-65% of burn patients (3).

All cardiopulmonary events were determined as not related to NexoBrid.

Four of these patients suffered from inhalation injury, and three of these patients had other cardiopulmonary background conditions, e.g., tobacco abuse, bronchial asthma, cardiomyopathy, hypertension, arrhythmia. One of these patients (no. 202030) also had shock, hypothermia, and multiple fractures at study entry.

All AEs recovered, except two: ventricular extrasystoles (no. 202006), in which outcome was recorded as unknown, and atrial fibrillation (no. 504010), which was recorded as ongoing at the end of the study period.

Reference: Summary Table 23.1, 23.2.1, 23.2.2, 23.2.3, 23.2.4, 23.2.5, and Raw Data Listings; TOC Summary Tables & Figures in Section 14; TOC Raw Data Listings in Section 15.

11.5.4 Incidence of Wound-Related Complications

Wound-related complications were identified and assessed in the data review meeting based on AEs with unknown or at least possible relatedness to NexoBrid®. Accordingly, 2/164 patients (1.2%) fulfilled the definition.

In one patient, the burn was at the palmar side of the right hand, on 1.5 %TBSA, with wound depth unknown. The graft loss occurred 15 days after NexoBrid® application, and was following necrosis of phalanges and phalanges amputation in the same hand.

The other patient had three wounds representing a TBSA of 17.0%, which were located at the buttocks, arms, hands, thighs, and legs. The wound thicknesses were classified as superficial, full, and deep partial. All wounds were treated with NexoBrid® and were covered by autograft five days after treatment with NexoBrid®. This patient had AIDS, anorexia, and drug addiction in medical history. The graft loss occurred on the wound on the buttocks and lower limbs, 13 days after NexoBrid application. The other two autografts were taken.

Reference: Summary Table 24.1, 24.2.1, 24.2.2, 24.2.3, 24.2.4, 24.2.5, 24.2.6, 24.2.7; TOC Summary Tables & Figures in Section 14.

11.5.5 Incidence of Severe Blood Loss

Severe blood loss (reported as blood transfusions) was based on blood transfusions including red-blood cells and whole blood recorded within 24 hours from the debridement procedure.

Overall, severe blood loss was documented in 8/164 patients (4.9%). These patients had total burns of 14-65 %TBSA. Six out of the eight patients were treated with surgical SoC in addition to NexoBrid® (on consecutive days or on the same day) before receiving the blood transfusion.

Reference: Summary Table 28.1, 28.2.1, 28.2.2, 28.2.3; TOC Summary Tables & Figures in Section 14.

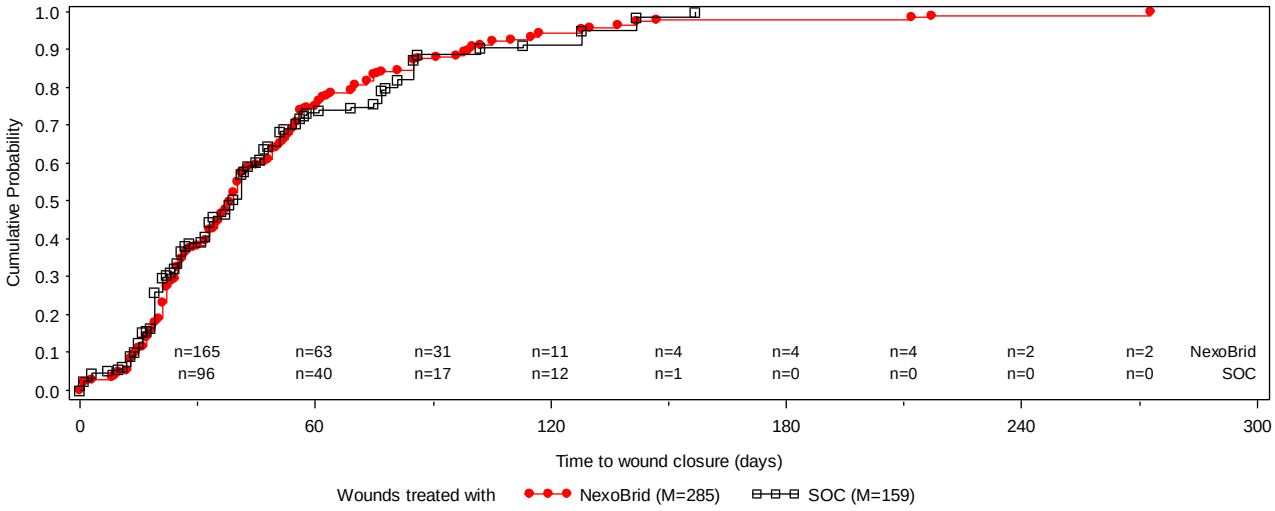
11.5.6 Time to Complete Wound Closure

The time was calculated from injury date to wound-closure date (wound level) and from injury date to wound-closure date of the last wound (patient level).

Median time to reach wound closure was 42.0 days. Data was available for 150/164 patients (91.5%), of these, data was censored for 23 patients. For 14/164 patients (8.5%), no wound closure assessments were available.

At the wound level, overall 410/444 wounds (92.3%) with data for wound closure available were closed. 259/285 wounds (90.9%) treated with NexoBrid® and 151/159 wounds (95.0%) treated with SoC procedures were closed after 39.0 days (median) for both treatment modalities.

In-Text Figure 1: Time to Complete Wound Closure [Kaplan-Meier] per Wound Analysis



Source: Figure 5.

Sub-group analyses are provided by use of autografts, country, age group, gender, TBSA cut-off groups.

References wound level:
Summary Table 25.1 (wound closure); 25.2.1, 25.2.2, 25.2.3, 25.2.4, 25.2.5, 25.2.6, 25.2.7 (subgroup analyses).
References patient level:
Table Summary 25.3 (wound closure); 25.4.1, 25.4.2, 25.4.3, 25.4.4, 25.4.5, 25.4.6, 25.4.7 (subgroup analyses).
TOC Summary Tables & Figures in Section 14.

11.5.7 Proportion of Off-Label-Treated Patients

Off-label use of NexoBrid® was documented in overall 32/164 patients (19.5%).

Reasons for documented off-label use were treatment of facial / perineal / genital burns in 14/164 patients (8.5%), treatment of paediatric patients in 4/164 patients (2.4%), NexoBrid® application at wounds representing >15 %TBSA in one session in 10/164 patients (6.1%), and repeated NexoBrid® application in more than one session in 9/164 patients (5.5%).

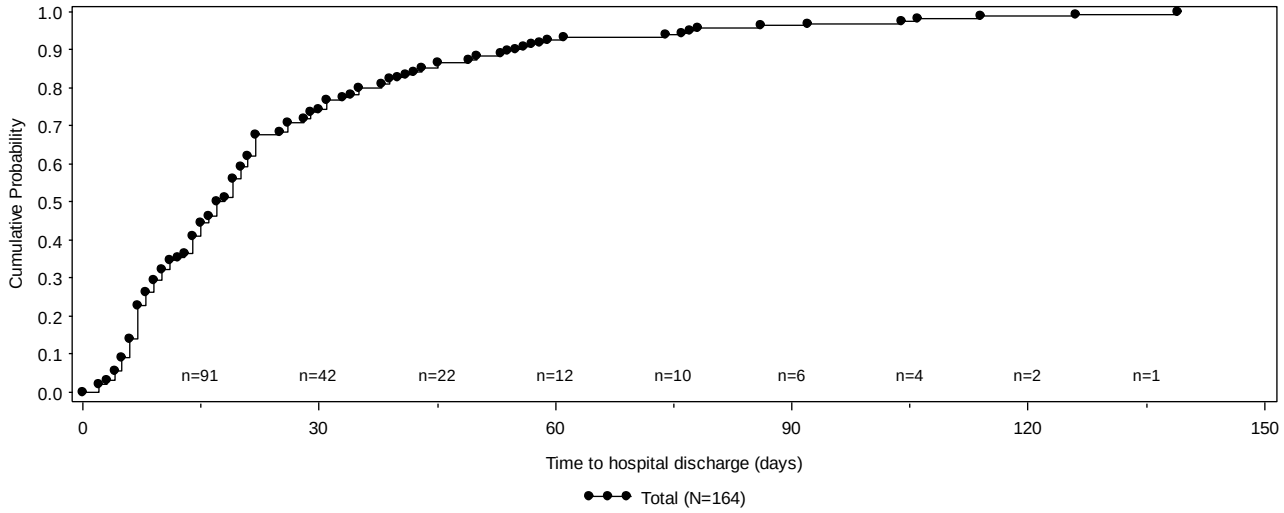
Sub-group analyses are provided by country.

Reference: Summary Table 26.1, 26.2; TOC Summary Tables & Figures in Section 14.

11.5.8 Time to Hospital Discharge

The Kaplan-Meier analysis yielded a mean time-to-hospital discharge of 24.9 ± 24.6 (median 17.5) days [95%-CI: 15.0; 20.0] (n = 164).

In-Text Figure 2: Time to Hospital Discharge [Kaplan-Meier]



Source: Figure 5.

Sub-group analyses are provided by country and site.

Reference: Summary Table 27.1, 27.2.1, 27.2.2; TOC Summary Tables & Figures in Section 14.

11.6 Adverse Events (AEs)

11.6.1 All (Overview)

In total, 582 AEs were recorded in 119/164 patients (72.6%), including 68 AEs in 33/164 patients (20.1%), which started before initiation of NexoBrid® treatment, and 514 AE in 119/164 patients (72.6%), which started after initiation of NexoBrid® treatment.

514 AEs with an onset after start of the first NexoBrid® application were found in 119/164 (72.6%) patients, thereof were 217 AEs in 100/164 patients (61.0%), which occurred within 72 hours after NexoBrid® application.

The relatedness to the NexoBrid® treatment was assessed (i.e., relatedness at least possible) for 65 AEs (12.6%) in 47/164 (28.7%) patients, thereof 5 AEs in 3/164 patients (1.8%), which were classified as serious.

One patient (no. 303014) had an AE that lead to early discontinuation of NexoBrid® treatment (reported as drug interrupted). This patient had an AE of MedDRA Preferred Term urticaria that developed two and a half hours after start of treatment with NexoBrid®. The patient received also tramadol and methimazole during NexoBrid® treatment.

In-Text Table 16: Summary of All AEs

AE Term	Patients		AE
	n	n/164 [%]	n
Adverse Event	119	72.6	582
Classification: mild	82	50.0	219
Classification: moderate	79	48.2	268
Classification: severe	44	26.8	86
Classification: serious (SAE) *	35	21.3	97
Onset: before start of NexoBrid®	33	20.1	68
Onset: after start of NexoBrid®	119	72.6	514
Onset: after start of NexoBrid® within 72 hours	100	61.0	217
Classification: related to NexoBrid®	47	28.7	65
Classification: related to NexoBrid® & serious (SAE)	3	1.8	5

Source: Summary Table 31.

* Including one AE with an unknown seriousness.

11.6.1.1 By Severity

The below In-Text Table 17 summarises all AEs that occurred both before and after NexoBrid® treatment. For 9 AEs, the severity was not documented (missing data).

In-Text Table 17: All AEs by Severity

Severity	Patients		AE
	n	n/164 [%]	n
Mild	82	50.0	219
Moderate	79	48.2	268
Severe	44	26.8	86
unknown	5	3.0	9
TOTAL	**-**	**-**	**582**

Source: Summary Table 33.

Most frequent, severe AEs attributed to the MedDRA System Organ Classes (> 10 AE attributions) were general disorders and administration site conditions (36 AEs), including most frequently (MedDRA Preferred Term) pain (20 AEs), and infections and infestations (10 AEs).

A complete account by severity is given in Summary Table 33; TOC Summary Tables & Figures in Section 14.

11.6.1.2 By Relationship to NexoBrid®

The below In-Text Table 18 summarises all AEs that occurred both before and after NexoBrid® treatment. For 4 AEs, the relationship was not documented (missing data).

In-Text Table 18: All AEs by Relationship

Relationship	Patients		AE
	n	n/164 [%]	n
Not feasible	9	5.5	14
Not related	100	61.0	478
Remotely related	16	9.8	21
Possibly related	26	15.9	36
Probably related	7	4.3	11
Related	17	10.4	18
unknown	3	1.8	4
TOTAL	**-**	**-**	**582**

Source: Summary Table 34.

According to the protocol, AEs are considered related to NexoBrid® when they were assessed as possibly, probably, or related.

According to this definition, 65 AEs in 47/164 patients were related to the NexoBrid® application.

Most frequent, related AEs attributed to the MedDRA System Organ Class (> 10 AE attributions) and appropriate Preferred Terms were general disorders and administration site conditions (possibly = 18/164 patients (11.0%) with 24 AEs; probably = 7/164 patients (4.3%) with 9 AEs); related = 16/164 patients (9.8%) with 16 AEs) including most frequently pain (possibly = 11/164 patients (6.7%) with 15 AEs; probably = 3/164 patients (1.8%) with 5 AEs); related = 15/164 patients (9.1%) with 15 AEs) and pyrexia (possibly = 6/164 patients (3.7%) with 6 AEs; probably = 4/164 patients (2.4%) with 4 AEs); related = 1/164 patients (0.6%) with 1 AE).

A complete account by relationship is given in Summary Table 34; TOC Summary Tables & Figures in Section 14.

11.6.1.3 By Seriousness

In total, 97 SAEs were recorded in 35/164 patients (21.3%).

The below In-Text Table 19 summarises all SAEs that occurred both before and after NexoBrid® treatment. For 1 AEs, the seriousness was not documented (missing data).

In total, 97 serious adverse events (SAE) were reported.

The following In-Text Table 19 provides an overview of all MedDRA System Organ Class attributions (preferred terms displayed, when >4 AE attributions).

In-Text Table 19: All SAEs by MedDRA System Organ Class

SOC	Patients		SAE
	n	n/164 [%]	n
Infections and infestations	18	11.0	22
pneumonia 8/164 patients (4.9%), 8 AEs wound infection 5/164 patients (3.0%), 5 AEs			
General disorders and administration site conditions	13	7.9	21
impaired healing 8/164 patients (4.9%), 16 AEs			
Injury, poisoning and procedural complications	7	4.3	13
graft loss 4/164 patients (2.4%), 9 AEs			
Respiratory, thoracic and mediastinal disorders	7	4.3	8
Psychiatric disorders	7	4.3	7
delirium 6/164 patients (3.7%), 6 AEs			
Vascular disorders	4	2.4	4
Blood and lymphatic system disorders	3	1.8	3
Cardiac disorders	3	1.8	3
Renal and urinary disorders	3	1.8	3
Metabolism and nutrition disorders	3	1.8	3
Skin and subcutaneous tissue disorders	2	1.2	2
Gastrointestinal disorders	2	1.2	2
Nervous system disorders	1	0.6	2
Eye disorders	1	0.6	1
Hepatobiliary disorders	1	0.6	1
Musculoskeletal and connective tissue disorders	1	0.6	1
Surgical and medical procedures	1	0.6	1
TOTAL	**##**	**##**	**97**

Source: Summary Table 37.

Most frequent, serious AEs attributed to the MedDRA System Organ Classes (> 10 AE attributions) were infections and infestations (22 AEs in 18/164 patients), general disorders and administration site conditions (21 AEs in 8/164 patients), and injury, poisoning and procedural complications (13 AEs in 7/164 patients).

A complete account by MedDRA System Organ Class and Preferred Term is given in Summary Table 37; TOC Summary Tables & Figures in Section 14.

11.6.2 Onset After NexoBrid® Application

514 out of the 582 reported AEs started after first NexoBrid® application. These were found in 119/164 (72.6%) patients.

The following In-Text Table 20 provides an overview of all MedDRA System Organ Class attributions (preferred terms displayed, when >10 AE attributions).

In-Text Table 20: All AEs After NexoBrid® Application

SOC Preferred Terms (>10 AE attributions)	Patients n	 n/164 [%]	AE n
General disorders and administration site conditions pain 64/164 patients (39.0%), 130 AEs pyrexia 35/164 patients (21.3%), 66 AEs impaired healing 18/164 patients (11.0%), 28 AEs	89	54.3	231
Infections and infestations wound infection 15/164 patients (9.1%), 15 AEs pneumonia 11/164 patients (6.7%), 12 AEs	41	25.0	72
Skin and subcutaneous tissue disorders pruritus 20/164 patients (12.2%), 20 AEs	27	16.5	29
Injury, poisoning and procedural complications graft loss 9/164 patients (5.5%), 14 AEs	17	10.4	28
Gastrointestinal disorders nausea 11/164 patients (6.7%), 14 AEs	19	11.6	26
Psychiatric disorders delirium 10/164 patients (6.1%), 10 AEs	23	14.0	25
Vascular disorders	15	9.1	15
Metabolism and nutrition disorders	11	6.7	13
Blood and lymphatic system disorders	10	6.1	10
Cardiac disorders	9	5.5	10
Nervous system disorders	9	5.5	11
Respiratory, thoracic and mediastinal disorders	8	4.9	10
Investigations	7	4.3	10
Musculoskeletal and connective tissue disorders	5	3.0	8
Renal and urinary disorders	5	3.0	5
Immune system disorders	4	2.4	4
Hepatobiliary disorders	2	1.2	2
Surgical and medical procedures	2	1.2	2
Ear and labyrinth disorders	1	0.6	1
Endocrine disorders	1	0.6	1
Eye disorders	1	0.6	1
TOTAL	**-**	**-**	**514**

Source: Summary Table 32.

Most frequent AEs, which started after first NexoBrid® application, attributed to the MedDRA System Organ Classes (> 10 AE attributions) were general disorders and administration site conditions (231 AEs in 89/164 patients), infections and infestations (72 AEs in 41/164 patients), skin and subcutaneous tissue disorders (29 AEs in 27/164 patients), injury/poisoning/procedural complications (28 AEs in 17/164 patients), gastrointestinal disorders (26 AEs in 19/164 patients), and psychiatric disorders (25 AEs in 23/164 patients).

Most frequent MedDRA Preferred Terms (>10 AE attributions) were pain (130 AEs in 64/164 patients), pyrexia (66 AEs in 35/164 patients), impaired healing (28 AEs in 18/164 patients), pruritus (20 AEs in 20/164 patients), wound infection (15 AEs in 15/164 patients), graft loss (14 AEs in 9/164 patients), nausea (14 AEs in 11/164 patients), pneumonia (12 AEs in 11/164 patients), and delirium (10 AEs in 10/164 patients). It should be noted that this analysis includes both patients treated with NexoBrid® only (89 patients) and those who were treated with NexoBrid® and surgical & non- surgical SoC (75 patients).

A complete account by MedDRA System Organ Class and Preferred Term is given in Summary Table 32; TOC Summary Tables & Figures in Section 14.

11.6.3 Onset Within 72 Hours After NexoBrid® Application

11.6.3.1 All AEs

217 out of the 582 reported AEs (37.3%) started within 72 hours after start of first NexoBrid® treatment in 100/164 patients (61.0%).

The following In-Text Table 21 provides an overview of all MedDRA System Organ Class attributions (preferred terms displayed for >10 AE attributions).

In-Text Table 21: All AEs Within 72 h After NexoBrid® Application

SOC Preferred Terms (>10 AE attributions)	Patients		AE n
General disorders and administration site conditions	65	39.6	85
pain 42/164 patients (25.6%), 54 AEs pyrexia 23/164 patients (14.0%), 23 AEs			
Infections and infestations	23	14.0	25
pneumonia 11/164 patients (6.7%), 11 AEs			
Psychiatric disorders	20	12.2	21
Gastrointestinal disorders	16	9.8	18
nausea 10/164 patients (6.1%), 11 AEs			
Injury, poisoning and procedural complications	6	3.7	10
Skin and subcutaneous tissue disorders	8	4.9	8
Vascular disorders	8	4.9	8
Respiratory, thoracic and mediastinal disorders	6	3.7	6
Metabolism and nutrition disorders	5	3.0	6
Cardiac disorders	4	2.4	5
Blood and lymphatic system disorders	4	2.4	4
Immune system disorders	4	2.4	4
Investigations	4	2.4	4
Nervous system disorders	4	2.4	4
Renal and urinary disorders	4	2.4	4
Musculoskeletal and connective tissue disorders	2	1.2	3
Endocrine disorders	1	0.6	1
Hepatobiliary disorders	1	0.6	1
TOTAL	**-**	**-**	**217**

Source: Summary Table 35.1.

Most frequent AEs, which started within 72 hours after first NexoBrid® application, attributed to the MedDRA System Organ Classes (> 10 AE attributions) were general disorders and administration site conditions (85 AEs in 65/164 patients), including mostly pain (54 AEs in 42/164 patients) and pyrexia (23 AEs in 23/164 patients), infections and infestations (25 AEs in 23/164 patients), including mostly pneumonia (11 AEs in 11/164 patients), psychiatric disorders (21 AEs in 20/164 patients), gastrointestinal disorders (18 AEs in 16/164 patients), including mostly nausea (11 AEs in 10/164 patients), and injury, poisoning and procedural complications (10 AEs in 6/164 patients).

A complete account by MedDRA System Organ Class and Preferred Term is given in Summary Table 35.1; TOC Summary Tables & Figures in Section 14.

11.6.3.2 Related AEs

AEs which occurred within 72 hours after start of first NexoBrid® application, which were assessed as related (i.e. relationship at least possible) are presented in In-Text Table 22. These conditions apply for 52 AEs in 42/164 patients (25.8%).

The following In-Text Table 22 provides an overview of all MedDRA System Organ Class and Preferred Terms attributions.

In-Text Table 22: Related AEs Within 72 h After NexoBrid® Application

SOC		Patients		AE
Preferred Terms		n	n/164 [%]	n
General disorders and administration site conditions		37	22.6	40
pain	28/164 patients (17.1%), 30 AEs			
pyrexia	10/164 patients (6.1%), 10 AEs			
Skin and subcutaneous tissue disorders		4	2.4	4
pruritus	3/164 patients (1.8%), 3 AE			
urticaria	1/164 patients (0.6%), 1 AE			
Psychiatric disorders		2	1.2	2
anxiety	1/164 patients (0.6%), 1 AE			
nervousness	1/164 patients (0.6%), 1 AE			
Vascular disorders		2	1.2	2
hypertension	2/164 patients (1.2%), 1 AE			
Injury, poisoning and procedural complications		1	0.6	2
wound haemorrhage	1/164 patients (0.6%), 1 AE			
wound secretion	1/164 patients (0.6%), 1 AE			
Cardiac disorders		1	0.6	1
bradycardia	1/164 patients (0.6%), 1 AE			
Musculoskeletal and connective tissue disorders		1	0.6	1
pain in extremity	1/164 patients (0.6%), 1 AE			

Source: Summary Table 35.2.

The AEs were predominantly attributed to the MedDRA System Organ Class general disorders and administration site conditions in 37/164 patients (22.6%) for 40 AEs, namely pain (30 AEs) and pyrexia (10 AEs).

The remaining 12 AEs belong to the MedDRA System Organ Classes skin and subcutaneous tissue disorders (3 AEs pruritus in 3/164 patients [1.8%] and 1 AE urticaria in 1/164 patient [0.6%]), psychiatric disorders (1 AE anxiety in 1/164 patient [0.6%] and 1 AE nervousness in 1/164 patient [0.6%]), vascular disorders (1 AE hypertension in 2/164 patients [1.2%]), injury, poisoning and procedural complications (1 AE wound haemorrhage in 1/164 patient [0.6%] and 1 AE wound secretion in 1/164 patient [0.6%]), cardiac disorders (1 AE bradycardia in 1/164 patient [0.6%] that suffered electrical burn), and musculoskeletal and connective tissue disorders (1 AE pain in extremity in 1/164 patient [0.6%]).

A complete account by MedDRA System Organ Class and Preferred Term is given in Summary Table 35.2; TOC Summary Tables & Figures in Section 14.

11.6.3.3 SAEs

Of interest are also SAEs, which occurred within 72 hours after start of first NexoBrid® application and which were assessed as related to NexoBrid® treatment (i.e. relationship at least possible, or unknown). Three (3) out of 36 SAEs were assessed as related or the relationship was unknown to the NexoBrid® application. In-Text Table 23 provides more details:

In-Text Table 23: Related SAEs Within 72 Hours after NexoBrid® Application

Patient ID / Treatment	CRF term	Preferred term	SOC	Seriousness	Severity	Relationship	Action	Duration	Outcome
101011 NexoBrid®	Urine infection	Urinary tract infection	Infections ...	UNK	UNK	UNK	ConMed	UNK	recovered
502006 NexoBrid®	Pain	Pain	General disorders ...	serious	moderate	related	ConMed	2 days	recovered
502022 NexoBrid®	Pain	Pain	General disorders ...	serious	severe	related	ConMed	8 days	recovered

Source: Raw Data Listing 27

(UNK = unknown, no data collected).

However, a relationship to the NexoBrid® (related) application was assessed for 2 SAEs (pain) in 2 patients (1.2%). The below sub-sections provide more details:

Patient 502006 (Spain):

This is a 51-years old, native Hawaiian / Pacific Islander female with an elevated BMI (38.7 kg/m^2) and a history of an arterial hypertension and of a mycosis since 14-Jul-2015.

The burn was caused by scald on 31-Oct-2015 20:00. It affected 1 wound at the right hand representing a TBSA of 1.0%. Apart from the injury, the physical examination did not reveal any pathological findings.

On 02-Nov-2015, NexoBrid® and soaking were applied, and the wound was covered with biobrane. On 21-Dec-2015, wound closure by the graft was confirmed, other relevant details regarding the wound treatment with NexoBrid® and follow-up are not documented.

Pain management was performed prior to application and removal of NexoBrid®. Midazolam, fentanyl, ropivacaine, metamizole, paracetamol, biobrane, nitrofurazone, dressing post-NexoBrid®, mepivacaine, and fentanyl were administered as concomitant medication to the patient on the same day.

Pain was recorded on 02-Nov-2015 and assessed as serious. Recovered the day after on 03-Nov-2015.

Patient 502022 (Spain):

This is a 35-years old, Hispanic or Latino male with a history of an ocular burn (see below).

The burn was caused by fire / flame on 05-Nov-2016 14:00, inducing an ocular burn and 2 burn wounds at both lower arms and both hands, which represented 8.0% of the TBSA. Apart from the injury, the physical examination did not reveal any pathological findings.

On 08-Nov-2015, NexoBrid® was applied on both wounds in assumed compliance to the educational material, although duration of soaking was not documented. On 09-Nov-2016, the wound was covered with nitrofural plus Mepitel®. On 07-Dec-2016, 100% wound closure by the graft was confirmed.

Between 08-Nov-2016 and 15-Nov-2016, the patient received paracetamol, dexketoprofen, morphine, tramadol, ibuprofen, diazepam, lorazepam, and clorazepate, as well as chloramphenicol, dexamethasone, and carbomer for the ocular burn. RBC and Leukocytes were out of normal ranges.

The following AEs were recorded:
- 08-Nov-2016 00:00 pain (related, severe, serious; therapy; recovered on 15-Nov-2016),
- 09-Nov-2016 18:30 pyrexia (possible, mild; therapy; recovered on 09-Nov-2016),
- 10-Nov-2016 hypertension (possible, mild; therapy; recovered on 25-Nov-2016).

Displays of serious adverse events by patient are provided in Raw Data Listing 27; TOC Raw Data Listings in Section 15.

11.7 Vital Signs

The last recorded parameters were at hospital discharge:

Systolic blood pressure 124.0 ± 15.7 [120.5] mmHg (n = 154), diastolic blood pressure 72.1 ± 9.8 [70.0] mmHg (n = 154), pulse rate 77.9 ± 12.5 [76.0] beats/minutes (n = 155), and body temperature 36.49 ± 0.46 [36.50] °C (n = 156). Data for body weight were available in 6 patients only.

All median values decreased from hospital admission to discharge (absolute changes): systolic/diastolic blood pressure by -6.0/-3.5 mmHg, pulse rate by -4.0 beats per minutes, and body temperature by -0.05 °C.

11.8 Physical Examination

The number of patients with available data was reduced from hospital admission to discharge by almost half from 153/164 patients (93.3%) to 64/164 patients (39.0%). Based on these frequencies, 92/164 patients (56.1%) had at least one documented abnormal finding at admission and 42/164 patients (25.6%) at discharge.

The most frequent abnormal body systems (> 10% attributions) were skin (75/164 patients, 45.7%), head / neck (24/164 patients, 14.6%), and extremities / back (29/164 patients, 17.7%) at admission, and skin (40/164 patients, 24.4%) at discharge.

Reference: Summary Table 39; TOC Summary Tables & Figures in Section 14.

11.9 Laboratory Parameters

The analysis of laboratory values was not performed, as in many cases the recorded unit did not match with the appropriate value (reference: DRM meeting minutes). Laboratory values were documented only for hospital admission before NexoBrid® application.

See also Section 9.10.2, changes to planned analyses.

Reference: Raw Data Listing 12, 13; TOC Raw Data Listings in Section 15.

11.10 Summary and Conclusions on Data Evaluation

Primary and Key-Secondary Endpoints:

The primary efficacy variable "pain incidence" is defined as "at least 2 pain events during the debridement procedure, from start of treatment until end of soaking period 2 hours post-NexoBrid® removal with subsequent pain medication". The rate of 0.6% lies below the given non-inferiority limit of 13.6% (p<0.0001). Conclusively, the incidence of pain in routine clinical practice after implementation of risk-minimisation measures did not exceed the incidences of pain in the previously conducted clinical trials before implementation of risk-minimisation measures.
The result could be confirmed in patients with available data, who were treated with NexoBrid® in compliance with the educational material (p<0.0001), but not in a worst-case scenario, which included also any "possible" pain events, defined as any pain assessed in the eCRF module "pain assessment" that occurred within 2 hours soaking after NexoBrid® removal (p=0.0636).

The primary efficacy variable "pyrexia incidence" is defined as "temperature >38.5 °C within 48 hours from start of NexoBrid® treatment, i.e. requiring fever relief medications prescribed due to high temperature within 1 hour from complaint or consecutive measurements of high temperature (>38.5 °C) 4 to 6 hours apart. The rate of 3.7% lies below the given non-inferiority limit of 29.1% (p<0.0001). Conclusively, the incidence of "pyrexia in routine clinical practice after implementation of risk-minimisation measures " did not exceed the incidences of pyrexia in the previously conducted clinical trials before implementation of risk-minimisation measures.
The result was confirmed in patients with available data, who were treated with NexoBrid® in compliance with the educational material (p<0.0001) and in a worst-case scenario, which includes also any "possible" pyrexia events, defined as any body temperature recorded in the eCRF modules "pyrexia assessment" or "vital signs" that lies above 38.5 °C (p<0.0001).
Pyrexia was observed with similar rates in patients suffering from both small and large burn areas (%TBSA burned). As the dose of NexoBrid® is defined according to the size of the burn, 2g NexoBrid® per 1 %TBSA, this could suggest that there is no dose relationship.

Both null-hypotheses (regarding pain and pyrexia) were rejected simultaneously, which implicates that the primary study objective was achieved at a significance level of p<0.025.

The key-secondary variable "wound-infection incidence" is defined as "prescription of antibiotics during the first week following debridement with NexoBrid® to a patient captured with positive swabs and/or positive wound biopsies performed".
The wound infection incidence rate of 7.3% lies below the given non-inferiority limit of 15.2% (p<0.0051). By conclusion, the incidence of wound infections in routine clinical practice after implementation of risk-minimisation measures did not exceed the incidences of wound infections in the previously conducted clinical trials before implementation of risk-minimisation measures. The incidence rate of infection found in this study is very similar to that observed in clinical studies for both NexoBrid® and SoC treated patients (8.2% and 7.9% respectively).
The result was confirmed in patients with available data, who were treated with NexoBrid® in compliance with the educational material (p=0.0076), but not in a worst-case scenario, which includes also "possible" wound infections, defined as any hint for wound infection (i.e., an antibiotic recorded in the eCRF module previous and concomitant medication that was given within 1 week after debridement, a positive wound culture as assessed in the eCRF module "wound culture", or a positive wound biopsy as assessed in the eCRF module "wound biopsy"). Inclusion of any antibiotic recorded in the eCRF within 1 week after debridement in this worst-case scenario, includes patients receiving antibiotics for prophylaxis and for general infections as pneumonia and who do not experience wound infections. Additionally, positive wound cultures do not necessarily represent a burn wound infection. All burn wounds are contaminated and clinical diagnosis between a contaminated wound to various degrees of wound infections and invasive wound infections depends on objective criteria of quantitative culture. Other definitions of wound infections are uniformly accepted by all and greatly depended on aetiology and subjective impressions.
For patients that had reported adverse events of wound infection, none of these adverse events were reported as related (at least possibly) to NexoBrid® treatment.

In 79.9% patients [95%-CI: 72.9; 85.7], the responsible physicians treated all wounds of the respective patient in "total compliance" (key-secondary efficacy variable) with the educational material. Total compliance, meant that all wounds were applied an antibacterial soaking before and after NexoBrid® application and pain was adequately managed before NexoBrid® application and removal.
The observed total compliance rate of 79.9% [95%-CI: 72.9%; 85.7%] is consistent with the predefined desired rate of compliance of 80% based on available study data. The results were comparable in the best-case scenario (81.7% [74.9; 87.3]), which includes also all missing data imputed to compliance, and about half lower in the worst-case scenario (43.9% [36.2; 51.9]), which includes also all missing data imputed to non-compliance.
Comparing all compliance criteria separately, it was found that the partial compliance rates differ by 41% from the highest to the lowest compliance level: in detail, from 93.9% for pain managed before applying NexoBrid® and 79.2% for pain managed before removing NexoBrid®, to 57.8% for antibacterial soaking applied after NexoBrid® and 52.7% for antibacterial soaking applied before NexoBrid®.
The above results at the patient level were comparable to the results at the wound level.
Although higher compliance rates were observed for pain management before application / removal of NexoBrid® versus compliance rates for applying antibacterial soaking before / after application of NexoBrid®, higher percentages of missing data were found for application of antibacterial soaking compared to pain management and therefore the difference in compliance rates may also be due to missing data and not entirely due to actual incompliance. The high percentages of missing data for application of antibacterial soaking may be due to the fact that this is not necessarily a standard procedure that is routinely documented in hospital files as is documentation of pain medication provided.

Based on the primary and key secondary endpoints results it can be concluded that the applied risk-minimisation measures in burn patients treated with NexoBrid® in the first two years from national product launch are effective.

Risk-Factor Analyses:

Pain, pyrexia, and wound infection were tested against pre-defined, potential risk factors (definition, see In-Text Table 7) applying univariate and multivariate risk-factor analyses. The univariate risk-factor analysis identified the TBSA, Tobiasen's abbreviated Burn Severity Index, and off-label treatment as potential risk factors for wound infection, but a statistically relevant influence of the variables on the incidence of wound infection was not confirmed in the final multivariate logistic regression model, which resulted in higher p-values for TBSA (p = 0.1288), Tobiasen's abbreviated Burn Severity Index (p = 0.6474), and off-label treatment (p = 0.0931). The p value and the estimate for off-label treatment hypothesises that off-label treatment may be associated with higher wound infections.

Additional Secondary Endpoints:

No severe irritations were observed within this study, allergic reactions were observed in 1/164 patients (0.6%), cardiopulmonary events in 7/164 patients (4.3%), all assessed as not related to NexoBrid, wound-related complications in 2/164 patients (1.2%), severe blood loss in 8/164 patients (4.9%), and off-label treatment of NexoBrid® in 32/164 patients (19.5%). Off-Label application of NexoBrid® was due to treatment of facial/perineal/genital burns (14/164 patients, 8.5%), treatment of children (2/164 patients, 2.4%), application to wounds representing >15 %TBSA in one session (10/164 patients, 6.1%), and repeated application in more than one session (9/164 patients, 5.5%).

All treated patients were discharged from hospital after a median of 17.5 days [15.0; 20.0].
The median time to wound closure was 42.0 days [38.0; 51.0] at the patient level. At the wound level, the median time until wound closure was 39.0 days [36.0; 41.0]; the results were comparable between wounds treated with NexoBrid® and SoC procedures. Assessment of wound closure was done in many cases after hospital discharge, so earlier wound closures could not be captured in real time, but only during the next follow-up visit and the frequency of follow-up visits is not standardised between sites or countries.

Adverse Events:

Overall, 582 AEs in 119/164 patients (72.6%) were entered in the eCRF.

The severity of all AEs was assessed as mild (219 AEs), moderate (268 AEs), and severe (86 AEs), for 9 AEs, severity was unknown.
The highest incidences of severe AEs at the MedDRA preferred term level were observed for general disorders and administrative site conditions (36 AEs) and infections and infestations (10 AEs).

For 65 AEs in 47/164 (28.7%) patients, the investigators assumed a relationship (of at least possible) to the NexoBrid® application.
Most frequent, related AEs attributed to the MedDRA System Organ Classes were general disorders and administration site conditions (49 AEs, thereof 35 AEs pain and 11 AEs pyrexia).

In total, 97 SAEs were documented in 35/164 (21.3%) patients. For 5 SAEs in 3/164 (1.8%) patients, the investigators assumed a relationship (of at least possible) to the NexoBrid® application.
Most frequent, SAEs attributed to the MedDRA System Organ Classes were infections and infestations (22 SAEs), general disorders and administration site conditions (21 SAEs, thereof 16 SAEs impaired healing), and injury, poisoning and procedural complications (13 SAEs).

514 AEs were found in 119/164 patients (72.6%), which started after the first NexoBrid® application.
Most frequent AEs attributed to the MedDRA System Organ Classes were general disorders and administration site conditions (231 AEs, thereof 130 AEs pain, 66 AEs pyrexia, 28 AEs impaired healing), infections and infestations (72 AEs, thereof 15 AEs wound infection, 12 AEs pneumonia), skin and subcutaneous tissue disorders (29 AEs, thereof 20 AEs pruritus), injury/poisoning/procedural complications (28 AEs, thereof 14 AEs graft loss), gastrointestinal disorders (26 AEs, thereof 14 AEs nausea), and psychiatric disorders (25 AEs, thereof 10 AEs delirium).

217 AEs were found in 100/164 patients (61.0%), which started within 72 hours after first NexoBrid® application.
Most frequent AEs attributed to the MedDRA System Organ Classes were general disorders and administration site conditions (85 AEs, thereof 54 AEs pain, 23 AEs pyrexia), infections and infestations (25 AEs, thereof 11 AEs pneumonia), psychiatric disorders (21 AEs), gastrointestinal disorders (18 AEs, thereof 11 AEs nausea), and injury, poisoning and procedural complications (10 AEs).

Of the 217 AEs, which started within 72 hours after NexoBrid® first application, 52 AEs in 42/164 patients (25.8%) were identified, which were assessed by the investigators as related, i.e. at least possibly related. The AEs were predominantly attributed to the MedDRA System Organ Class general disorders and administration site conditions in 37/164 patients (22.6%) for 40 AEs, namely pain (30 AEs) and pyrexia (10 AEs). The relationships to NexoBrid® was assessed for these AEs retrospectively, and 7 of the 10 AEs of pyrexia that were assesses as related to NexoBrid® were not compliant with the minimal characteristics to be included in the primary endpoint of incidence of pyrexia, meaning that either no fever-relief medications were prescribed, the temperature measured was under 38.5 ºC, or there was only one measurement of a high temperature with no consecutive measurements. This, again, emphasises the difficulty in retrospective assessments of adverse events and specifically of the causality.

Of the 217 AEs, which started within 72 hours after NexoBrid® first application, 7 AEs in 7/164 patients (4.8%) were assessed by the investigators as serious. However, a relationship to the NexoBrid® application (i.e. relatedness is at least possible) was confirmed by the investigators for only 2 SAEs (pain) in 2 patients (1.2%). For one additional SAE (urinary tract infection), the relationship to NexoBrid® is unknown.

12 DISCUSSION AND OVERALL CONCLUSIONS

12.1 Discussion

The main goal of this study was to assess the effectiveness of the risk-minimisation measures based on the incidence rate of pain and pyrexia (primary key endpoints) in burn patients treated with NexoBrid® reported in the first two years from product launch in each participating country in routine clinical practice.
The incidence rates of both primary efficacy variables were below their pre-defined non-inferiority limits (both at $p < 0.0001$) demonstrating that the incidences of pain and pyrexia in this retrospective study of routine clinical practice did not significantly exceed the incidence rates in clinical trials. Therefore, the results of this study are supportive of the applied risk-minimisation measures as effective measures.

Of specific interest from the secondary endpoints were the incidence rate of wound infections (also in comparison to prior clinical trials) and the compliance of the physicians with the instructions from the educational material that relate to the risk-minimisation measures. Therefore, these parameters were defined as key-secondary endpoints.

The incidence rate of the key-efficacy variable wound infection was below its pre-defined non-inferiority limit $p = 0.0051$), which provides evidence that the incidence of wound infections in the study did not exceed the appropriate incidence rate in prior clinical trials.

Physicians were in total compliance with the educational material in 131/164 patients (79.9%). Total compliance was assessed to have occurred when for all wounds an antibacterial soaking was applied before and after NexoBrid® application and pain was adequately managed before NexoBrid® application and before NexoBrid® removal. The observed compliance rate is consistent with the predefined desired rate of 80% based on available study data. The results show very high compliance rate in pain management prior to application / removal of NexoBrid®, 93.9% and 79.3%, respectively. The compliance with soaking was in lower rates before and after treatment with NexoBrid®, 56.1% and 64.0%, however this incompliance was not identified as a risk factor for infection rate. Additionally, higher percentages of missing data were found for the application of antibacterial soaking compared to pain management and therefore the difference in compliance rates may also be due to missing data and not entirely due to actual incompliance (3,6,7,8,11,13).

Additional secondary outcomes were analysed and are summarised below. Overall, the reported rates are similar to the rates reported in the literature for burn patients.

Severe Irritations were not observed in any patient. Any allergic reaction within 96 hours from start of first wound treatment occurred in 1/164 patient (0.6%).

Cardiopulmonary events, which occurred 48 hours from start of first treatment with NexoBrid®, were recorded in 7/164 patients (4.3%). Cardiopulmonary adverse events recorded during the study for these patients were all assessed as not related to NexoBrid®. Cardiopulmonary AEs reported in those patients included the following: ventricular extrasystoles, supraventricular tachycardia (both in the same patient who suffered electrical burn), atrial fibrillation, each in one patient. According to the literature, arrhythmias are reported in burn patients, occurring in approximately 30% of burned patients (3,7). In addition, 4 of these patients suffered from inhalation injury, and three of these patients had other cardiopulmonary background conditions, e.g., tobacco abuse, bronchial asthma, cardiomyopathy, hypertension, and arrhythmia.

Wound-related complications were identified and assessed in the data review meeting based on AEs with unknown or at least possible relatedness to NexoBrid®. 2/164 patients (1.2%) fulfilled the definition. Both patients suffered from graft loss assessed by the investigator as possibly related to NexoBrid®. Overall, 140/313 wounds (44.7%) were grafted following NexoBrid® treatment.

Severe blood loss was based on blood transfusions for packed red-blood cells and whole blood provided recorded within 24 hours from the debridement procedure. Overall, 8/164 patients (4.9%) received blood transfusions within 24 hours from the debridement procedure. Seven of the 8 patients were treated also with surgical SoC and 4/8 patients suffered from severe burns on areas above 30 %TBSA. The rates of burn patients that are reported in the literature for receiving blood transfusions during hospitalisation for acute burn care are 22-34% (6,7,11,13).

Off-label use of NexoBrid® was documented in overall 32/164 patients (19.5%). Reasons for documented off-label use were treatment of facial / perineal / genital burns in 14/164 patients (8.5%), treatment of paediatric patients in 4/164 patients (2.4%), NexoBrid® application at wounds representing >15 %TBSA in one session in 10/164 patients (6.1%), and repeated NexoBrid® application in more than one session in 9/164 patients (5.5%).

Data was collected in this study retrospectively and was based on chart reviews for patients that were discharged a few years earlier. This design, as discussed in the study protocol, has many limitations. These limitations resulted in, as expected, higher percentages of missing data in comparison with prospective, clinical studies, which was handled with additional sensitivity analyses.

Furthermore, it was anticipated in the protocol that collecting data retrospectively, especially for parameters that are being reported in routine practice and might result from the disease condition itself rather than from the medication (e.g. adverse events), may be difficult to interpret. This concern was addressed by defining relevant time windows and guidelines for adverse event reporting and specific causality assessment. In addition, while in the clinical studies patients were debrided only per their randomisation arm (NexoBrid® or SoC), in this study, patients were treated with mixed modalities and therefore the cause of some of the AEs cannot be determined.

The AE profile observed in this study was comparable to the profile reported in the Summary of Product Characteristics (SmPC). However, as anticipated due to the study design limitations, a higher number of AEs were reported as compared with the observed rate in clinical studies; in this study, 3.5 events were reported on average per patient, while in MW2004-11-02, 1.7 events were reported on average per patient. 514 AEs were found in 119/164 patients (72.6%), which started after the first NexoBrid® application.

Overall, 514 AEs were found in 119/164 patients (72.6%), which started after the first NexoBrid® application. Out of the 514, 217 AEs (42%) started within 72 hours after first NexoBrid® application. Of the 217 AEs, 52 AEs in 42/164 patients (25.8%) were assessed by the investigators as related, i.e. at least possibly related. The AEs were predominantly attributed to the MedDRA System Organ Class general disorders and administration site conditions in 37/164 patients (22.6%) for 40 AEs, namely pain (30 AEs) and pyrexia (10 AEs).

Pain is a well-known entity in deep partial thickness and full-thickness burn patients appearing during the burn treatment and healing period (1,14,16).

According to the data collected in this study, only one patient suffered from pain during the NexoBrid® treatment (repeated patient's complaints followed by prescription of pain management medications). The majority of pain AEs reported in the first 72 hours were post-NexoBrid® treatment and not procedural pain.

The events reported as pain AEs after NexoBrid® treatment did not comply with a consistent definition as usually done in controlled trials or as it is clearly defined for the primary endpoint in this study, and it was based on retrospective assessment of the patient's records a few years after the patient was discharged from the hospital. Most of the pain AEs that were assessed as related to NexoBrid® treatment did not consist of the minimal defined criteria to be included as cases for the primary endpoint of pain AEs.

NexoBrid® educational material does not refer to pain management post treatment. The latter is done according to the site's standard practice for pain management. Indeed, investigation of the data revealed that most of the pain AEs (25/30 pain AEs, 83.3%) reported after NexoBrid® treatment were from 4/14 sites (2 sites in Germany, 1 site in Belgium, and 1 site in Spain) that consist of 48.8% of all patients enrolled into the study. Each of these 4 sites reported 5 to 8 pain AEs in 21.4% to 57.1% of patients at each site, while in all other 10 sites, the frequency of AEs of pain in 72 hours post treatment ranged between 0 to 2 pain events per site.

As mentioned above, causality assessments were performed by the investigators retrospectively, which greatly differs from prospective assessments while patients are being treated. Hence, comparison of related rates to those observed in prospective and controlled clinical studies is inappropriate.

Pyrexia is a well-known phenomenon in burn patients. The burn patient is catabolic (18,19) with a very high basal metabolic rate (BMR), and often has elevated body temperature.

The rate of AEs of pyrexia assessed as related (6.1%) is well below the observed rate of 19.1% [12.9%; 27.4%], reported for NexoBrid® in clinical trials after implementation of risk-minimisation measures. Within the reported events of pyrexia, 7 of the 10 AEs of pyrexia that were assesses as related to NexoBrid® were not compliant with the minimal characteristics to be included in the primary endpoint of incidence of pyrexia, meaning that either no fever-relief medications were prescribed, the temperature measured was under 38.5 ºC, or there was only one measurement of a high temperature with no consecutive measurements. This, again, emphasises the difficulty in retrospective assessments of adverse events and specifically of causality.

No wound infection AE was assessed as related to study treatment.

12.2 Overall Conclusions

The main objective of this post-authorisation safety study (PASS) was to assess the effectiveness of the risk-minimisation measures based on the incidence rate of pain and pyrexia reported in the first two years from product launch in each participating country in routine clinical practice.

Overall, the training program was found to be effective, with comparable incidence rates of reported pain and pyrexia events in routine clinical practice compared to those obtained in clinical trials. For key-secondary variables, incidence of wound infection and physicians' compliance with educational materials, the results further confirm the conclusion that the training program is effective. For all data collected for the secondary variables, no safety concerns were raised, and the overall incidence rates were below the reported ones in the literature (for the variables that incidence rates from literature is available for comparison).

The AE profile observed in this study was comparable to the profile reported in the Summary of Product Characteristics (SmPC). However, as anticipated due to the study design limitations, a higher number of AEs were reported as compared with the observed rates in clinical studies. This can be attributed to the retrospective nature of data collected in this study.

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14 SUMMARY TABLES & FIGURES

(Pagination refers to: final Tables, version 16-May-2019)

15 RAW DATA LISTINGS

(Pagination refers to: final Listings, version 03-May-2019)

16 APPENDIX

The clinical study report refers to the following essential documents:

- NexoBrid® SmPC.
- Study protocol 7.0, 04-Jan-2018 (last signature date).
- Sample consent forms:
  - Master informed consent form for adults or children over 14 years old, Version 1.0, 05-Oct-2017,
  - Master informed consent form for children younger than 14 years old, Version 1.0, 27-Jun-2017,
  - Master informed consent form for parents, Version 1.0, 24-May-2017.
- CRF mock-Up 3.0, 26-Feb-2018.
- Statistical analysis plan, 22-May-2018 (last signature date).
- Data management plan, 21-Aug-2017 (last signature date).
- Data review meeting minutes, 23-Jan-2019 (last signature date).
- Tables, figures, listings, 03-May-2019.