SYNOPSIS

Protocol Number:	**MW 2012-01-01**
Name of Investigational Medicinal Product (IMP):	NexoBrid
EudraCT.-No.:	**2014-003066-24**
IND	**065448**
Name of Active Ingredient:	Concentrate of proteolytic enzymes enriched in bromelain
Study Title:	A multicenter, multinational, randomized, controlled, open label study, performed in children with thermal burns, to evaluate the efficacy and safety of NexoBrid as compared to standard of care (SOC) treatment
Clinical Phase:	3
Study Duration:	The total duration of the study treatment and follow up period of each participating subject is expected to be. at least 30 months after wound closure confirmation. Study duration will range from 31 months to 7 years and dependent on when the subject was enrolled.
Study Population:	Pediatric patients with thermal burn wounds defined as deep partial thickness and/or full thickness requiring hospitalization and who meet the entrance criteria will be enrolled in the study.
Study Objective(s):	To evaluate the safety and clinical benefit of NexoBrid in hospitalized children (0-18 years) with deep partial and/or full thickness thermal burns of 1-30% TBSA and to compare NexoBrid to standard of care (SOC).
Study Design Overview:	A total of 160 patients will be randomized into NexoBrid and SOC treatment (80 patients per arm)[1]. Age distribution will be managed as follows: o 45 patients ≥0 months and ≤23 months old o 45 patients ≥24 months and ≤3 years old o 30 patients ≥4 years and ≤11 years old

[1] The study was completed with 145 patients (please refer to Appendix 14 – Update to study sample size due to COVID-19 pandemic for additional information)

	o 20 patients ≥12 years and <18 years old In addition, the remaining 20 patients will be enrolled to any of the above groups, per their age during enrollment. The study will be conducted in three stages. In Stage I, at least 24 children age 4-18 years, hospitalized in burn units, with deep partial thickness burns ranging from 1%-30% TBSA, and who meet the entrance criteria, will be enrolled. Upon completion of stage I, a safety analysis will be performed on safety parameters and the results will be evaluated by a Data Safety Monitoring Board (DSMB) as defined in the agreed charter. If the DSMB does not have any safety concerns, Stage II will commence, this time enrolling at least 26 additional children aged of 1-18 years according to the study procedures. A DSMB will be convened to assess the safety data of the first 50 patients enrolled at stages 1 & 2. If the DSMB has not found any safety concerns, stage III will commence in which patients from the age of birth to 18 years will be included (stage III will include 110 remaining patients required to reach a total of 160 patients). Following the enrollment of a subject to the study and prior to randomization, physicians will define one or more Target Wounds (TWs) per subject according to TWs definition. All subjects' DPT and FT burns that fit the specified criteria are intended to receive study treatment per randomized study arm and therefore, must be designated as TWs. Patients will be stratified on the basis of age groups (as applicable at each study stage): 0-23 months, 24 months-3yrs, 4-11yrs and 12-18 yrs, on the basis of %TBSA, depth and center. Prior to eschar removal treatment with NexoBrid or SOC subjects will be medicated with appropriate analgesia and undergo wound cleansing and dressing of all wounds with antibacterial solutions. Following wound cleansing and antibacterial treatments, subjects will undergo the eschar removal process as per treatment assignment (NexoBrid or SOC, following randomization). Subsequent to eschar removal, all wounds will be assessed and treated in the same manner, in accordance with post-eschar removal wound care strategy. Furthermore, subjects will undergo daily assessments (Vital signs (VS) and pain assessments) from start of treatment until hospital discharge. Weekly follow-up assessments will be performed until complete wound closure. Following wound closure, subjects will be followed up at 6 weeks, 12 weeks, and after that, at 6, 12, 18 and 24 months (for a blinded assessment of cosmesis, function and QoL evaluation).

	All subjects will be invited to one additional extended follow up visit that will occur at least 30 months after wound closure confirmation for a blinded assessment of cosmesis, function and QoL evaluation
Dosage and route of administration:	Two grams or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle to obtain NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2g NexoBrid/20g Gel per 180cm² for four hours. In most cases, NexoBrid is effective after a single application; however it may be applied for a second time to the same burn area based on the investigator's judgment of debridement efficacy. NexoBrid should not be applied more than twice to the same burn wound area. NexoBrid should not be applied to more than 15% TBSA in one session.
Inclusion/ Exclusion Criteria:	**Inclusion Criteria- Patient level** 1. Stage 1: Males and females between 4 years to 18 years of age, Stage 2 (upon DSMB review): Males and females between 1 year to 18 years of age. Stage 3 (upon DSMB review): Males and females between 0 years to 18 years of age. 2. Thermal burns caused by fire/flame, scalds or contact. 3. Patient total burns area ≥ 1% DPT and / or FT, 4. Patient total burns area should be ≤ 30% TBSA; SPT, DPT and/or FT in depth, 5. Signed written informed consent by a legal guardian can be obtained within 84 hours of the burn injury. **Inclusion Criteria - Wound level** At least one wound (a continuous burn area which can be treated in one session; might include several anatomical areas) in a patient should meet all following criteria: 1. Wound that is ≥ 1% TBSA (DPT and/or FT) (not including face, perineal or genital), 2. Wound is composed of DPT and/or FT in depth. Superficial partial thickness areas may be included in the wound area only if cannot be separated from deeper areas (e.g. surrounded by or mixed with DPT areas) and might interfere with the treatment of the deeper areas, 3. Wound that is intended for surgical eschar removal, 4. Wound's blisters can be unroofed, as judged by the investigator.

	Exclusion Criteria 1. Patients weighing less than 3kg, 2. Patients who are unable to follow study procedures and follow up period, 3. Patients with electrical or chemical burns, 4. Patient with a continuous burn area above 15% TBSA, 5. Patients with no DPT and/or FT burn area (only SPT wounds), 6. Patient with circumferential anterior/posterior trunk fire/flame burns, >15% TBSA (Circumferential is defined as encircling ≥ 80% of the trunk circumference), 7. The following pre-enrolment dressings: a. Flammacerium, b. Silver Nitrate (AgNO3), 8. Serious pre-existing infection likely to impair the patient's safety or to interfere with study procedures[2] 9. Diagnosis of smoke inhalation injury, 10. Patients with pre-enrolment wounds which are covered by eschar heavily saturated with iodine or by SSD pseudoeschar (e.g. pseudoeschar as a result of >12h SSD treatment), 11. Patients with pre-enrolment escharotomy, 12. Pregnant women (positive pregnancy test) or nursing mothers, 13. Poorly controlled diabetes mellitus (HbA1c>9%)[3], 14. Known Cardio-pulmonary disease, oxygen-dependent pulmonary diseases, broncho-pneumonia, uncontrolled asthma, 15. Known conditions which interfere with circulation (peripheral vascular disease, edema, lymphedema, surgery to the regional lymph nodes, obesity), 16. Any known conditions that would preclude safe participation in the study or add further risk to the basic acute burn trauma (such as immuno-compromising diseases, life threatening trauma, severe pre-existing coagulation disorder, pulmono-cardiovascular, liver or neoplastic disease),

[2] as described in Section **Error! Reference source not found.**of study protocol

[3] For patients weighing under 18 kg at screening, HbA_1C will not be collected as a screening test. If an HbA_1C result is available from the past 3 months, the result can be taken into consideration for inclusion. Otherwise, diabetic patients weighing less than 18 kg cannot be included.

	17. ASA greater than 2 (see Appendix 13 in study protocol) 18. Chronic systemic steroid intake, 19. History of allergy and/or known sensitivity to pineapples, papaya, Bromelain or papain, 20. Current (within 12 months prior to screening) suicide attempt, 21. Enrollment in any investigational drug trial within 4 weeks prior to screening, 22. Current (within 12 months prior to screening) alcohol (daily consumption > 3 units for males and >2 units for females) or drug abuse4, 23. Prisoners and incarcerated 24. Patients who might depend on the clinical study site or investigator. 25. Patient expresses objection to participate in the study. 26. Patients with other severe cutaneous trauma at the same sites as the burns (i.e. blunt, avulsion or deep abrasion) or previous burn(s) at the same treatment site(s) 27. General condition of patient would contraindicate surgery
Outcome Measures:	**Primary Endpoint** The below primary endpoint will be investigated primarily at the subject level, on the ITT population (please refer to Section **Error! Reference source not found.**). Earlier eschar removal (in days): Demonstrate superiority over SOC for eschar removal as measured by a survival analysis of incidence of complete eschar removal as a function of time. Eschar removal will be measured at the end of the debridement starting from randomization date.

4 DSM-IV Criteria for substance abuse:
A pattern of substance use leading to significant impairment or distress, as manifested by one or more of the following during in the past 12 month period:
Failure to fulfill major role obligations at work, school, home such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household
Frequent use of substances in situation in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
Frequent legal problems (e.g. arrests, disorderly conduct) for substance abuse
Continued use despite having persistent or recurrent social or interpersonal problems (e.g., arguments with spouse about consequences of intoxication, physical fights)

Secondary Endpoints

The following secondary endpoints will be evaluated in this study and compared between NexoBrid and SOC on the ITT population, unless otherwise specified (please refer to Section **Error! Reference source not found.**).

1. Reduction in surgical need- Demonstrate superiority of NexoBrid over SOC in reduction of surgical need for excisional eschar removal as measured by an analysis of incidence of surgical eschar removal (tangential/ minor/ avulsion/ Versajet and/or dermabrasion excision).
2. Blood loss related to eschar removal- Demonstrate superiority of NexoBrid over SOC with regard to the blood loss occurred during the eschar removal procedures.
3. Reduction in the need for autograft - Percent area of deep partial thickness wounds autografted
4. Reduction in the need for autograft - Incidence of autograft performed in deep partial thickness wounds

Safety Outcome Measures:

1. Time to reach complete wound closure assessed in days, starting from randomization date
2. Cosmesis and Function- will be measured using MVSS, to demonstrate that treatment with NexoBrid does not have any clinically meaningful deleterious effect on burns scars quality as compared to the quality of burns scars treated with SOC, measured at 12 months from wound closure date, by a blinded assessor.
3. Cosmesis and Function- will be measured using MVSS, to demonstrate that treatment with NexoBrid does not have any clinically meaningful deleterious effect on burns scars quality as compared to the quality of burns scars treated with SOC, measured at 24 months from wound closure date, by a blinded assessor.
4. Additional Safety Outcome Measures:
    a. General parameters: Systemic adverse events, vital signs, pain assessment (using FPS-R and as reported as AEs), laboratory tests, units (and volume) of blood transfusion given during hospitalization, Immunogenicity evaluation for NexoBrid patients, Pyrexia and Hyperthermia, Systemic infections, Extent of antibiotic use (i.e. number of days of exposure), Rates

	of hospital readmission, Change in INR/PTT and incidence of change to > upper limit of normal (after treatment), Change in blood glucose and incidence of change to above upper limit of normal (after treatment). b. Long term functionality evaluation of the extremities using the 'Lower Extremity Functional Scale', 'QuickDASH' questionnaires and 'Range Of Motion' measurements, c. Long term Quality of Life using EQ5D and BOQ for a subset of patients. d. Local parameters: Local adverse events defined by treating physician or designee; graft loss, wound related infections, etc. **Exploratory Endpoint** 1. Incidence of surgical escharotomy procedures on circumferential extremities target wounds, 2. Incidence of reduction in interstitial/compartment pressure in circumferential extremity wounds (measured immediately following eschar removal), 3. Reduction in surgical needs as measured by an analysis of % wound area surgically excised for eschar removal. 4. Reduction in surgical need as measured by analysis of incidence of surgically harvested donor sites scars, 5. Reduction in surgical need as measured by analysis of % area of surgically harvested donor site scars. 6. Blood loss related to eschar removal assessed by changes in Hemoglobin incurred during the eschar removal procedures 7. PK evaluation in NexoBrid patients 8. Cosmesis and Function: Demonstrate non-inferiority to SOC in quality of scars of burns using POSAS treated with NexoBrid, measured at 12 months from wound closure, 9. Cosmesis and Function: Demonstrate non-inferiority to SOC in quality of scars of burns using POSAS treated with NexoBrid, measured at 24 months from wound closure,

	10. Duration of hospitalization.
Statistical Plan & Sample size:	**Primary Endpoints** The following primary endpoint will be evaluated in this study at a 'per patient' level: 1. Earlier eschar removal- Analysis will be based on the time from the date of randomization. NexoBrid will be compared with SOC using Cox regression analysis. Kaplan-Meier curves will be presented graphically to display the distribution of time to complete eschar removal under the two treatments. Subgroup analyses are based on the following: Age groups (Comparison of 0-23 months; 24 months-3 years; 4-11 years; 12-18 years). **Safety** The assessment of safety will be based on the safety collective and mainly on the frequency of adverse events and on the observation of clinically significant abnormalities of laboratory values as well as additional safety data (e.g., vital signs, pain by FPS-R, etc). PK parameters will be presented in summary tables including sample size, mean, SD, median, minimum and maximum values. Graphical presentation will be produced presenting the calculated AUC for each subject, a summary PK profile for all subjects, and summary PK profiles according to age groups and % TBSA treated. Antibodies presence will be determined based on a three-tiered approach analysis of plasma samples drawn prior to start of eschar removal and up to follow up visit at 24 months. **Sample Size Calculation** The following sample size calculation is based on the consideration of the primary endpoint of this study. *Primary Endpoint: Time to Complete eschar removal* Based on calculated HR (Hazard Ratio) from study MW2004-11-02, for 90% overall power, number per group = 22. In accordance with the European regulatory requests and planned age distribution, we believe that a sample size of 80 patients per arm will detect with a 90% power a difference on the primary endpoint, which is well within what would be expected based on the results from the previous study. *Based on the above calculations, we plan a study with total sample size of 160 patients; 80 (NexoBrid) + 80 (SOC).*

	Stages of Analysis The analysis is planned to be carried out in three stages, as described below. The first analysis will be performed at the end of the 12 months follow up period. This analysis will be the only inductive analysis of the trial and will include statistical tests for the primary and secondary endpoints as described above, as well as the 12 months safety endpoints. At this time-point, data will be available for all patients on the primary and secondary end-points, as well as the 12 months safety endpoints. Missing values for early dropouts etc. will be handled as described in Section 15.8.4 and the SAP. The complete data set documented so far will be locked and analyzed as described above. The 24 months MVSS data, although captured in the eCRF for a few of the subjects at this stage, will not be included, revealed (the medical assessor will remain blinded to the treatment arm) or analyzed during the first stage of analyses. The second analysis covers the data of the full 24 months safety follow up. It will be conducted after the last patient has reached the 24 months assessment, 12 months after the first stage of analysis. At this analysis, all accumulated safety endpoints at the 24 months follow up will be evaluated. The third and final analysis will cover the data derived from the additional long term follow up visit that will be performed at least 30 months post wound closure confirmation. Study results will be summarized in descriptive manner. Descriptive statistics for continuous variables will include n, mean, standard deviation, standard error of the mean, median, minimum and maximum. Descriptive statistics for categorical variables include patient counts and percentages.