CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761192Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Medical Officer's Memorandum: Resubmission of BLA 761192

Seq (SD)	0036 (36)
MO/TL:	Brenda Carr/David Kettl
Project Manager:	Jennifer Harmon
Submit date:	07/01/2022
Sponsor:	MediWound Ltd (MediWound)
Product:	concentrate of proteolytic enzymes enriched in bromelain; proposed tradename: Nexobrid
Pharmacologic Category:	proteolytic enzymes
Dosage Form:	gel
Route of Administration:	topical
Indication:	eschar removal in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns

Background

Nexobrid is a new botanical and biologic that contains proteolytic enzymes enriched in bromelain. It is extracted from the stems of the pineapple plant (*Ananas comosus*). The Applicant submitted the original BLA on 6/29/2020.The application received a Complete Response on 06/25/2021 due to numerous product quality (PQ) and Office of Scientific Investigations (OSI) deficiencies. Clinical identified no deficiencies from review of the original BLA submission.

From the Benefit-Risk Assessment of the review of the original submission, regarding PQ deficiencies:

> Product Quality
>
> The Office of Pharmaceutical Quality (OPQ) concluded that the submitted data were "not sufficient to support a conclusion that the manufacture of NEXOBRID is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a product quality standpoint, OPQ is recommending a Complete Response letter be issued to MediWound, Ltd. to outline the deficiencies…and the information and data that will be required to support approval."
>
> The identified deficiencies were numerous and pertained to botanical raw material authentication, bromelain special production and drug substance microbial controls, drug product microbial controls, and product quality chemistry, manufacturing and controls. Additionally, for approval, inspections are required of the drug substance intermediate manufacturing facility (Challenge BioproduCompany Ltd.) and the drug substance, drug product, and gel vehicle manufacturing facility (MediWound Ltd.). However, due to restrictions on travel

because of the coronavirus disease 2019 (COVID-19) public health emergency, the Agency was unable to conduct the inspections during the current review cycle.

From the Benefit-Risk Assessment of the review of the original submission, regarding the OSI deficiencies:

Issues with Conduct of Study 2010

Study 2010 was intended to be assessor-blinded; however, clinical inspections identified significant unblinding in the assessment of the eschar removal and wound closure endpoints. Additionally, these assessments were largely conducted only by review of photographs, when the protocol also required clinical assessment for these endpoints (as well as for the MVSS assessment). Although there were significant issues with unblinding in study 2010, the evidence supports that the Applicant successfully demonstrated the effectiveness of Nexobrid for eschar removal in the target population:

- In study 2010, Nexobrid was convincingly statistically superior to vehicle in the target burn population for the incidence of ≥95% eschar removal.
- In study 2010, fewer Nexobrid-treated subjects had a DPT wound excised or dermabraded compared to SOC, and the difference between treatment groups was convincingly statistically significant.
- The Applicant provided additional supportive evidence of effectiveness from a second Phase 3 study, study 2004.

Although the widespread unblinding indicates poor conduct of the study, the extent to which bias from assessor knowledge of treatment group may have ultimately impacted the results for wound closure is unclear. For the wound closure results to be the product of bias, it seems assessors would have had to have known or recalled the time point they designated as closure for a Nexobrid photograph, then made the wound closure designation at a more distant time point for a SOC photograph, and this practice would have had to have occurred consistently and across study sites (i.e., study-wide). The likelihood of such machinations seems low.

The assessment of eschar removal and wound closure outcomes nearly exclusively by photographs was not in accordance with the protocol for study 2010. This approach to assessment is additionally problematic because measures for ensuring the quality and integrity of the photographs are unclear i.e., the extent of standardization (lighting, angle, distance, etc.) and measures to protect against manipulations (e.g., photoshopping). However, for outcomes for eschar removal and wound closure to favor Nexobrid, in the way that the results demonstrated, would seemingly have required systematic manipulation of photographs across study sites. While this is possible, it seems unlikely.

Comment: *A reader is referred to the CR letter for full details of the numerous PQ and OSI deficiencies.*

In the original submission, the Applicant provided data from 8 clinical studies:

- 2 pivotal Phase 3 studies: 2010-03-02 (DETECT or 2010) and 2004-11-02 (2004)
- 4 Phase 2 studies
- a "noninterventional" study
- a "retrospective data collection" study.

The Applicant considered all but the DETECT study to be "legacy" studies, as those 7 studies were included in the marketing application submitted to the European Medicines Agency (EMA) on 10/29/2010. The Applicant relied on legacy study 2004 for establishment of effectiveness for the EMA (the EMA granted marketing authorization on 12/18/2012).

For the BLA, the Applicant is relying on the DETECT study to provide the primary evidence of effectiveness and safety to support licensure in the United States. DETECT is a randomized, controlled, phase 3 study which evaluated Nexobrid, vehicle and standard of care (SOC) for eschar removal in adult subjects with DPT and/or FT thermal burns involving up to 30% body surface area (BSA). Post treatment, subjects were followed until complete wound closure. Subjects were then evaluated at 3 months post wound closure for assessment of durability of healing, then at 12 and 24 months post closure for assessment of "cosmesis" (scar quality) at the treatment area(s). The Applicant included data from DETECT through Month 12 in the original BLA submission.

From review of the clinical data submitted in the original BLA, DETECT was found to have provided substantial evidence of effectiveness for eschar removal in the target population, with a favorable risk-benefit assessment. Supportive evidence of effectiveness in eschar removal was provided from study 2004 (the study relied on for EMA marketing authorization), an open-label study in which Debrase (now Nexobrid) was compared to standard of care (SOC) for the incidence of excision in DPT wounds, where a smaller proportion of subjects with DPT wound underwent excision compared to subjects in the SOC group. The safety data suggested that the safety profile of Nexobrid in the target population could be similar to SOC. However, ultimately, the safety of Nexobrid could not be established given that the microbial control strategy did not mitigate the risk of potential adventitious agents that may be introduced during the manufacturing process.

The effectiveness and safety data submitted in the original BLA will not be further discussed in this memorandum, as those data were reviewed and discussed under the initial review cycle. A reader is referred to the Multi-disciplinary Review of the original BLA submission for the discussion of those data.

The Resubmission

The resubmission provided for the following new clinical data:

- 24-month, long-term data from DETECT

- Added safety data from NEXT, an expanded access protocol
- Added safety data from CIDS, a pediatric study

The Applicant is not relying on any of the clinical information in the resubmission to support approval or any labeling claims. The Applicant continues to rely only on effectiveness and safety data provided in the original submission for those purposes. This memorandum will present high-level discussion of the new clinical data provided in the resubmission.

Comment: *The Applicant discussed the NEXT and CIDS studies in the Summary of Clinical Safety and in the "Resubmission Safety Update," both of which were submitted in the resubmission submitted on 07/01/2022. The resubmission did not include interim study reports for these 2 studies.*

DETECT (MW2010-03-02): Pivotal Phase 3

The resubmission included a Clinical Study Report (CSR) Addendum for the DETECT. The DETECT CSR addendum provided for follow-up data through 24 months following wound closure. The specified endpoint for that timepoint was "cosmesis and function" as assessed by the Modified Vancouver Scar Scale (MVSS). The MVSS was among the group of safety endpoints in DETECT, and it was the only endpoint specified for long-term assessment. (The Applicant submitted data for the MVSS at 12 months in the original submission).

The MVSS evaluates six parameters using a point system (0 to 18 points possible): pigmentation, pliability, height, vascularity, pain, and pruritus. However, the MVSS does not assess function, and the specified 24-month assessment is therefore an evaluation only of cosmesis. Per Section 12.1.1.2.1 (p. 15) of the DETECT CSR addendum, the Applicant set the clinically meaningful difference as being an average MVSS score for Nexobrid that is not worse by more than 1.9 compared to SOC ("worse" being a difference greater than 1.9). The Applicant reported the following mean (standard deviation) MVSS scores at month 24: Nexobrid 3.04 (2.20) and vehicle 2.93 (2.15).

The Applicant concluded that the MVSS scores at 24 months were comparable between the Nexobrid and SOC arms and that their product does not negatively impact outcomes for scarring. However, this reviewer notes that the quality of scarring 24 months following complete wound closure would not likely have been solely impacted by the method of debridement (i.e., Nexobrid versus SOC), performed more than two years prior to the assessment. For example, risk factors for hypertrophic scarring following deep FT burns include prolonged time to heal, burn location, darker skin tone, genetic susceptibility, and wounding during puberty and pregnancy (the last two not being relevant factors for the DETECT study population).[1] Therefore, other factors that may

[1] Gauglitz GG. Hypertrophic scarring and keloids following burn injuries. In: UpToDate, Jeschke MG (Ed), UpToDate, Waltham, MA. (Accessed on December 8, 2022.)

impact scarring outcomes confound the interpretation of the meaningfulness of the MVSS results.

NEXT (MW2018-06-21): Expanded Access

The NEXT expanded access protocol (EAP) allows treatment of adult and pediatric burn patients with Nexobrid at burn centers in the United States that participated in the DETECT and CIDS studies, as well as at additional centers where personnel have been trained in Nexobrid procedures. It is a single-arm, open-label study and is intended to allow investigators to maintain their competency in Nexobrid procedures after completion of enrollment in DETECT and pending product licensure. NEXT will enroll up to 200 subjects with DPT and/or FT burns involving 1% to 30% body surface area (BSA). Evaluations include adverse events, labs, pain, vital signs, wound closure, MVSS, blood transfusion, pharmacokinetics (PK). Assessments include follow-up 3 and 12 months post wound closure. The Applicant will include the laboratory assessments in the final study report. At the time of the data cutoff date for the resubmission (01/31/2022), 120 subjects had been treated in this study.

The one new death reported in the BLA occurred in NEXT (and occurred after data cut-off for the resubmission): Subject (b) (6) was a 68-year-old male with a history of alcohol and tobacco abuse, "chronic intracranial vascular disease," bipolar disorder, and opioid dependence, who was admitted to the hospital with 22% BSA flame burn injury and possible inhalation injury. Additionally, he tested positive for the COVID 19 virus on admission. He was in acute respiratory failure on admission. He underwent Nexobrid treatment two days after admission, eschar removal was incomplete, and he underwent surgical excision two days after the Nexobrid treatment. He experienced an ischemic stroke the day of surgery (the event may have occurred intraoperatively), and he died on Day 14. The ischemic stroke was reported as the probable cause of death; an autopsy was not performed. The investigator assessed the ischemic stroke as being not related to Nexobrid treatment.

Six subjects experienced serious adverse events (SAEs), and the most common SAE was wound infection, which was experienced by four subjects (3.3%). No other SAE was experienced by more than one subject. Serious adverse events (SAEs) that occurred during Weeks 0 to 12 are presented in Table 1.

Table 1. Summary of Serious TEAEs by System Organ Class and Preferred Term: 0 to 12 Weeks Follow-up Period*

	Nexobrid (N=120)
System Organ Class Preferred Term	**Subjects n (%)**
Any SAE	**6 (5.0)**
General disorders and administration site conditions	1 (0.8)
Pain	1 (0.8)

Infections and infestations	4 (3.3)
Wound infection	4 (3.3)
Arthritis bacterial	1 (0.8)
Injury, poisoning and procedural complications	1 (0.8)
Lower limb fracture	1 (0.8)
Investigations	1 (0.8)
Oxygen saturation decreased	1 (0.8)
Nervous system disorders	1 (0.8)
Spinal cord infarction	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (0.8)
Hypoxia	1 (0.8)
Vascular disorders	1 (0.8)
Deep vein thrombosis	1 (0.8)

*Source: Table 101 Summary of Clinical Safety

Two subjects experienced hypersensitivity events (both non-serious). One of these subjects ((b) (6)) discontinued the study due to the hypersensitivity event, which occurred during treatment with Nexobrid. Approximately 1.5 hours into the four-hour treatment period, this 42-year-old male developed an erythematous rash (upper torso), pruritus, tachycardia, low grade fever, and a drop in oxygen saturation. He was treated with diphenhydramine and Nexobrid was removed. The hypersensitivity reaction was considered resolved approximately an hour and forty-five minutes later. The investigator considered the event to be possibly treatment-related and of mild severity. The other subject was reported as experiencing "an allergy to a gauze pad" (p. 37 of the Resubmission Safety Update).

CIDS (MW2012-01-01): Pediatric study

This multinational, randomized, controlled, open-label study enrolled pediatric subjects ages 0 to 18 years and evaluated Nexobrid compared to SOC in the treatment of DPT/FT thermal burns involving 1% to 30% BSA. A total of 145 subjects were randomized (72 Nexobrid and 73 SOC), and 139 were treated (69 Nexobrid and 70 SOC). Follow-up includes assessments at 3, 12, and 24 months following wound closure, with an optional 30-month evaluation. At the time of the resubmission, all subjects had completed the 12-month assessment, and the database had been locked for the 12-month follow-up period. The study was ongoing for the 24- and 30-month follow-up assessments at the time of the resubmission. The Applicant does not currently propose labeling for use of Nexobrid in pediatric patients.

Per Table 14.1.2 of the Resubmission Safety Update, the mean [standard deviation (SD)] age of subjects was 5.77 (4.857) years, with the following breakdown by age group [n (%)]:

- 0-23 months: 45 (31.0%).
- 24 months-3 years: 30 (20.7%),

- 4-11 years: 50 (34.5%), and
- 12-18 years: 20 (13.8%).

Most subjects in both treatment groups had sustained scald burns: 49 (68.1%) in the Nexobrid group and 48 (65.8%) in the SOC group, and the overall mean target wound area %BSA was 5.85 (4.431) and 5.30 (4.273), respectively.

There were no deaths. SAEs were experienced by two subjects (2.9%) in the Nexobrid group and by five subjects (7.1%) in the SOC group. No one type of SAE was reported for more than one subject. See Table 2.

Table 2. Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term– 0-12 Week Follow-up Period (Combined Age Groups: 0 to 18 years of age)*

System Organ Class **Preferred Term**	**Nexobrid (N=69)** **n (%)**	**SOC (N=70)** **n (%)**
At Least One SAE	**2 (2.9%)**	**5 (7.1%)**
Cardiac Disorders		
Tachycardia	1 (1.4)	0
General Disorders and Administration Site Conditions		
Pyrexia	1 (1.4)	0
Systemic Inflammatory Response Syndrome	1 (1.4)	0
Withdrawal Syndrome	0	1 (1.4)
Infections and Infestations		
Viral Infection	0	1 (1.4)
Injury, Poisoning and Procedural Complications		
Injury	0	1 (1.4)
Procedural Pain	0	1 (1.4)
Wound Complication	0	1 (1.4)
Musculoskeletal and Connective Tissue Disorders		
Joint Contracture	1 (1.4)	0
Respiratory, Thoracic and Mediastinal Disorders		
Laryngospasm	0	1 (1.4)

*Source: Table 102 Summary of Clinical Safety

There were no discontinuations due to adverse events in the safety population.

Pruritus was the commonly reported treatment-emergent adverse event in both treatment groups: 9 subjects in the Nexobrid group (13.0%) and 7 subjects in the SOC group (10.0%).

Thus far, no new safety issues are apparent from use of Nexobrid in pediatric subjects.

Product Quality: The Office of Pharmaceutical Quality (OPQ) concluded that the data in the resubmission were "adequate to support the conclusion that the manufacture of NexoBrid is well-controlled and leads to a product that is pure and potent." The OPQ recommended approval of the application for the conditions of use specified in the package insert. A reader is referred to the OPQ Executive Summary for details from the Quality Assessment Team review.

Quality Control Audits:

Based on the deficiencies identified from clinical inspections and detailed in the CR letter, the Applicant conducted quality control (QC) audits to review source documents and other records with the objective of reconstructing DETECT to identify protocol deviations not identified during conduct of the trial (audit report titled, "*Addendum 2: Evaluation of Extent and Impact of Unblinding and Protocol Deviations in the Study MW2010-03-02 (DETECT) A Multicenter, Multinational, Randomized, Controlled, Assessor Blinded Study, Performed in Patients with Thermal Burns, to Evaluate the Efficacy and Safety of NexoBrid Compared to Gel Vehicle and Compared to Standard of Care*").

From review of the QC audit report, the OSI team concluded that the Applicant had adequately addressed all deficiencies related to clinical inspections detailed in the CR letter. A reader is referred to the OSI review for details of their assessment of the audit report.

Conclusions: The clinical data provided in the resubmission raised no new safety concerns. The OPQ and OSI assessments of the data in the resubmission support approval of the application.

Regulatory Recommendation: The clinical team recommends approval of the BLA.

Brenda Carr, M.D.
Medical Officer
Division of Dermatology and Dentistry

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BRENDA CARR
12/27/2022 02:49:48 PM

DAVID L KETTL
12/27/2022 03:35:38 PM

Clinical Pharmacology Review Memo

Application Information			
BLA Number	761192	**SDN**	36
Applicant	MediWound	**Submission Date**	July 1, 2022
Generic Name	Concentrate of proteolytic enzymes enriched in Bromelain	**Brand Name**	NexoBrid
Drug Class	Mixture of proteolytic enzymes (Partially purified Bromelain, a complex mixture of natural components from botanical origin that are extracted from the stem of the *Ananas comosus*, the pineapple plant)		
Indication	For eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns		
Dosage Regimen	The proposed dose is 5g NexoBrid powder mixed with 50g Gel Vehicle per 2.5% TBSA of an adult.		
Dosage Form	Topical gel	**Route of Administration**	Topical
OCP Division	DIIP		
OND Division	CDER/OND/OII/DDD		
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Anand Balakrishnan, Ph.D.	Chinmay Shukla, Ph.D.	
Pharmacometrics	NA	NA	
PDUFA Goal Date	1/1/2023		

Background

NexoBrid is a complex mixture of a concentrate of proteolytic enzymes enriched in Bromelain extracted from pineapple stems (Ananas comosus [L.] Merr.) for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

The Applicant (MediWound) had previously submitted BLA 761192 for NexoBrid on 29 June 2020. The Agency issued a Complete Response (CR) letter to the Applicant (dated 25th June 2021) detailing the deficiencies in the submission. In the current submission the Applicant has provided their responses to the comments listed in the CR letter.

The original BLA was reviewed by clinical pharmacology and no approvability related issues were identified (See Unireview dated 24th June 2021). The application was recommended for approval provided that the Applicant and the Agency come to an agreement on the dosing regimen and labeling for the proposed product.

The following comments were included in the CR letter from Clinical pharmacology regarding the proposed dosing regimen in the product label.

- The completed maximal use study would not support the labeling that was submitted with the BLA application. If you desire to seek the labeling which is currently proposed, then you will need to conduct a new maximal use study designed to address the systemic safety of your product and support the proposed dosing regimens. In particular, you should ensure that you study adequate numbers of patients that are treated with two applications of the product who have % total body surface area (TBSA) within the upper range and are treated with doses within the upper range to support systemic safety and desired labeling.
- If you choose to proceed with labeling in accordance with the currently completed maximal use study, then labeling will be restrictive in terms of number of applications, %TBSA and total dosing.

Summary Of Clinical Pharmacology Findings

In the current submission the Applicant has provided their responses to questions received from the Agency in the Complete Response Letter on 25 June 2021.

In response to the clinical pharmacology comments about the maximal usage study, the Applicant has provided a summary of the clinical experience with NexoBrid across their Phase 2 and Phase 3 studies including PK and safety data.

The Applicant has not conducted any new clinical studies and have not provided any new PK data and/or safety data in this submission. As a follow-up to our comments in the CR letter regarding

the limited maximal use data, the Applicant has modified the original dosing regimen. The Applicant has lowered the limit for the highest TBSA treated from (b) (4) % TBSA (2 applications) to 20 % TBSA (2 applications). The limit for single application remains the same (15 % TBSA). The revised dosing regimens proposed by the Applicant is reasonable from a clinical pharmacology perspective given the data from the Phase 2 and Phase 3 studies (Refer to Unireview dated 24th June 2021 for additional details). However, we defer to clinical regarding the adequacy of the available safety data. We have also provided specific comments to the Applicant regarding the language in the USPI for Nexobrid.

Recommendation

From a Clinical Pharmacology perspective there are no issues that would preclude the approval of this BLA (NexoBrid) for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

Post-marketing requirement/ Post-marketing commitment: None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANAND BALAKRISHNAN
12/21/2022 10:01:37 AM

CHINMAY SHUKLA
12/21/2022 10:05:14 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761192
Supplement #:	Resubmission: SDN/Seq 36/0036
Drug Name:	NEXOBRID (anacaulase)
Indication(s):	Eschar removal in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns
Applicant:	Mediwound
Date(s):	Submitted: 7/1/2022
Review Priority:	Resubmission
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Kathleen Fritsch, PhD
Concurring Reviewers:	Mohamed Alosh, PhD
Medical Division:	Dermatology and Dentistry
Clinical Team:	Brenda Carr, MD / David Kettl, MD
Project Manager:	Jennifer Harmon

1 Regulatory History

1.1 Original Submission and Complete Response

BLA 761192 was originally submitted on June 29, 2020. The application received a Complete Response on June 25, 2021. During the clinical site inspections for Study MW2010-03-02, a significant number of potential unblinding events were identified for assessments that were supposed to be conducted by blinded assessors. Cases where assessments were conducted using photographs rather than live assessments were also identified during the inspection. The Complete Response letter noted that the unblinding events and use of photographic assessments could cause the key findings to be unreliable. These issues were listed in the Complete Response Letter as follows:

CLINICAL SITE INSPECTIONS

43. During routine PDUFA and for-cause good clinical practice (GCP) inspections for Protocol MW2010-03-02, significant issues related to the conduct of the trial and GCP noncompliance were observed that impact the reliability of the eschar removal and wound closure assessments made by the first and second blinded assessors. The following significant issues were noted during inspections:

(b) (4)

[redacted]

(b) (4)

In summary, based on inspection observations, this study was not conducted in accordance with the protocol and current GCP standards, making the data generated from the inspected sites of poor quality. Moreover, because of the significant unblinding events that occurred during the conduct of the study, the study data generated should be evaluated as if they were obtained from an open label study. Provide your perspective on how these inspection observations impact the interpretability of the efficacy findings in Study MW2010-03-02.

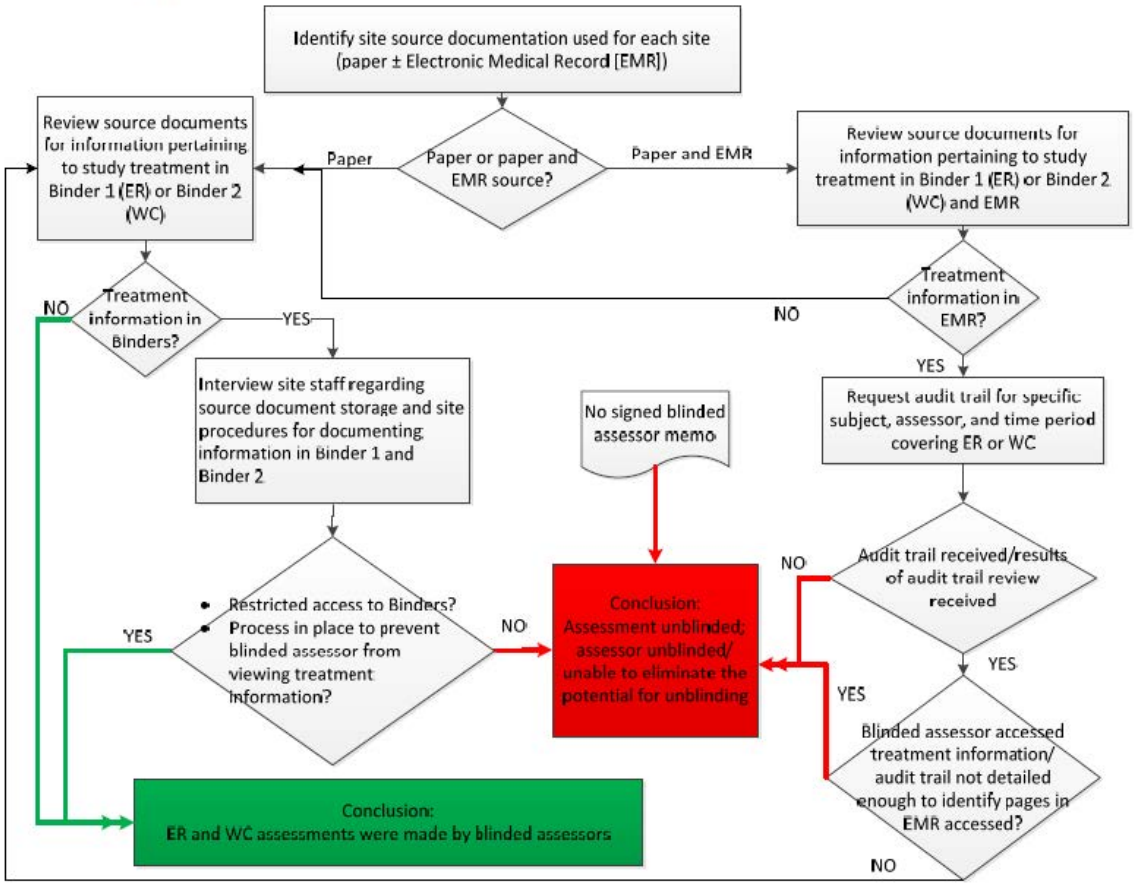
A Type A meeting was held with the applicant on October 6, 2021 to discuss ways to address the concerns listed in the Complete Response letter. FDA advised the applicant to review source documents and other records necessary to reconstruct the study from all sites to identify protocol deviations not identified during the conduct of the trial, such as use of photographs in lieu of live assessments and blinded assessments being performed by unblinded study personnel. The applicant proposed conducting sensitivity analyses based on the findings of the site audits.

1.2 Quality Control Audit and Sensitivity Analyses

In response, the applicant conducted a Quality Control audit of sites that participated in Study MW2010-03-02. Of the 29 sites that randomized subjects, 26 sites were audited. For the three sites that were not included in the audit, each site enrolled only a single subject. Two of the subjects already had protocol violations reported in the original study report related to unblinding of the assessors or assessments based on photographs. The third subject was randomized but did not receive treatment. All of the remaining sites that participated in the trial were assessed to evaluate compliance with protocol-specified eschar removal and wound closure assessments by blinded assessors and use of photographic assessments.

During the audit, the sponsor used the following process to classify whether subjects were assessed for eschar removal or wound closure by a blinded assessor for whom the sponsor could not eliminate the potential for unblinding (Figure 1).

Figure 1 – Unblinding Assessment Decision Process for Study MW2010-03-02



Source: pg 20 of \\CDSESUB1\EVSPROD\bla761192\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eschar-removal-in-burns\5351-stud-rep-contr\mw-2010-03-02-gcp\mw2010-03-02-csr-gcp.pdf

The applicant conducted sensitivity analysis based on alternative handling of subjects who had certain protocol violations identified in the Complete Response letter. The applicant classified subjects into five sets based on the type of protocol violation. These sets were identified separately for eschar removal (ER) assessments and wound closure (WC) assessments. The applicant conducted sensitivity analyses based on the following five classifications

- Set 1 – Potential unblinding of blinded assessor for ER or WC
- Set 2 – Important protocol deviations related to assessment of ER or WC
- Set 3 – Use of photographic assessments for ER or WC
- Set 4 – Sites with for-cause inspections (Sites 117 and 120 vs. other sites)
- Set 5 – any of the above

This review will evaluate the sensitivity analyses based on Set 1 and Set 3 and evaluate the impact of potential unblinding and use of photographic assessments on the efficacy conclusions for Study MW2010-03-02.

2 Sensitivity Analyses for Study MW2010-03-02

2.1 Study Design and Endpoints

Refer to the Multi-Disciplinary Review and Evaluation dated June 24, 2021 for details on the design and results for Study MW2010-03-02. In brief, Study MW2010-03-02 was a randomized, vehicle- and standard of care (SOC)-controlled, assessor-blinded study to evaluate the efficacy and safety of NexoBrid in subjects with thermal burns. The study periods included an eschar removal stage, a wound closure stage, and a follow-up stage. Subjects randomized to SOC were treated per the investigator's judgment until the eschar was removed. Subjects randomized to NexoBrid or vehicle gel were treated using the topical treatment process. If >50% to <95% of eschar was removed following the first application of topical treatment, the subject was to be treated with a second application of topical treatment. In addition, if the subject had >15% TBSA burn area, two treatments would be planned, while treating no more than 15% TBSA per treatment session. If eschar remained after the one or two topical treatments, the remaining eschar was removed using surgical or non-surgical SOC methods as rescue treatment. An assessor blinded to whether a subject was treated with NexoBrid or vehicle was to evaluate eschar removal following the topical treatment. Weekly evaluations for wound closure were to be done by a second blinded assessor blinded to all treatment arms.

The primary efficacy endpoint was the incidence of ≥95% eschar removal at the end of the topical treatment soaking period for NexoBrid versus gel vehicle. The first key secondary endpoint was the incidence of surgical eschar removal for NexoBrid versus SOC. The first safety endpoint was time to ≥95% wound closure for NexoBrid versus SOC. Blinded assessors were used to evaluate the primary efficacy endpoint (eschar removal) and the key safety endpoint (wound closure). The key secondary endpoint of incidence of surgical eschar removal did not rely on assessments by blinded evaluators.

Table 1 presents number of subjects classified by the applicant following the quality control audit into each of the 5 sets for eschar removal and wound closure. Approximately 18% of NexoBrid or vehicle subjects had potential unblinding by the eschar removal blinded assessor, and approximately 24% of NexoBrid or SOC subjects had potential unblinding for the wound closure blinded assessor.

Table 1 – Sensitivity Analysis Sets in Study MW2010-03-02

Eschar Removal (ER)	NexoBrid	Vehicle
Randomized	75	25
Potential unblinding for ER (Set 1)	13 (17.3%)	5 (20.0%)
Important protocol deviations relevant to ER (Set 2)	5 (6.7%)	2 (8.0%)
Photographic assessments for ER (Set 3)	11 (14.7%)	4 (16.0%)
All subjects from sites with for-cause FDA inspections (Set 4)	8 (10.7%)	1 (4.0%)
All subjects excluded in Sets 1-4 (Set 5)	25 (33.3%)	10 (40.0%)

Wound Closure (WC)	NexoBrid	SOC
Randomized	75	75
Potential unblinding for WC (Set 1)	21 (28.0%)	15 (20.0%)
Important protocol deviations relevant to WC (Set 2)	11 (14.7%)	17 (22.7%)
Photographic assessments for WC (Set 3)	13 (17.3%)	5 (6.7%)
All subjects from sites with for-cause FDA inspections (Set 4)	8 (10.7%)	4 (5.3%)
All subjects excluded in Sets 1-4 (Set 5)	39 (52.0%)	32 (42.7%)

Source: pages 3-7 of \\CDSESUB1\EVSPROD\bla761192\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eschar-removal-in-burns\5351-stud-rep-contr\mw-2010-03-02-gcp\mw2010-03-02-csr-add-2-sec-14.pdf and reviewer analysis.

2.2 Eschar Removal Analyses

The overall results from the original study report for Study MW2010-03-02 for the primary endpoint of incidence of ≥95% eschar removal at the end of the topical treatment period (NexoBrid vs. vehicle) and subgroup analyses for Set 1 and Set 3 are presented in Table 2. The results from each of the subgroup analysis after removal of the subjects who had potential unblinding events or photographic assessments, were similar to the results in the overall population. Among subjects with potential unblinding or photographic assessments, most of the subjects on the NexoBrid arm were responders, while all of the subject on the vehicle arm were non-responders.

Table 2 – Incidence of **≥95%** Eschar Removal at the End of Topical Treatment Period

	NexoBrid N=75	Vehicle N=25
All subjects (FAS)	70/75 (93.3%)	1/25 (4.0%)
p-value	p<0.0001	
Risk difference (95% CI)	89.3% (73.6%, 96.2%)	
Set 1 (Potential unblinding)		
No unblinding	58/62 (93.6%)	1/20 (5.0%)
Potential unblinding	12/13 (92.3%)	0/5 (0%)
Set 3 (Photographic Assessments)		
No photographic assessments for ER	59/64 (92.2%)	1/21 (4.8%)
Photographic assessments for ER	11/11 (100%)	0/4 (0%)

FAS = Full analysis set; CI= Confidence interval

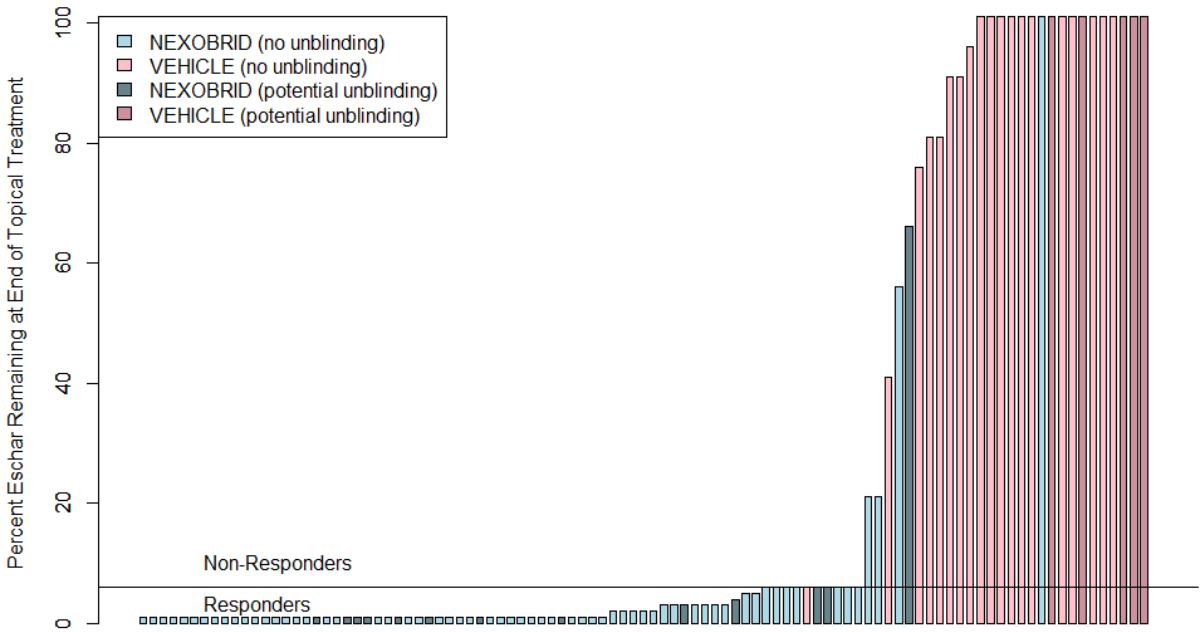
Source: page 45-46 of \\CDSESUB1\EVSPROD\bla761192\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eschar-removal-in-burns\5351-stud-rep-contr\mw-2010-03-02-gcp\mw2010-03-02-csr-gcp.pdf and reviewer analysis.

If all 13 subjects on the NexoBrid arm with potential unblinding events were classified as non-responders, and all 5 subjects on the vehicle arm with potential unblinding events were classified as responders, the estimated response rates would be 77.3% vs. 24.0%, which would still meet the statistical significance criteria (p<0.0001). The results for the comparable

sensitivity analysis for Set 3 (photographic assessments) are similar (78.6% vs. 20.0%, p<0.0001). With the large magnitude of the treatment effect for this endpoint, potential unblinding appears to have had minimal impact on the primary endpoint results.

To further visualize the potential impact of blinded assessors for eschar removal being unblinded, a waterfall plot was constructed for the percent of eschar remaining at the end of the topical treatment period (Figure 2). Each bar of the plot represents the percentage of eschar *remaining* for an individual subject sorted from smallest to largest and color-coded to randomized treatment. Note that because the protocol defined success as ≥95% eschar removal, the subjects who met the success criterion have ≤5% eschar remaining at the end of the topical treatment period. Subjects who were potentially impacted by unblinding (Set 1) are indicated on the plot with the darker-shaded bars. Because all non-responders had at least 20% eschar remaining at the end of the topical treatment period, it is unlikely that any subjects classified as non-responders were improperly classified as non-responders due to unblinding, as none of these subjects were close to meeting the response criterion. Because a number of subjects had the maximum amount of eschar remaining while still be classified as responders (5% eschar remaining), it is possible that unblinding could have played a role in classifying these subjects as responders rather than non-responders. However, as noted above, even if all unblinded NexoBrid subjects were instead classified as non-responders, it would not impact the conclusions for the primary efficacy endpoint.

Figure 2 – Waterfall Plot of the **Percent Eschar Remaining at End of Topical Treatment**



Note: each bar represents the results for one subject, sorted from smallest to largest.
Source: reviewer analysis.

2.3 Wound Closure Analyses

The applicant's sensitivity analyses for time to wound closure handled subjects who had a protocol deviation due to potential unblinding or use of photographic assessments at the time of the deviation by censoring the subjects at the time of the protocol deviation, rather than using the observed wound closure times for the affected subjects. Because the time to wound closure endpoint proposed in the protocol was defined at the wound level, rather than at the subject level, the applicant's proposed sensitivity analyses were also conducted at the wound level. The applicant's sensitivity analyses for the time to wound are presented in Table 3. The applicant noted that for these two sensitivity analyses that use censored observations at the time of the protocol violation led to longer times to wound healing than the original analysis that did not include such censoring, though in each case, the treatment effect estimates were similar.

Table 3 – Median Time (Days) to **≥95%** Wound Closure (Wound-Level) using Censoring of Subjects with Protocol Violations

	NexoBrid N=75 Subjects N=129 Wounds	SOC N=75 Subjects N=128 Wounds
Original Analysis Median (95% CI)	27 (22, 33) 27% censored	28 (24, 37) 38% censored
Set 1 (Censoring for Potential unblinding) Median (95% CI)	34 (28, 43) 49% censored	33 (28, 37) 47% censored
Set 3 (Censoring for Photographic Assessments) Median (95% CI)	31 (23, 38) 38% censored	29 (27, 37) 40% censored

CI=confidence interval
Source: page 50 of \\CDSESUB1\EVSPROD\bla761192\0036\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eschar-removal-in-burns\5351-stud-rep-contr\mw-2010-03-02-gcp\mw2010-03-02-csr-gcp.pdf.

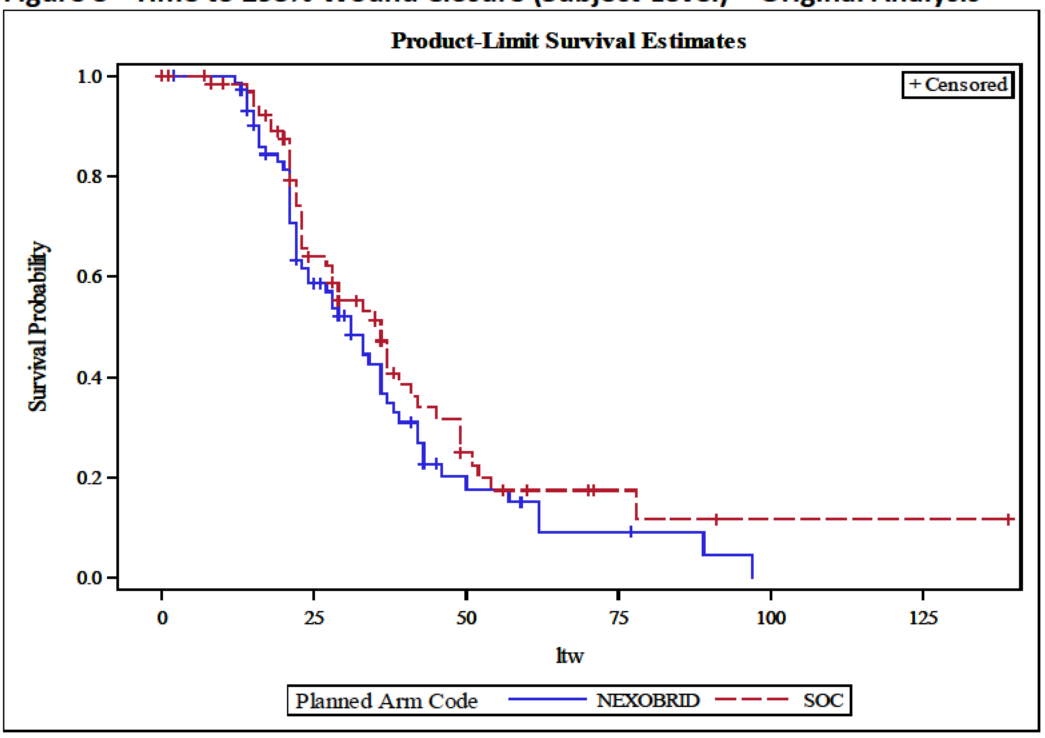
However, incorporating censoring at the time of the protocol violation increases the number of subjects subject to censoring and can make it difficult to interpret the results. In addition, because protocol violations such as potential unblinding or use of photographic assessments could impact all assessments on a subject, it may be more appropriate to consider subject-level rather than wound-level assessments for time to wound closure. Rather than applying censoring to subjects with these protocol deviations, it may also be useful to instead look at subgroup analyses based on the set designations (protocol deviation vs no deviation). Subgroup analyses conducted by the reviewer are presented in Table 4. The Kaplan-Meier curves corresponding to each of these analyses are presented in Figure 3, Figure 4, and Figure 5.

Table 4 – Median Time (Days) to **≥95%** Wound Closure (Subject-Level) by Set Classification

	NexoBrid N=75 Subjects	SOC N=75 Subjects
All subjects (original analysis) Median (95% CI)	N=75 31 (23, 36) 28% censored	N=75 36 (27, 41) 40% censored
Set 1 (Potential unblinding)		
No unblinding Median (95% CI)	N=54 29 (22, 36) 28% censored	N=60 33 (23, 37) 37% censored
Potential unblinding Median (95% CI)	N=21 36 (22, 46) 29% censored	N=15 52 (22, NE) 53% censored
Set 3 (Photographic Assessments)		
No photographic assessments for WC Median (95% CI)	N=62 31 (23, 36) 24% censored	N=70 36 (28, 41) 40% censored
Photographic assessments for WC Median (95% CI)	N=13 24 (16, NE) 46% censored	N=5 23 (8, NE) 40% censored

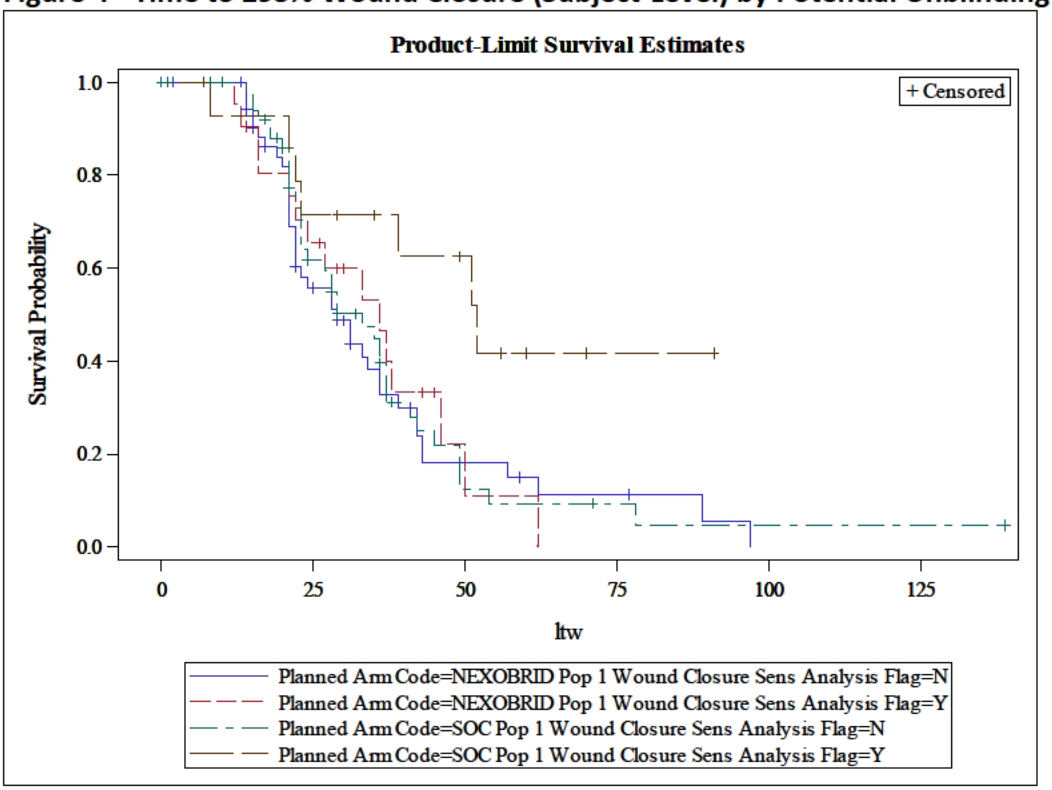
CI=confidence interval; NE = Not estimable
Source: reviewer analysis

Figure 3 - Time to ≥95% Wound Closure (Subject-Level) – Original Analysis



Source: reviewer analysis

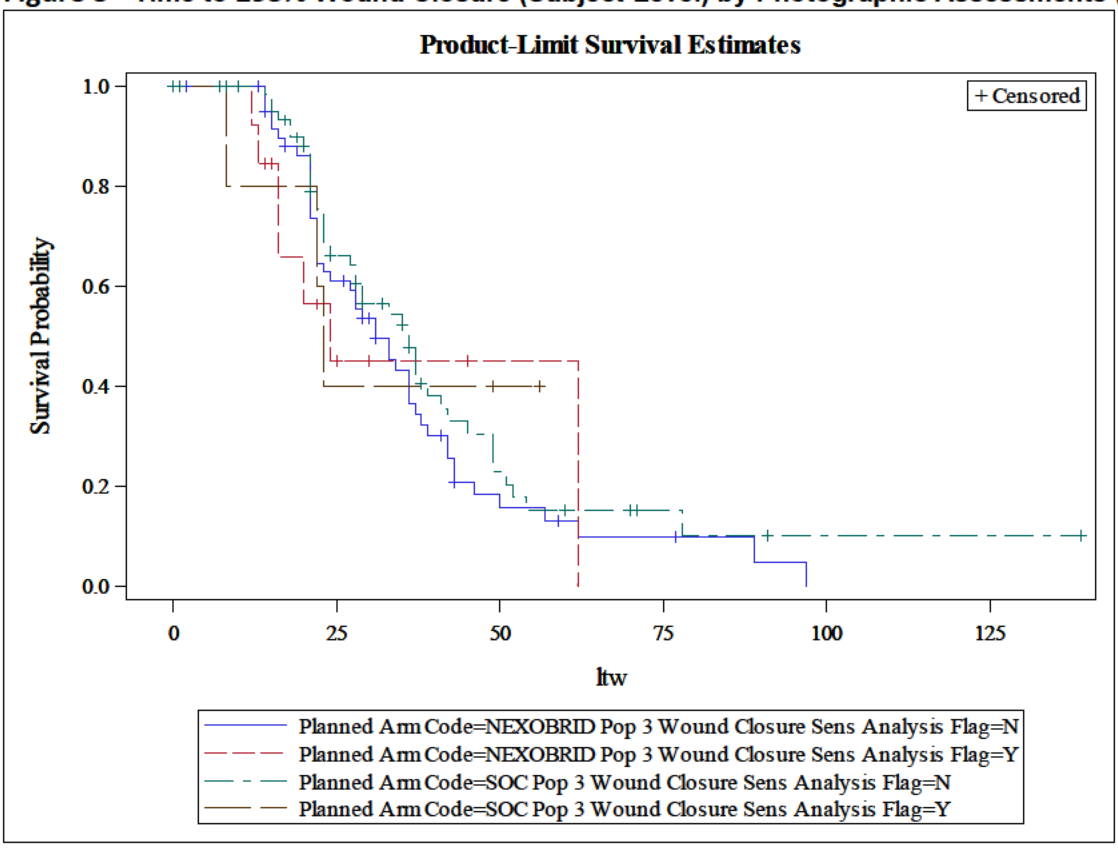
Figure 4 - Time to ≥95% Wound Closure (Subject-Level) by Potential Unblinding (Set 1)



Flag = N is 'No unblinding'; Flag = Y is 'Potential unblinding'

Source: reviewer analysis

Figure 5 - Time to ≥95% Wound Closure (Subject-Level) by Photographic Assessments (Set 3)



Flag = N is 'No photographic assessments'; Flag = Y is 'Photographic assessments'
Source: reviewer analysis

The results for subjects with no unblinding and no photographic assessments are similar to the overall results. Among subjects with potential unblinding, the observed time to ≥95% wound closure was faster for NexoBrid than SOC. Among subjects with photographic assessments, in both arms, the observed time to wound closure was shorter among subjects with photographic assessments than with live assessments, but there was no observed difference between the treatment arms, Note, however, that the number of subjects with photographic assessments differed between the two treatment arms.

Because time to ≥95% wound closure was faster for NexoBrid than SOC among subjects with potential unblinding, we cannot rule out that there was some bias present due to the unblinding. However, over 50% of subjects with potential unblinding on the SOC arm were censored prior to assessment of wound closure and this group included only 15 subjects, making any estimates for this group unreliable. Thus, while it may be reasonable to assume that the treatment effect estimate could be biased, it is difficult to assess the magnitude of any potential bias. One ad hoc way of assessing the overall impact of potential bias would be to switch the treatment arms of subjects impacted by the identified treatment violations and see how much of an impact the treatment assignment switch would have. The ad hoc analyses for Set 1 and Set 3 where subjects with potential unblinding or photographic assessment protocol

violations are swapped to the other treatment arm do not appreciably impact the point estimates for the two sets (Table 5). Thus, any potential bias does not appear to be sufficiently large to impact the conclusion that NexoBrid is not clinically meaningfully worse than SOC with regard to time to wound closure.

Table 5 – Ad Hoc Analysis with Treatment Code Swap for Subjects with Protocol Violations for time to **≥95%** Wound Closure (Subject-Level)

	NexoBrid N=75 Subjects	SOC N=75 Subjects
Potential unblinding (Set 1) Median (95% CI)	N=69[a] 33 (23, 42) 33% censored	N=81[b] 33 (27, 37) 35% censored
Photographic assessments (Set 3) Median (95% CI)	N=67[c] 31 (23, 36) 25% censored	N=83[d] 36 (27, 41) 41% censored

[a] includes 54 blinded NexoBrid subjects and 15 'swapped' SOC unblinded subjects
[b] includes 60 blinded SOC subjects and 21 'swapped' NexoBrid unblinded subjects
[c] includes 62 NexoBrid subjects with live assessments and 5 'swapped' SOC subjects with photographic assessments
[d] includes 70 SOC subjects with live assessments and 13 'swapped' NexoBrid subjects with photographic assessments
Source: reviewer analysis

3 Conclusions

The applicant conducted a Quality Control audit of sites that participated in Study MW2010-03-02 and conducted sensitivity analysis with alternate handling of subjects with potential unblinding and use of photographs for assessments related to the primary endpoint of incidence of ≥95% eschar removal at the end of the topical treatment period and the safety endpoint of time to ≥95% wound closure.

For the primary endpoint of incidence of ≥95% eschar removal at the end of the topical treatment period, the treatment effects were so large that even if the assessments impacted by potential unblinding or photographic assessments were handled as non-responders on the NexoBrid arm and responders on the vehicle arm, efficacy would still be demonstrated on the primary endpoint. Thus, the results on the primary endpoint are robust to the identified protocol deviations.

The intent of the safety endpoint of time to ≥95% wound closure was to ensure that NexoBrid treatment was not associated with a clinically meaningful increase in time to wound closure. Because time to wound closure was faster for NexoBrid than SOC among subjects with potential unblinding, we cannot rule out that there was some bias present due to the unblinding. However, any potential bias does not appear to be sufficiently large to impact the

conclusion that NexoBrid is not clinically meaningfully worse than SOC with regard to time to wound closure.

The original review of Study MW2010-03-02 determined that the efficacy of NexoBrid was supported by the following endpoints:

- the primary endpoint of incidence of ≥95% eschar removal at the end of the topical treatment period (NexoBrid vs. vehicle)
- the key secondary endpoint of incidence of surgical excision for eschar removal (NexoBrid vs. SOC)
- the safety endpoint of time to ≥95% wound closure (NexoBrid vs. SOC)

The conclusions related to the primary endpoint related to eschar removal and the safety endpoint related to wound closure did not appear to be materially impacted by the incidents of unblinded assessors and use of photographic assessments. Along with the key secondary endpoint of incidence of surgical excision for eschar removal, which was not assessed by a blinded assessor and thus not impacted by the concerns related to unblinding or photographic assessments, the results of Study MW2010-03-02 support the efficacy of NexoBrid for eschar removal in adults with deep partial thickness and/or full thickness thermal burns.

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/s/

KATHLEEN S FRITSCH
12/15/2022 11:02:09 AM

MOHAMED A ALOSH
12/15/2022 11:04:12 AM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761192
Priority or Standard	Standard
Submit Date(s)	6/29/2020
Received Date(s)	6/29/2020
PDUFA Goal Date	6/29/2021
Division/Office	Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	6/23/2021
Established/Proper Name	Concentrate of proteolytic enzymes enriched in bromelain
(Proposed) Trade Name	NexoBrid
Pharmacologic Class	proteolytic enzymes
Code name	
Applicant	MediWound, Ltd.
Dosage form	Gel
Applicant proposed Dosing Regimen	NexoBrid Gel is applied at 2 g NexoBrid sterile powder mixed with 20 g sterile Gel Vehicle per 1% TBSA of an adult ((b) (4) 3 mm thick) to a clean, (b) (4) moist wound bed and covered with an occlusive dressing (b) (4) for a period of 4 hours.
Applicant Proposed Indication(s)/Population(s)	NEXOBRID is indicated for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	10132008 Burns of multiple sites (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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APPEARS THIS WAY ON ORIGINAL

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TBSA	total body surface area
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

NexoBrid is a new botanical and biologic that contains proteolytic enzymes enriched in bromelain. It is extracted from stems of the pineapple plant (*Ananas comosus*). The Applicant proposes the product for eschar removal (or debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. The mechanism of action of NexoBrid, to dissolve eschar, is mediated by enzyme activity; however, the specific enzymes responsible for the debridement effect have not been identified.

NexoBrid has 2 components: NexoBrid powder (the active component) and gel vehicle. The components are mixed at the patient's bedside to form NexoBrid gel (NexoBrid). The Applicant intends for the product to be applied to a burn wound of up to 15% total body surface area (TBSA) for 4 hours. The Applicant proposes that NexoBrid may be applied twice to one area of (b) (4)% TBSA or a single time to 2 different areas, each of (b) (4)% TBSA. However, the Applicant recommends that total area treated with NexoBrid not exceed (b) (4)% TBSA in toto.

The product was known as "Debrase" and "Debridase" in early development, and any such references in this review refer to the product now known as "NexoBrid."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness from a Phase 3 study, MW2010-03-02 (2010) that evaluated NexoBrid for eschar removal in the target population of adult subjects with DPT and/or FT thermal burns. The primary evidence was from study 2010, and NexoBrid was superior to Gel Vehicle for the primary endpoint, incidence of ≥95% eschar removal: 70/75 (93.3%) versus 1/25 (4.0%), respectively ($p<0.001$). These findings were supported by the results for the secondary endpoint, Incidence of Excision for Eschar Removal, where a smaller proportion of subjects in the NexoBrid group underwent eschar excision compared to subjects in the SOC group: 3/75 (4.0%) and 54/75 (72.0%), respectively ($p<0.001$).

Supportive evidence of effectiveness in eschar removal was provided from study MW2004-11-02 (2004), an open-label study in which Debrase (now NexoBrid) was compared to standard of care (SOC) for the incidence of excision in DPT wounds, where a smaller proportion of subjects with DPT wound underwent excision compared to subjects in the SOC group: 11/49 (22.5%) and 37/48 (77.1%), respectively ($p<0.0001$).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

NexoBrid is a new botanical and biologic that contains proteolytic enzymes enriched in bromelain. It is extracted from stems of the pineapple plant (*Ananas comosus*). The Applicant proposes the product for eschar removal (or debridement) in adults with deep partial thickness and/or full thickness thermal burns. The mechanism of action of NexoBrid, to dissolve eschar, is mediated by enzyme activity. Thermal burns are most commonly caused by flames, hot liquids, hot solid objects, or steam, and a burn eschar is thick necrotic skin that results from deep burn injuries. In the absence of intervention, the burn eschar eventually spontaneously detaches, revealing granulation tissue. Deep partial thickness (DPT) burns involve the epidermis and superficial and deeper dermis, including hair follicles and glandular tissue. DPT burns heal in 2 to 9 weeks (if no infection develops) and with hypertrophic scarring and joint dysfunction. Full-thickness (FT) burns destroy the entire dermis and may extend into the underlying subcutaneous tissue and never fully heal spontaneously. Devitalized tissue in the burn wound serves as a medium for microbial growth, and all burn wounds are colonized (bacteria, fungi, viruses). Wound infection and sepsis may follow. Additionally, damaged cells in the burn wound release inflammatory cytokines and growth factors. Therefore, early excision of the eschar generally appears to represent the current standard of care for deep burn injuries. Complex, systemic pathophysiologic responses may be seen with extensive, severe burn injury e.g., involving > 20% TBSA. These responses may impact circulatory, metabolic, respiratory and immunologic functions. Early burn excision and wound closure alone do not eliminate the hypermetabolic response. However, early excision may decrease the release of inflammatory mediators and attenuate the hypermetabolic and systemic responses.

Effectiveness

The Applicant provided substantial evidence of effectiveness from a randomized, vehicle-controlled, Phase 3 study, MW2010-03-02 (2010 or 03-02), which evaluated NexoBrid for eschar removal in the target population of adult subjects with DPT and/or FT thermal burns. NexoBrid was superior to Gel Vehicle for the primary endpoint, Incidence of ≥95% Eschar Removal: 70/75 (93.3%) versus 1/25 (4.0%), respectively ($p<0.001$). These findings were supported by the results for the secondary endpoint, Incidence of Excision for Eschar Removal, where a smaller proportion of subjects in the NexoBrid group underwent eschar excision compared to subjects in the SOC group: 3/75 (4.0%) and 54/75 (72.0%), respectively ($p<0.001$).

Supportive evidence of effectiveness in eschar removal was provided from the Phase 3 study, MW2004-11-02 (2004 or 11-02), an open-label study in which Debrase (now called NexoBrid) was superior to standard of care (SOC) for the incidence of excision in DPT wounds, where a smaller proportion of subjects with DPT wound underwent excision compared to subjects in the SOC group: 11/49 (22.5%) and 37/48 (77.1%),

respectively (p<0.0001)

Wound Closure

The Applicant assessed wound closure as a safety endpoint. Despite the Agency's repeated recommendation to define wound closure as "skin reepithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart," the Applicant persisted in defining "complete" wound closure as ≥ 95% closed in the main analysis. Although an analysis was performed that considered the Agency's definition (100% closure), the results of that analysis may not be reliable because of the substantial amount of missing data in both treatment arms (52-68%), because not all subjects who achieved ≥ 95% closure had assessments for 100% closure at the same frequency as for the ≥ 95% closure assessment. This is due to the study design which called for less frequent follow-up visits after the 2-week, confirmatory visit for ≥ 95% wound closure: the schedule went from follow-up weekly to follow-up at Months 1, 3, 6, 12. The results of the 3 analyses conducted for the wound closure endpoint follow:

- In the *per-wound analysis of ≥95% wound closure* (Applicant's main analysis), the median number of days to wound closure was 27 in the NexoBrid arm and 28 in the SOC arm.
- In the *per-subject analysis ≥95% wound closure*, the median number of days to wound closure was 31 in the NexoBrid arm and 36 in the SOC arm.
- In the *per-subject analysis of 100% wound closure*, the median number of days to wound closure was 38 in the NexoBrid arm and 52 in the SOC arm.

Thus, in all 3 analyses, the median time to wound closure was shorter for the NexoBrid group compared to SOC.
Cosmesis of target wounds (TWs) at Month 12 was a key safety endpoint and was assessed using the Modified Vancouver Scar Scale (MVSS) instrument. The MVSS assesses pigmentation, pliability, height, vascularity, pain, and pruritus. The lower the score (range 0 to 18), the "better" the scar (0= normal skin). Outcomes were lower for the NexoBrid arm compared to SOC: means 3.70 (2.10) and 5.08 (3.11), respectively. However, it is not clear that the method of eschar removal is the sole determinant of the characteristics of the scar at Month 12. Additionally, it is not clear that a difference of 1.38 in mean scores translates to a clinically-significant difference in outcomes. Thus, while the results were more favorable on the NexoBrid arm than the SOC arm, the information may not be suitable for labeling.

Issues with Conduct of Study 2010

Study 2010 was intended to be assessor-blinded; however, clinical inspections identified significant unblinding in the assessment of the eschar

removal and wound closure endpoints. Additionally, these assessments were largely conducted only by review of photographs, when the protocol also required clinical assessment for these endpoints (as well as for the MVSS assessment). Although there were significant issues with unblinding in study 2010, the evidence supports that the Applicant successfully demonstrated the effectiveness of NexoBrid for eschar removal in the target population:

- In study 2010, NexoBrid was convincingly statistically superior to vehicle in the target burn population for the incidence of ≥95% eschar removal.
- In study 2010, fewer NexoBrid-treated subjects had a DPT wound excised or dermabraded compared to SOC, and the difference between treatment groups was convincingly statistically significant.
- The Applicant provided additional supportive evidence of effectiveness from a second Phase 3 study, study 2004.

Although the widespread unblinding indicates poor conduct of the study, the extent to which bias from assessor knowledge of treatment group may have ultimately impacted the results for wound closure is unclear. For the wound closure results to be the product of bias, it seems assessors would have had to have known or recalled the time point they designated as closure for a NexoBrid photograph, then made the wound closure designation at a more distant time point for a SOC photograph, and this practice would have had to have occurred consistently and across study sites (i.e., study-wide). The likelihood of such machinations seems low.

The assessment of eschar removal and wound closure outcomes nearly exclusively by photographs was not in accordance with the protocol for study 2010. This approach to assessment is additionally problematic because measures for ensuring the quality and integrity of the photographs are unclear i.e., the extent of standardization (lighting, angle, distance, etc.) and measures to protect against manipulations (e.g., photoshopping). However, for outcomes for eschar removal and wound closure to favor NexoBrid, in the way that the results demonstrated, would seemingly have required systematic manipulation of photographs across study sites. While this is possible, it seems unlikely.

<u>Blood Loss</u>

The Agency recommended "blood loss related to eschar removal" as an endpoint in study 2010 to potentially demonstrate a clinical benefit of NexoBrid. While, the results for this secondary endpoint suggest that blood loss related to eschar removal may be less in the NexoBrid group compared to the SOC group, the considerable amount of missing data (approximately half of subjects in the SOC arm) limited the interpretability of results related to this endpoint. The interpretability of the data is further challenged because blood loss calculations could have reflected eschar removal procedures that may have occurred over extended periods, due to the nature of SOC procedures. However, even if the results were interpretable, it is not clear that demonstration of statistically significant differences in blood loss between the treatment groups during eschar removal would necessarily represent an inherently significant benefit of NexoBrid over SOC. Information relating to

transfusions may be a measure of the clinical significance of blood loss, and blood loss sufficient to require transfusion during eschar removal occurred in ≤ ~3% of subjects in study 2010 (1 subject in the NexoBrid arm and 2 in the SOC arm). The low and similar proportions of subjects who required transfusions during eschar removal may indirectly suggest that NexoBrid did not cause more bleeding than SOC during eschar removal.

Safety

The 2 Phase 3 studies provided the primary safety data, with enrollment as follows: NexoBrid- n=177, SOC- n=149, and Gel Vehicle- n= 24. The Applicant reported 8 deaths in the clinical development program, 7 in subjects who received NexoBrid and 1 in a subject who received SOC. Despite the imbalance in reported deaths, generally there was no apparent relatedness to study treatment, or there were confounders to the assessment of relatedness. The overall percentage of subjects who experienced serious adverse events in the Phase 3 studies was slightly higher in the NexoBrid arm [15 (8.5%)] compared to SOC [10 (6.7%)]. There were only single reports of most SAEs. Sepsis and "Wound infection bacterial" were the only 2 SAEs that were reported in more than one NexoBrid-treated subject, and there were more reports in the NexoBrid arm (5 reports) as compared to SOC (1 report).

Treatment-emergent adverse events (TEAEs) were most frequently reported in the Infections and Infestations system organ class for both the NexoBrid and SOC groups, 23.2% and 19.5%, respectively. For both treatment groups, Wound infection was the most frequently reported preferred term (PT) in this system organ class and was reported with similar frequency in both treatment groups: NexoBrid- 9 subjects (5.1%) and SOC- 7 subjects (4.7%). Events were next most frequently reported in the Skin and subcutaneous tissue disorders system organ class: NexoBrid- 20.9% and SOC- 16.8%. For both treatment groups, Pruritus was the most frequently reported PT in this system organ class and was reported with a higher frequency in NexoBrid- 27 subjects (15.3%) compared to SOC- 19 subjects (12.8%). Also, Pruritus was the overall most frequently reported PT in both treatment groups.

The Applicant identified pain, pyrexia, wound infection, immediate hypersensitivity reactions, and coagulation parameter abnormalities as key risks of NexoBrid treatment. With pain management control for NexoBrid treatment, pain-related TEAEs were reported at similar rates in the NexoBrid and SOC groups: 8 (4.5%) and 6 (4.0%), respectively. Overall, "fever-related" TEAEs were reported in a higher proportion of subjects in the NexoBrid group, 27 (15.3%), compared to the SOC group, 18 (12%). Non-fungal TW infections occurred at a higher incidence in the SOC arm compared to the NexoBrid arm, 9% and 6%, respectively. All of the fungal TW infection events (n=3) were reported in the NexoBrid arm, ~2%. A total of 4 events were reported in the Immune system disorders system organ class in NexoBrid subjects in study 2010: 2 events were apparent reactions to hydromorphone, and 2 were vague reports of "rash." The single report of anaphylactic shock in the Phase 3 studies (study 2004) was due to a latex allergy. There was 1 TEAE report of "coagulopathy" and 2 of "hemorrhagic anemia"; all 3 reports were in the

SOC arm. The overall incidences of sepsis-related TEAEs were similar in the NexoBrid group 5 (2.8%) and the SOC group 3 (2.0%). Of the 5 events that occurred in the NexoBrid arm, 4 were SAEs, and a relatedness of the SAEs to NexoBrid could either not be determined from the narrative information (n=2) or seemed unrelated (n=2).

Dosing

The Applicant intends that NexoBrid may be applied 1 or 2 times, to ≤15% TBSA, with the duration of each application being 4 hours and that it may be applied to up to (b) (4)% TBSA (in 2 separate sessions treating up to (b) (4)% TBSA each). The Applicant intends that NexoBrid be applied at a dose of 2 g NexoBrid per 1% of TBSA. However, in the Phase 3 studies (2010 and 2004), only 18 subjects (10%) received 2 applications of NexoBrid, and only 19 subjects (11%) had TBSA > 15%. Maximal use data are limited for use on mean TBSA > 10%. Of 19 subjects who applied 2 doses and had maximal use data (studies 2010 and MW2008-09-03), only 2 subjects received the (b) (4) dosage of 60 g, and the data are limited for doses greater than 20 g per application. Thus, the data are too limited to adequately assess the safety of 2 applications, use in subjects with > 15% TBSA or the (b) (4) dosage of 60 g. Additionally, the Applicant did not define the interval between the 2 applications. The estimated systemic half-live is ~ 12 hours. Therefore, applications should be spaced at appropriate intervals to avoid systemic accumulation. The PK data revealed quantifiable serum concentrations through 48 hours following topical application. In summary, the provided data are inadequate to support the dosing regimen proposed by the Applicant in draft labeling. Based on the available data, the labeled dosing regimen would need to be very restrictive and redefine the target population according to %TBSA, number of applications and maximum dosage.

Product Quality

The Office of Pharmaceutical Quality (OPQ) concluded that the submitted data were "not sufficient to support a conclusion that the manufacture of NEXOBRID is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a product quality standpoint, OPQ is recommending a Complete Response letter be issued to MediWound, Ltd. to outline the deficiencies…and the information and data that will be required to support approval."

The identified deficiencies were numerous and pertained to botanical raw material authentication, bromelain special production and drug substance microbial controls, drug product microbial controls, and product quality chemistry, manufacturing and controls. Additionally, for approval, inspections are required of the drug substance intermediate manufacturing facility (Challenge BioproduCompany Ltd.) and the drug substance, drug product, and gel vehicle manufacturing facility (MediWound Ltd.). However, due to restrictions on travel because of the coronavirus disease 2019 (COVID-19) public health emergency, the Agency was unable to conduct the inspections during the current review

cycle.

Conclusions and Recommendations

The Applicant provided substantial evidence of effectiveness from a randomized, vehicle-controlled, Phase 3 study, MW2010-03-02 (2010), which evaluated NexoBrid for eschar removal in the target population of adult subjects with DPT and/or FT thermal burns. The available safety information suggests that the safety profile of NexoBrid in the target population could be similar to SOC. However, the OPQ could not conclude that manufacture of NexoBrid is well-controlled, such that production of a pure product that is potent for the duration of shelf-life would result. Therefore, the Division of Dermatology and Dentistry recommends a Complete Response action at this time. This application cannot be approved until the requisite manufacturing facility inspections are conducted and any findings are assessed. Additionally, to support the proposed dosing regimen, the Applicant will need to conduct an adequate maximal use study, consisting of an appropriate number of subjects, with %TBSA in the upper range, who receive 2 applications of NexoBrid, at doses at the upper end of what is proposed in draft labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Thermal burns are most commonly caused by flames, hot liquids, hot solid objects, or steam, and a burn eschar is thick necrotic skin that results from deep burn injuries. In the absence of intervention, the burn eschar eventually spontaneously detaches, revealing granulation tissue. DPT burns involve the epidermis and superficial and deeper dermis, including hair follicles and glandular tissue. Deep partial thickness (DPT) burns heal in 2 to 9 weeks (if no infection develops) and with hypertrophic scarring and joint dysfunction. Full-thickness (FT) burns destroy the entire dermis and may extend into the underlying subcutaneous tissue and never fully heal spontaneously. The depth of a thermal burn correlates with the thickness of skin and the temperature and duration of contact with the heat source. These may be serious wounds. Determinants of overall burn severity include burn depth, extent (percentage total	Devitalized tissue in the burn wound serves as a medium for microbial growth, and all burn wounds are colonized (bacteria, fungi, viruses). Wound infection and sepsis may follow. Additionally, damaged cells in the burn wound release inflammatory cytokines and growth factors. Therefore, early excision of the eschar generally appears to represent the current standard of care for deep burn injuries. Complex, systemic pathophysiologic responses may be seen with extensive, severe burn injury e.g., involving > 20% TBSA. These responses may impact circulatory, metabolic, respiratory and immunologic functions. Early burn excision

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	burn surface area), and location.	and wound closure alone do not eliminate the hypermetabolic response. However, early excision may decrease the release of inflammatory mediators and attenuate the hypermetabolic and systemic responses.
Current Treatment Options	• Generally, early surgical excision appears to be the standard of care (SOC) for eschar removal in DPT and FT wounds. However, some question the benefits of this practice e.g., concerns that the surgical trauma could potentially worsen the acute-phase response in these patients. Techniques include tangential excision and dermabrasion. • Collagenase ointment is the only product approved for debridement of burn wounds (Approved 06/04/1965). Specifically, it is indicated for "debriding chronic dermal ulcers and severely burned areas." Silver sulfadiazine cream, 1% (approved 11/26/1973) is "a topical antimicrobial drug indicated as an adjunct for the prevention and treatment of wound sepsis in patients with second- and third-degree burns. Mafenide acetate cream (approved: 01/24/1969) is indicated for "adjunctive therapy of patients with second- and third-degree burns."	With NexoBrid, the Applicant proposes a new, topical alternative to surgical removal of the burn eschar. Although collagenase ointment is approved for debridement of "severely burned areas,it is an old product, and the label includes no information on its treatment effect. Additionally, the extent of product use in the burn population (i.e., real-world use) is unclear. Although topical antimicrobials (e.g., silver sulfadiazine cream, 1% and mafenide acetate cream) may be considered as part of the non-surgical armamentarium for burn wound care, these are not debriding agents.
Benefit	• The Applicant assessed wound closure as a safety endpoint, defining "complete" wound closure as ≥ 95% closed in the main analysis. The results of the 3 analyses conducted for the wound closure endpoint follow: 1. In the *per-wound analysis of ≥95% wound closure* (Applicant's main analysis), the median number of days to wound closure was 27 in the NexoBrid arm and 28 in the SOC arm. 2. In the *per-subject analysis ≥95% wound closure*, the median	The Agency defines wound closure as "skin reepithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart." Although an analysis was performed that considered the Agency's definition (100% closure), the results of that analysis may not be reliable because of the substantial amount of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	number of days to wound closure was 31 in the NexoBrid arm and 36 in the SOC arm. 3. In the *per-subject analysis of 100% wound closure*, the median number of days to wound closure was 38 in the NexoBrid arm and 52 in the SOC arm. • The Agency recommended "blood loss related to eschar removal" as an endpoint in study 2010 to potentially demonstrate a clinical benefit of NexoBrid. While, the results for this secondary endpoint suggest that blood loss related to eschar removal may be less in the NexoBrid group compared to the SOC group, the considerable amount of missing data (approximately half of subjects in the SOC arm) limited the interpretability of results related to this endpoint. The interpretability of the data is further challenged because blood loss calculations could have reflected eschar removal procedures that may have occurred over extended periods, due to the nature of SOC procedures.	missing data in both treatment arms (52-68%). This is due to the study design which called for less frequent follow-up visits after the 2-week, confirmatory visit for ≥ 95% wound closure: the schedule went from follow-up weekly to follow-up at Months 1, 3, 6, 12. • In all 3 analyses, the median time to wound closure was shorter for the NexoBrid group compared to SOC. • Even if the blood loss results were interpretable, it is not clear that demonstration of statistically significant differences in blood loss between the treatment groups during eschar removal would necessarily represent an inherently significant benefit of NexoBrid over SOC. Information relating to transfusions may be a measure of the clinical significance of blood loss, and blood loss sufficient to require transfusion during eschar removal occurred in ≤ ~3% of subjects in study 2010 (1 subject in the NexoBrid arm and 2 in the SOC arm). The low and similar proportions of subjects who required

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		transfusions during eschar removal may indirectly suggest that NexoBrid did not cause more bleeding than SOC during eschar removal.
Risk and Risk Management	• The Applicant identified pain, pyrexia, wound infection, immediate hypersensitivity reactions, and coagulation parameter abnormalities as key risks of NexoBrid treatment. • There are numerous, unresolved product quality issues pertaining to bromelain special production and drug substance microbial controls, and drug product microbial controls.	Product labeling and routine pharmacovigilance activities may be adequate for management of the identified risks. Safety of the product cannot be adequately assessed, given that the microbial control strategy does not mitigate the risk of potential adventitious agents that may be introduced during the manufacturing process.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.2.1
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Intact skin functions as a barrier to the external environment, protecting against infection, water loss, and ultraviolet irradiation.[1,2] Other functions include heat regulation (protection from overheating and heat loss) and sensory organ functions (pain, temperature, and touch perception).[1,2] A burn injury disrupts these functions by transforming intact skin into an open wound.[2,3]

The Applicant proposes NexoBrid for eschar removal or debridement of deep partial thickness (DPT) and/or full thickness (FT) thermal burns. Thermal burns are most commonly caused by flames, hot liquids, hot solid objects, or steam,[4] and a burn eschar is thick necrotic skin that results from deep burn injuries. In the absence of intervention, the burn eschar eventually spontaneously detaches, revealing granulation tissue.[3,4] Unless closed surgically, the wound then heals via reepithelialization from the wound edges (wound contracture) and, ultimately, with severe scarring, including contractures if the burn overlies a joint.[4] However, complete spontaneous healing of FT burn wounds does not occur.[4] The primary objective of burn wound care is wound closure.[2,3]

Patients with DPT and FT wounds may be critically ill, and management of these patients may extend beyond local wound care to include treatment of profound associated systemic complications, including hemodynamic instability, metabolic derangements (hypermetabolic state), sepsis, acute respiratory distress syndrome, multiple organ dysfunction syndrome (MODS), and associated injuries (e.g., inhalation injury).[5] Death may be the outcome. The following discussion is high-level and is not intended to represent a comprehensive discussion of the complex management of patients with serious burn injuries.

The depth of a thermal burn correlates with the thickness of skin and the temperature and

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[1] Kubo A, Amagai M. Skin Barrier. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, Orringer JS. eds. Fitzpatrick's Dermatology, 9e. McGraw-Hill; Accessed May 10, 2021. https://accessmedicine.mhmedical.com/content.aspx?bookid=2570&sectionid=210416253

[2] Cancio LC, Barillo DJ, Kearns RD, Holmes JH et al. Guidelines for burn care under austere conditions: surgical and nonsurgical wound management. J Burn Care Res.2017;(38)4:203-214.

[3] Phelan HA, Bernal E. Treatment of deep burns. In: UpToDate, Jeschke MG (Ed), UpToDate, Waltham, MA. (Accessed on December 16, 2020.)

[4] Rice PL, Orgill DP. Assessment and classification of burn injury. In: UpToDate, Jeschke MG (Ed), UpToDate, Waltham, MA. (Accessed on April 06, 2021.)

[5] Ipaktchi K, Arbabi S. Advances in burn critical care. Crit Care Med 2006; 34[Suppl.]:S239–S244.

duration of contact with the heat souce.[4,6] Determinants of overall burn severity include burn depth, extent (percentage TBSA), and location.[4,7] Initial assessments (extent and depth) are generally made clinically and are key to follow-on decisions regarding triage (e.g., burn center referral) and management planning.[3] However, these clinical assessments are subjective, and their accuracy and reliability may vary considerably.[3,4] Assessment instruments for clinical determination of percentage TBSA affected include the Wallace Rule of Nines, the Palm Method, and the Lund-Browder Chart. Superficial burns are not included in the assessment of extent of injury.[4]

Burn depths are classified as below:[4,6]

- Superficial or epidermal (first-degree) burns are limited to the epidermis. These generally heal in less than a week. The classic example is a sunburn.
- Partial-thickness (second-degree) burns involve the epidermis and portions of the dermis and may be further classified as:
  - *superficial* partial-thickness: involve the superficial dermis; typically heal within 1-3 weeks without scarring, but pigmentary changes may result.
  - *deep* partial thickness: involve the deeper dermis, and hair follicles and glandular tissue are damaged; these burns heal in 2 to 9 weeks (if no infection develops) and with hypertrophic scarring and joint dysfunction, as discussed above.
- Full-thickness burns (third degree) destroy the entire dermis and may extend into the underlying subcutaneous tissue and never fully heal spontaneously.
- Fourth-degree burns extend into the underlying fascia, muscle, and bone.

Thus, burn depth is a key determinant of the potential for spontaneous healing and the need for surgical intervention e.g., excision, grafting.[6,7] Additionally, burn depth is a major determinant of survivability and the main determinant of longterm cosmesis and functionality.[6]

Features distinguishing DPT and FT burns may not be apparent during initial assessment, and serial assessments, allowing for burn demarcation, may be required for making such determinations.[3] A wound that is assessed as possibly being DPT or FT should be considered a FT burn, pending a more certain determination of burn depth. However, burn injuries are generally not of uniform depth.[3,6] Because of this lack of uniformity, different parts of a burn injury may receive different treatments on different schedules.[6]

See Figure 1 and Table 1 for additional clinical characteristics of burn injuries.

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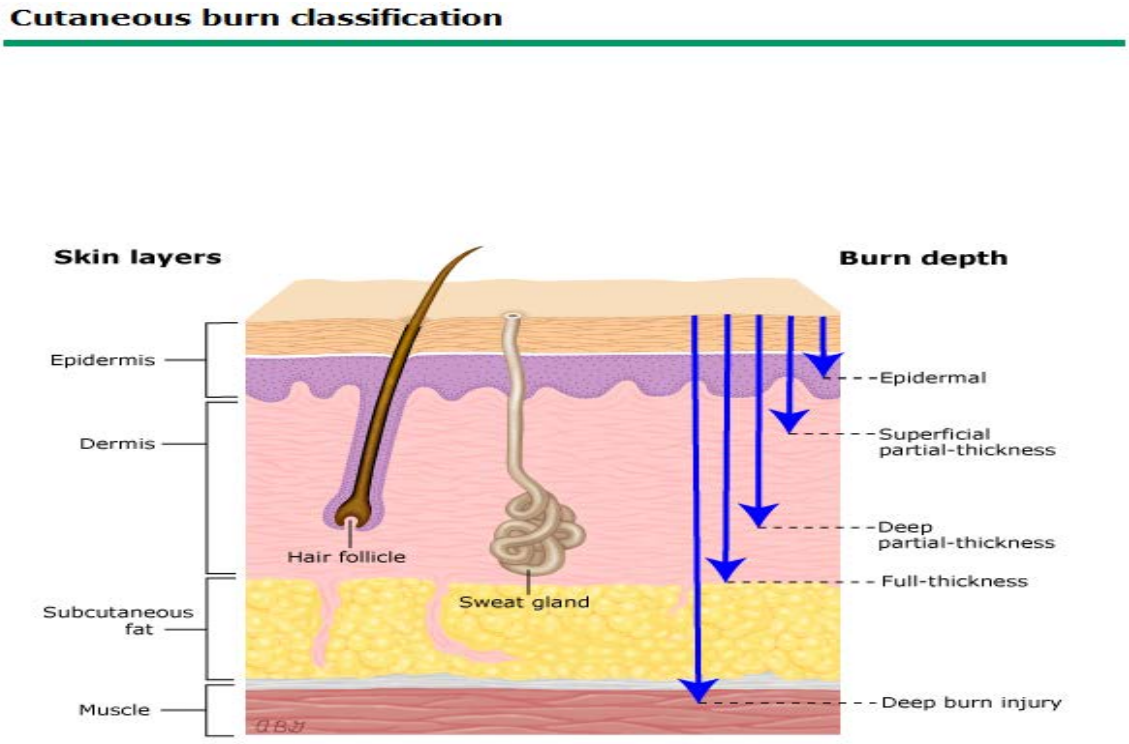
[6] Kagan RJ, Peck MD, Ahrenholz DH Hickerson WL et al. Surgical management of the burn wound and use of skin substitutes: An expert panel white paper. J Burn Care Res.. 2013;(34)2:e60-e79.
[7] Benson A, Dickson WA, Boyce DE. ABC of wound healing Burns. BMJ 18 March 2006;(332)649-652.

Figure 1. Illustration of Burn Depths[4]



*Source: Rice PL, Orgill DP. Assessment and classification of burn injury. In: UpToDate, Jeschke MG (Ed), UpToDate, Waltham, MA. (Accessed on April 06, 2021.)

Table 1. Classification of burns by depth of injury[4]

Depth	Appearance	Sensation	Healing time
Superficial (epidermal)	Dry, red Blanches with pressure	Painful	3 to 6 days
Superficial partial-thickness	Blisters Moist, red, weeping Blanches with pressure	Painful to temperature and air and touch	7 to 21 days
Deep partial-thickness	Blisters (easily unroofed) Wet or waxy dry Variable color (patchy to cheesy white to red) Blanching with pressure may be sluggish	Painful to pressure only	>21 days, usually requires surgical treatment
Full-thickness	Waxy white to leathery gray to charred and black Dry and inelastic No blanching with pressure	Deep pressure only	Rare, unless surgically treated
Deeper injury (ie, fourth degree)	Extends into fascia and/or muscle	Deep pressure	Never, unless surgically treated

Source: Rice PL, Orgill DP. Assessment and classification of burn injury. In: UpToDate, Jeschke MG (Ed), UpToDate, Waltham, MA. (Accessed on April 06, 2021.)

Devitalized tissue in the burn wound serves as a medium for microbial growth,[8,9] and all burn wounds are colonized (bacteria, fungi, viruses).[8] Wound infection and sepsis may follow. Additionally, damaged cells in the burn wound release inflammatory cytokines and growth factors.[8,9] Therefore, "early" excision of the eschar generally appears to represent the current

[8] Singer AJ, Ahrenholz DH, Chang P, Clark RAF et al. Burn wound healing outcomes in American Burn Association Consensus Statements. J Burn Care Res.2013;(34)4:21-25.
[9] Ong Ys, Samuel M, Song C. Meta-analysis of early excision of burns. Burns 2006;32: 145–150.

standard of care for deep burn injures (also see Section 2.2).[2,3,9,10] However, the timeframe that constitutes "early" seems somewhat unclear e.g., ranging from being ideally within 24 to 72 hours of injury[3] to being unspecified.[8] Additionally, some authors acknowledge a lack of consensus on the timing of excision.[8] However, the feasibility of early excision is highly dependent on the clinical status of the patient.[3]

Complex, systemic pathophysiologic responses may be seen with extensive, severe burn injury e.g., involving > 20% TBSA.[10,11,12] These responses may impact circulatory, metabolic, respiratory and immunologic functions.[5,13] The acute phase of this response has been termed "burn shock" and may be marked by depletion of intravascular volume (hypovolemia) due to protein and fluid movement into the interstitial space.[10,12] Thus, fluid resuscitation is a critical part of initial management to restore intravascular volume and maintain tissue and organ perfusion.[12] Increased systemic vascular resistance due to catecholamines, antidiuretic hormone, and hemoconcentration is also part of the burn shock picture.[12] The hypermetabolic phase begins 48 to 72 hours post injury[12] and marks a relatively prolonged period of chronic inflammation,[10] with increased oxygen consumption and protein wasting,[12] and increased cardiac output.[12] Wound healing may be impaired.[5] Pulmonary complications (insufficiency and failure) are multifactorial, relating to possible inhalation injury, the systemic inflammatory response and delayed injury from sepsis and pneumonia.[5] The release of inflammatory mediators changes the patient's metabolic profile.[11] Metabolic responses in the severely burned patient include metabolic acidosis and respiratory alkalosis.[13] Immunologic disturbances include disruptions in macrophage function and cellular and humoral immunity. Coagulation abnormalities may develop. [13] Infection and sepsis are major risks, and the principal cause of death is MODS, if the patient survives the first 24 hours.[11] Longer term, tachycardia and tachypnea may persist for months, and the baseline temperature may be reset to ~38.5°C. [11]

Early burn excision and wound closure alone do not eliminate the hypermetabolic response.[3] However, early excision may decrease the release of inflammatory mediators[9] and attenuate the hypermetabolic and systemic responses.[6,9,14]

Circumferential eschar (neck, trunk, limbs, digits) subject the underlying tissues to increased interstitial pressure, to which fluid from the interstitial space, fluid from resuscitation and

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[10] Rowan MP, Cancio LC, Elster EA, Burmeister DM et al. Burn wound healing and treatment: review and advancements. Crit Care 2015;19:243.
[11] Greenhalgh DG, Saffle JR, Holmes JH, Gamelli RL et al. American Burn Association Consensus Conference to define sepsis and infection in burns. J Burn Care Res 2007;28:776–790.
[12] Bittner EA, Shank E, Woodson L, Martyn JAJ Acute and perioperative care of the burn-injured patient. Anesthesiology. 2015 February ; 122(2): 448–464.
[13] Atiyeh BS, Gunn SW, Hayek SN. State of the art in burn treatment. World J. Surg. 2005;29:131–148.
[14] Barret JP, Herndon DN. Modulation of inflammatory and catabolic responses in severely burned children by early burn wound excision in the first 24 hours. Arch Surg. 2003;138:127-132.

edema related to the burn itself may contribute.[3,6,10,12] This is compartment syndrome.[6] Venous outflow and arterial inflow may eventually be compromised, with eventual tissue ischemia.

Ischemia and constriction may result in nerve and muscle death and organ dysfunction e.g., hepatic and renal failure, reduced pulmonary compliance.[6] Escharotomy (surgical incision through the eschar) is the appropriate preventative and therapeutic intervention.[6]

2.2. Analysis of Current Treatment Options

Collagenase ointment is the only product approved for debridement of burn wounds (approved 06/04/1965). Specifically, it is indicated for "debriding chronic dermal ulcers and severely burned areas."[15] The label includes no information on its treatment effect, and the extent of product use in the burn population is unclear.

Silver sulfadiazine cream, 1% (approved 11/26/1973) is "a topical antimicrobial drug indicated as an adjunct for the prevention and treatment of wound sepsis in patients with second- and third-degree burns."[16] Per the product label ("Clinical Pharmacology" section), "silver sulfadiazine has broad antimicrobial activity. It is bactericidal for many gram-negative and gram-positive bacteria as well as being effective against yeast…Sufficient data have been obtained to demonstrate that silver sulfadiazine will inhibit bacteria that are resistant to other antimicrobial agents and that the compound is superior to sulfadiazine."[16]

Mafenide acetate cream (approved 01/24/1969) is indicated for "adjunctive therapy of patients with second- and third-degree burns." Per the product label, it "produces a marked reduction in the bacterial population present in the avascular tissues of second- and third-degree burns. Reduction in bacterial growth after application of (mafenide acetate) Cream has also been reported to permit spontaneous healing of deep partial-thickness burns, and thus prevent conversion of burn wounds from partial-thickness to full-thickness. It should be noted, however, that delayed eschar separation has occurred in some cases."[17]

Although topical antimicrobials (e.g., silver sulfadiazine cream, 1% and mafenide acetate cream)

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[15] Label: Collagenase Santyl Ointment https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6b6fbfc6-98fa-46aa-88ef-ab00fbb08ffd

[16] Label: silver sulfadiazine cream. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c437213a-1cd4-445e-a39f-bbcacb9f746f

[17] Label: Mafenide acetate cream. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9972db4c-703f-4cbc-915c-ec993bff6fb9

may be considered as part of the non-surgical armamentarium for burn wound care, these are not debriding agents.

Generally, early surgical excision appears to be the standard of care (SOC) for eschar removal in DPT and FT wounds (also see Section 2.1).[2,3,9,10] However, some question the benefits of this practice e.g., concerns that the surgical trauma could potentially worsen the acute-phase response in these patients.[14]

Although practices may vary, excisional techniques typically include tangential excision, which involves successive removal of burned tissue down to viable dermis[4,6] and full-thickness excision, in which the burn wound is excised down to viable subcutaneous tissue or fascia.[6] High-pressure water jets may also be used.[4] Some authors advocate the use of dermabrasion.[18] However, this technique for treatment of burns may be controversial.[19]

The open wound that results from burn excision requires covering to reduce the risk of infection, decrease the loss of fluids, improve the cosmetic outcome, and lower the risk of contractures.[6,8] Temporary wound coverage may be achieved by use of allografts (e.g., cadaver skin) or xenografts (e.g., pigskin).[6] A burn wound is considered closed after placement and healing of an autograft. Autografts are harvested from areas of healthy skin (donor sites) and transferred onto the open wound (recipient site) and may be split-thickness (includes the entire epidermis and portions of dermis) or full-thickness (includes all skin components i.e., epidermis, dermis, hair follicles, and nerve endings).[6] Successful autografting results in permanent wound closure.[3,4] Agency guidance defines wound closure as, "skin reepithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart."[20]

With NexoBrid, the Applicant proposes a new topical alternative to surgical removal of the burn eschar.

In this review, "eschar removal" is considered synonymous with "debridement," and the 2 terms may be used interchangeably. NexoBrid is not intended for treatment of circumferential eschar.

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[18] Esposito G, Gravante G, Montone A. Use of early dermabrasion in pediatric burn patients. Plastic and Reconstructive Surgery.2006;118(2):573-575.
[19] Yenidunya MO. Dermabrasion is not a treatment for burns. Burns 2008;34:152.
[20] U.S. Department of Health and Human Services Food and Drug Administration Guidance for Industry, Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment. June 2006.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The product is not marketed in the United States.

The Biomedical Advanced Research and Development Authority (BARDA), in the office of the Assistant Secretary for Preparedness and Response (ASPR) awarded a contract to MediWound to support development of NexoBrid. As part of the United States mass casualty preparedness program, BARDA has procured NexoBrid as a medical countermeasure (MCM) for the removal of eschar in patients with DPT and FT thermal burns (b) (4). In the event of a declared emergency and after FDA authorization of Emergency Use Authorization (EUA), BARDA would deploy and distribute NexoBrid directly to burn centers. BARDA has been procuring NexoBrid since July 2020 (over (b) (4) units, as of 03/01/2021).[21]

On 05/30/2019, BARDA submitted a new Pre-Emergency Use Authorization (PEUA) Request (b) (4).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed NexoBrid under IND 65448, opened on 07/30/2002. The general regulatory history of product development is long and complicated and includes numerous meetings and Agency communications.

The IND was opened with a protocol for an open-label, prospective, two-arm, randomized, multicenter Phase 2 study. The reviewing medical officer identified multiple deficiencies in the protocol, and these were communicated to the Applicant who agreed to revise the protocol and, thus, avoided a Clinical Hold. However, the IND was later placed on Clinical Hold (08/03/2004) because of the occurrences of 4 deaths in the Phase 2 study MW 2002-04-01 (2002), which was then ongoing in Europe and India. The information regarding the deaths was apparently APPEARS THIS WAY ON ORIGINAL provided in a briefing package for a pending meeting with the Agency. All of the deaths occurred in the Debrase (now NexoBrid) arm; standard of care (SOC) was the comparator. An imbalance was also noted in the reports of serious adverse events (higher in the Debrase arm).

[21] BARDA slide deck for teleconference with the Agency on 03/01/2021 (slide #4).

To address the deficiencies detailed in the hold letter, the Applicant was to have submitted the final study report for study 2002, as well as efficacy data, as no treatment benefit was observed in subjects receiving Debrase. The Agency found the Response to Clinical Hold to be inadequate. Ultimately, the Applicant received 3 Continue Clinical Hold letters due to inadequacy of responses and/or new issues raised by submission of a new protocol MW 2005-10-05, which appears to have been included in the 2nd Response to Clinical Hold submission. Hold issues included general study design, lack of appropriate efficacy endpoint (e.g., time to complete wound healing), not limiting the treatment area (5% was acceptable) or location (no high-value functional or cosmetic locations e.g., hands, face) or types of wounds (no circumferential eschar), study population (limit to adults), and patient monitoring. A CMC hold issue was added in the 2nd Continue Clinical Hold letter. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) The IND also included no CMC information to support the manufacturing, controls or stability of the new formulation. The Applicant eventually adequately addressed the deficiencies, and the Clinical Hold was removed on 11/10/2005. The Applicant continued to discuss the development program with the Agency, over the ensuing years. Discussions pertained to all disciplines.

The Applicant had an End-of-Phase 2 (EOP2) meeting on 07/25/2011. The Agency did not agree with the Applicant's proposed study design for Phase 3, the co-primary endpoints (superiority in eschar removal and superiority in reduction in surgical need), definition of the study population (e.g., extent and depth of burn) or definition of SOC.

The Applicant initially submitted the protocol for the pivotal Phase 3 study, MW2010-03-02 (2010) or DETECT on 06/29/2012. The regulatory history specifically relating to the Phase 3 program is also long and complicated and included 4 requests for Special Protocol Assessment (SPA) and 4 No Agreement letters. Areas of disagreement continued to include endpoints and how the Appplicant would establish that the benefits of NexoBrid outweighed its risks, relative to SOC. The Applicant appeared to consider eschar removal itself to be a demonstration of benefit, due to infection risk from the eschar and the potential for the eschar to contribute to systemic responses related to serious burn injuries. The Agency repeatedly requested that the Applicant evaluate endpoints that adequately characterized time to complete wound closure and cosmesis and function. Agency recommendations from the 4th and final No Agreement letter included the following:

- Evaluate superiority of the "incidence of complete eschar removal at the end of the topical agent soaking period" versus vehicle.
- Compare other endpoints to true SOC (surgical or nonsurgical) to allow adequate interpretation of these endpoints, rather than to Santyl for which expected outcomes are unknown.
- Define "Complete wound closure" as 100% re-epithelialized without drainage or dressing requirements confirmed at two consecutive study visits two weeks apart.
- "Cosmesis" would be acceptable as a safety endpoint and was recommended for assessment mainly using the modified Vancouver Scar Scale (mVSS).
- "Time to reach complete wound closure" would be acceptable as a safety endpoint.

- Propose a secondary endpoint that measures clinical benefit, e.g. need for less anesthesia, decreased blood loss.
- "Incidence of surgical excision" could be a secondary endpoint and would provide information on treatment failures that required follow-on surgery and could provide supportive evidence of efficacy.

The Applicant appeared to have been under the impression that SPA agreement was required from the Agency before they could start study 2010. Minutes from a post-SPA meeting held 04/23/2014 reflect that the Agency reminded the Applicant the IND was not on Clinical Hold and that the Applicant could proceed with study 2010 without obtaining agreements under a SPA. The Applicant subsequently attempted to address Agency recommendations from the final No Agreement letter by revising protocol 2010. The Applicant enrolled the first subject into study 2010 on 05/27/2015.

Orphan Drug Designation

On August 20, 2003 NexoBrid (then Debase) received orphan drug designation for debridement of acute, deep dermal burns in hospitalized patients.

Expanded Access Protocol

MediWound submitted an expanded access treatment protocol titled, "Use of NexoBrid for Treatment of Acute deep partial and full thickness Burn Injuries" [MW2018-06-21 (2018) or NEXT] on 02/17/2019. The protocol is intended to allow continued treatment of patients with DPT and/or FT thermal burns with NexoBrid in the United States at study 2010 investigational sites and at additional trained sites, until product licensure. BARDA is funding the study.

The last subject was enrolled into study 2010 in (b) (6) The study conducted under the expanded access protocol will continue to evaluate the safety and clinical performance of NexoBrid in the target population and is also intended to aid in the ability of practitioners to maintain their skills in the use of NexoBrid. Up to 150 hospitalized adults will be enrolled under the protocol. As of the Development Safety Update Report submitted to IND 65448 on 10/27/2020, 39 subjects had been treated under the expanded access protocol.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical inspections were requested for the following investigators for study 2010:

- *Sigrid Blome-Eberwein (site 103)*: high site efficacy, high serious adverse events (SAEs), and no prior inspections.
- *Jeremy Goverman (site 104)*: high enroller, high site efficacy, and no prior inspections
- *Adam Singer (site 117)*: high site efficacy, high SAEs and non-serious AEs, protocol deviations, complaints and prior inspectional history (for-cause in 2017; voluntary action indicated).

Findings from a for-cause inspection, at a fourth site, *Robert Mullins (site 120)*, were also included in the Clinical Inspection Summary. The for-cause inspection of Dr. Mullins' site was conducted prior to BLA submission (inspection dates 04/15 to 04/26/2019) in response to a report of Good Clinical Practice (GCP) noncompliance from the Institutional Review Board (IRB), based on a site monitoring visit by a Contract Research Organization (CRO). CRO observations included (b) (4) (b) (4)

Additionally, the findings from the for-cause inspection for Dr. Singer's site from 2017 were included in the Clinical Inspection Summary. That inspection was conducted in response to multiple reports from the IRB of GCP noncompliance, including that numerous study tests and assessments were performed late or not at all, unblinding of first and second blinded assessors, and dosing errors.

For all 4 investigators, the OSI made significant inspectional observations which raised concerns regarding the conduct of the study and the reliability of data (b) (4) (b) (4) and safety endpoints (b) (4) (b) (4) The concerns included:

(b) (4)

The summary conclusions from the Clinical Inspection Summary were: "…(T)his study was not conducted in accordance with the protocol and current Good Clinical Practice (GCP) standards. The quality of the data generated from the study are of poor quality, and OSI recommends that the study data be evaluated as if they were obtained from an open label study."

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommended a Complete Response (CR) action on the application.

Per the Executive Summary of the Integrated Quality Assessment (IQA), OPQ concluded that the submitted data were "not sufficient to support a conclusion that the manufacture of NEXOBRID is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a product quality standpoint, OPQ is recommending a Complete Response letter be issued to MediWound, Ltd. to outline the deficiencies…and the information and data that will be required to support approval."

The identified deficiencies were numerous and pertained to the botanical raw material authentication, bromelain special production (BSP) and drug substance (DS) microbial controls (also see Section 4.3), drug product (DP) microbial controls, and product quality chemistry, manufacturing and controls (CMC). Additionally, for approval, inspections are required of the drug substance intermediate manufacturing facility (Challenge Bioproducts Company Ltd.) and the drug substance, drug product, and gel vehicle manufacturing facility (MediWound Ltd.). However, due to restrictions on travel due to the coronavirus disease 2019 (COVID-19) public health emergency, the Agency was unable to conduct the inspections during the current review cycle.

4.3. Clinical Microbiology

The IQA identified CR deficiencies relating to the BSPand DS microbiology, including:

- The Applicant's overall microbial control strategy does not mitigate the risk of potential adventitious agents that may be introduced during the manufacturing process.
- Routine endotoxin testing cannot be performed due to the nature of the BSP and DS (b) (4)

4.4. Devices and Companion Diagnostic Issues

Not applicable

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

NEXOBRID is a mixture of proteolytic enzymes enriched in bromelain and it is indicated for eschar removal (debridement) in adults with burn wounds.

In pharmacology studies 10% NEXOBRID gel showed efficient debriding activity in pig wound models. It also exhibited certain selectivity toward eschar compared to normal skin. In an in vitro study the proteolytic activity of NEXOBRID was evaluated on substrates collagen and gelatin. NEXOBRID showed more than 2-fold higher (b) (4) than collagenase activity.

NEXOBRID gel up to 30% was generally tolerated when applied to intact minipig skin but caused severe irritation and pain when applied to abraded skin. In an acute dermal toxicity study in minipigs, 10% NEXOBRID gel was administered to minipigs with ~6-12% body surface area (BSA) burn wounds in two successive 4-hour applications. Successful debridement was achieved and no significant toxicity was noted. A higher degree of epithelialization of wounds was observed in NEXOBRID-treated animals, compared with the standard of care and vehicle control animals.

Single dose intravenous (IV) toxicity studies were conducted in minipigs. A NOEL was identified as 12 mg/kg but higher doses caused severe toxicity (mortality and generalized hemorrhage). Repeat-dose IV toxicity studies were conducted in minipigs and juvenile pigs. Repeated IV doses up to 12 mg/kg three times a week were generally tolerated for the first several doses but severe toxicities (hemorrhages in multiple tissues) were observed afterwards. No NOAEL could be identified in the repeat-dose IV toxicity studies. As NEXOBRID is a mixture of proteolytic enzymes, it is conceivable that overt toxicities were produced in IV toxicity studies. IV toxicity studies have limited value in assessing human risk and dermal toxicity studies are considered more relevant to human risk assessment.

A 4-week dermal toxicity study in minipigs was conducted with EX-02, which is a different topical formulation but has the same active ingredients as NEXOBRID. Topical doses up to 10% EX-02 gel were administered to minipigs either daily or three times per week with surgically established full-thickness open wounds. No significant toxicities were noted and the NOAEL was identified as the high dose (8 g/day 10% gel).

IV embryofetal development studies were conducted in rats and rabbits. Similar to repeat-dose IV toxicity studies, severe maternal toxicities were noted in these studies. However, no significant developmental toxicities were noted. The tolerable maternal systemic exposure levels were much lower compared with the maximum human exposure in clinical setting. These studies are considered of limited value in human risk assessment.

Although not considered necessary, NEXOBRID was tested for genotoxicity in a standard battery of tests (the Ames test, an in vitro mammalian chromosome aberration test, and an in vivo micronucleus test in mice). NEXOBRID was negative in the three studies. The in vitro mammalian chromosome aberration test was not optimal as doses were limited due to the nature of the test article. The micronucleus test in mice was not properly conducted as oral route is inappropriate for the administration of protein products. It is not recommended to include the result of the micronucleus study in the drug label.

NEXOBRID did not show skin sensitization potential in a guinea pig maximization test. Carcinogenicity studies are not needed for the development of NEXOBRID.

This BLA is approvable from a Pharmacology/Toxicology perspective. There is no recommended nonclinical PMC/PMR for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

All the pivotal nonclinical data have been reviewed under IND 65448. Summary pharmacology/toxicology information is provided in this review. Debrase is another name for NEXOBRID that was previously used in the nonclinical studies.

5.3. Pharmacology

Primary pharmacology

NEXOBRID is a lyophilized powder consisting of a mixture of proteolytic enzymes enriched in bromelain and a gel vehicle used for preparation of a gel for topical use. NEXOBRID is indicated for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

The proteolytic activity of NEXOBRID was evaluated in vitro on substrates collagen and gelatin. Collagen is one of the major structural components of skin and gelatin is a denatured form of collagen and a major component of eschar. NEXOBRID is comprised of different proteases that have different levels of activity towards gelatin and collagen. (b) (4) (b) (4) This was possible due to the dissociation of the (b) (4) from its intrinsic inhibitors.

In vivo pharmacology studies were conducted with pig wound models. In a study 16 comb burns were created on each of five female domestic pigs using a brass comb and treated with 10% NEXOBRID gel for 4 hours. NEXOBRID and control articles were wiped off after 4 hours. Histopathology examination was conducted at 4 and 48 hours post-treatment. NEXOBRID treatment resulted in eschar dissolution in all the burns in which the overlying burn blister/necrotic keratin was adequately removed. None of the control burns showed debridement, and normal uninjured skin exposed to NEXOBRID showed no macroscopic

evidence of injury. This study demonstrated efficient debriding activity of NEXOBRID and certain selectivity toward eschar.

Another pharmacology study was conducted to assess the selectivity of NEXOBRID by comparing its activity on normal, burned, and mechanically-injured exposed dermis of porcine skin. On one female domestic pig, eight 5 cm x 5 cm partial thickness cutaneous burn wounds (created using a radiant heating device), six 5 cm x 5 cm partial thickness donor sites (created using an electric dermatome), and two 5 cm x 5 cm intact skin sites were treated with 10% NEXOBRID gel (~5 g on each site) for 4 hours. Rapid eschar dissolution was noted in all NEXOBRID-treated wounds. There was no apparent damage to the underlying sub-eschar dermis, donor sites, or normal skin after exposure to NEXOBRID. NEXOBRID exhibited certain selectivity toward eschar under the study conditions.

Secondary Pharmacology

No secondary pharmacology studies were conducted as NEXOBRID is intended as a local treatment.

Safety Pharmacology

No stand-alone safety pharmacology studies were conducted. This is acceptable considering that 1) NEXOBRID is intended as a local treatment and 2) substantial human safety data have become available derived from the commercial use of NEXOBRID in Europe. In addition, safety pharmacology endpoints were evaluated in GLP toxicology studies conducted in pigs and minipigs.

5.4. ADME/PK

Table 1: Summary of TK data for NEXOBRID

Type of Study	Major Findings
TK data from general toxicology studies	
A single dose toxicity study of Debrase powder administered intravenously to minipigs with a 14-day observation period (Study# 20002067)	<u>Minipig (single IV doses)</u> $T_{1/2}$: 12.6-15.4 hr AUC_{inf} (sex combined): 4 mg/kg: 24150 ng•hr/ml 12 mg/kg: 75450 ng•hr/ml 24 mg/kg: 176500 ng•hr/ml Dose proportionality: The AUC increase was approximately dose-proportional
A 2-week toxicity study of Debrase powder administered intravenously to minipigs with a 2-week recovery period (Study# 20002068)	<u>Minipig (IV doses three times a week for 2 weeks)</u> $T_{1/2}$: 4.3-4.9 hr AUC_{inf} (Day 13, sex combined): 4 mg/kg: 40100 ng•hr/ml

Type of Study	Major Findings
Debrase powder: a 2-week intravenous toxicity study in juvenile farm pigs with a 2-week recovery period (Study# 1990-003)	8 mg/kg: 83350 ng•hr/ml 12 mg/kg: 132500 ng•hr/ml Accumulation: 1.6-2.6-fold comparing AUC at Days 13 and 1 Dose proportionality: The AUC increase was approximately dose-proportional <u>Pig (IV doses three times a week for 2 weeks)</u> $T_{1/2}$: 3.8-5.4 hr AUC_{inf} (Day 8, sex combined): 4 mg/kg: 22900 ng•hr/ml 8 mg/kg: 51200 ng•hr/ml 12 mg/kg: 97700 ng•hr/ml Accumulation: 1.3-1.6-fold comparing AUC at Days 8 and 1 Dose proportionality: The AUC increase was approximately dose-proportional
TK data from reproductive toxicology studies Intravenous developmental toxicity study of Debrase powder in rats (Study# SOD00002)	<u>Maternal rat (once daily IV doses during gestation days 7-17)</u> AUC_{inf} (gestation day 17): 0.5 mg/kg/day: 532 ng•hr/ml 1 mg/kg/day: 2250 ng•hr/ml 4 mg/kg/day: 16500 ng•hr/ml Systemic exposure decreased when comparing AUC at gestation days 17 and 7.
Intravenous developmental toxicity study of Debrase powder in rabbits (Study# SOD00004)	<u>Maternal rabbit (once daily IV doses during gestation days 7-19)</u> AUC_{inf} (gestation day 19): 0.01 mg/kg/day: insufficient data 0.05 mg/kg/day: 228 ng•hr/ml 0.10 mg/kg/day: 347 ng•hr/ml Systemic exposure decreased when comparing AUC at gestation days 19 and 7.

5.5. Toxicology

5.5.1. General Toxicology

Study 1 A single dose toxicity study of Debrase powder administered intravenously to minipigs with a 14-day observation period (Study# 20002067, GLP)

Single IV doses (slow bolus injection) of 0 (vehicle: 0.9% saline), 4, 12, and 24 mg/kg NEXOBRID were administered to Gottingen minipigs (3/sex/group), followed by a 14-day observation period. No mortality was noted in this study. Clinical signs including decreased activity, shivering, few feces, and decreased food consumption were noted in the high dose group. These observations were noted within 2 hours of dose administration and persisted through Day 7. No other significant test article-related clinical signs were noted. There were no significant test article-related changes in body weight, clinical pathology parameters, gross

pathology findings, organ weights, or histopathology findings during the study. A NOEL was identified as the mid dose, 12 mg/kg, under the study conditions. See the table in Section 5.4 for TK information.

Study 2 A 7-day study of Debrase powder by intravenous infusion in minipigs (Study# 20006035, GLP)

Single IV doses (2-hour intravenous infusion) of 0 (vehicle: sterile PBS), 24, 48, and 96 mg/kg NEXOBRID were administered to Gottingen minipigs (1/sex/group), followed by a 7-day observation period. Mortality was noted at the high dose on Day 1 as the male animal in this group was found dead and the female animal was euthanized moribund; the dosing of both animals had been stopped prior to completion of the 2-hour infusion. Clinical signs noted prior to death or euthanasia of the high dose animals included purple skin discoloration, red discharge from the eyes and nostrils, gasping, retching, vomiting, and tremors. Pathology examination indicated that the cause of death in these animals was due to generalized hemorrhage (acute hemorrhages noted in the heart, liver, lung, and stomach). There were no significant test article-related clinical signs, changes in body weight, or gross pathology findings for the low or mid dose animals. Histopathology examination showed that several test article-treated animals had thrombi in the pulmonary artery or arterioles that were in various stages of organization. The most serious one was in the low dose male which had a moderate early thrombus in a branch of the pulmonary artery as well as a smaller thrombus in an arteriole. The mid dose male and the low dose female also had a small thrombus in a pulmonary arteriole. The remaining tissues/organs examined were essentially normal. No NOAEL was identified in this study.

Study 3 Acute dermal toxicity study of Debrase in the burn wound healing pig model (Study# 20-6-0125-02, GLP)

Three groups of domestic pigs (2/sex/group, ~2 months of age) with burn wounds were treated with standard of care (SOC, excision debridement), vehicle gel, and 10% NEXOBRID gel. Seven to nine pairs of deep second and third degree burn wounds were created using a radiant heat device on the back of each pig under anesthesia. The total burn area per body side was 220-378 cm^2, with the total wound area per animal representing ~6-12% BSA. The wounds were treated by two successive 4-hour applications (with 1-hour recovery in between) of the test articles. The tested NEXOBRID dose was 15-18.5 mg/cm^2. After debridement all three groups were treated with silver sulfadiazine daily dressing until the end of the study (14 days).

Enzymatic debridement with NEXOBRID was successful in all animals. Wounds were dry and formation of scab was observed the day after burn infliction. In vehicle control animals, exuding wounds were seen in all animals for a few or more days. In SOC control animals, wounds were dry in two animals and exuding for about one week in the other two animals. At the end of the study, a higher degree of epithelialization was observed in NEXOBRID-treated animals (68.4%), compared with the SOC control animals (22.7%) and the placebo control animals (48.8%). No significant local infection or wound impairment was observed in the three

groups. There were also no treatment-related findings in body weight, food consumption, hematology, clinical chemistry, or urinalysis. There were no treatment-related findings in gross pathology or histopathology (liver and kidney). NEXOBRID gel, 10% was well tolerated in this study.

Study 4 A 2-week toxicity study of Debrase powder administered intravenously to minipigs with a 2-week recovery period (Study# 20002068, GLP)

IV doses of 0 (vehicle: 0.9% saline), 4, 8, and 12 mg/kg/day NEXOBRID were administered to Gottingen minipigs (4/sex/group) 3 times a week for 2 weeks, followed by a 2-week recovery period (2/sex/group for vehicle control and high dose groups). One mid dose female was euthanized moribund on Day 13. This animal displayed convulsions, decreased activity, labored breathing, and cyanosis prior to euthanasia. Starting on Day 10, animals in all dose groups were observed with convulsions, decreased activity, salivation, labored breathing, ataxia and erythema after dosing. The incidences and severity of the effects did not appear to be dose-related. There were no toxicologically significant findings in body weight, ophthalmology, ECG, or clinical pathology.

Treatment-related histopathological findings were noted in all dose groups (not dose-related), including hemorrhages in multiple tissues (stomach, lung, urinary bladder, ureter, gallbladder, skin/subcutis and heart) and lesions in the pancreas (acinar degeneration and single cell necrosis) and thymus (hemorrhage and depletion of lymphocytes in the cortex). Although most of the test article-related effects resolved following a 2-week recovery period, minimal hemorrhage in the gallbladder and lymphoid depletion in the cortex of the thymus were still present. Based on these findings, A NOAEL could not be identified. See the table in Section 5.4 for TK information.

Study 5 Debrase powder: a 2-week intravenous toxicity study in juvenile farm pigs with a 2-week recovery period (Study# 1990-003, GLP)

IV doses of 0 (vehicle: 0.9% saline), 4, 8, and 12 mg/kg/day NEXOBRID were administered to juvenile domestic Yorkshire crossbred swine (farm pigs, 34-36 days of age, 4/sex/group), 3 times a week for 2 weeks, followed by a 2-week recovery period (2/sex/group for vehicle control and high dose groups). After dosing of two animals/sex/group on Day 10 (the fifth dosing), severe clinical signs were observed, therefore dosing for the remaining animals was discontinued and animals were maintained on study until the scheduled necropsy. No mortality was noted. The treatment-related clinical signs included convulsion, reddening of the skin, activity decrease, breathing difficulty, and ataxia. Pretreatment with antihistamines (on Day 10) prior to dosing generally did not ameliorate the adverse clinical findings. There were no treatment-related effects on body weight, ophthalmology, or ECG. At the end-of-treatment necropsy treatment-related findings included gross hemorrhage seen in the lung and tracheobronchial lymph nodes and microscopic hemorrhage in gallbladder, lung, pancreas, kidney, ileum, and urinary bladder seen at all doses. These changes were not observed in the recovery animals, indicating reversibility.

A NOAEL could not be identified based on the hemorrhage findings noted in the piglets at the end of treatment. The findings were generally consistent with the results of the 2-week IV toxicity study in minipigs (Study# 20002068). See the table in Section 5.4 for TK information.

Study 6 Debrase gel: a 1-week dermal toxicity study in Gottingen minipigs (Study# 1990-001, GLP)

Topical doses of 0 (vehicle), 10%, 20%, and 30% NEXOBRID gel were applied to skin sites (5 g gel per skin site) on Gottingen minipigs (1/sex for low and mid doses and 2/sex for the high dose) on Days 1, 4, and 7 [nine 5 cm x 5 cm skin sites per animal: six intact skin sites (1-6) and 3 abraded skin sites (7-9)], followed by a 7-day recovery period (1/sex for the high dose). The vehicle was administered to sites 1-3 and the NEXOBRID gel was administered to sites 4-6 and 7-9. The dose sites were covered with semi-occlusive dressing for approximately 8 hours after dosing.

There was no mortality. On Day 1, animals were observed to be in significant pain as a result of administration of the 20% and 30% NEXOBRID gel formulations to abraded skin sites. This was no longer observed following the administration of buprenorphine. Decreased activity and ataxia were observed in mid dose and high dose animals, which were likely secondary to the pain caused by administration of the test article. Dosing on abraded sites were discontinued afterwards. Observed erythema on abraded skin was generally recovered within a week.

Very slight to well-defined erythema was observed at intact skin sites at all doses (no clear dose-relation). The irritation resolved within a couple days of recovery. Mild to moderate abrasion/scabbing of intact skin sites were observed macroscopically at all doses. The abrasion/scab correlated with serocellular crust microscopically. Other microscopic observations at these sites included bacterial colonies, edema, erosion/ulcer, subacute inflammation, and rarely epidermal hyperplasia. Partial recovery was noted for these findings.

The administration of NEXOBRID Gel at 10, 20, and 30% to intact skin was generally tolerated, producing dermal irritation and corresponding microscopic changes without a dose relation to severity. However, it was not tolerated when applied to abraded skin where severe irritation resulting in a significant pain response was observed.

Study 7 A 28-day EX-02 dermal toxicity study in minipigs with surgically-induced open wounds followed by a 2-week recovery period (Study# A1724, GLP)

This 4-week dermal toxicity study was conducted with EX-02 gel. EX-02 gel is a different topical formulation but has the same active ingredients as NEXOBRID. Topical doses of 0 (vehicle), 2%, 5%, and 10% EX-02 gel were applied to surgically established full-thickness open wounds in Gottingen minipigs (3 cm x 3 cm per wound, 4 wounds per minipig, a total area of 36 cm^2; 2 g test article per wound, a total of 8 g per minipig per application, 8, 20 or 40 mg/kg active

ingredients per application for a 20 kg minipig; 3 minipigs/sex/group), either daily or 3 times a week for a total of 20 days [two 10-day dosing periods with an 8-day treatment-free period in between; 4 new surgical wounds were produced per animal for the second dosing period and only the new wounds were treated in the second dosing period], followed by a 2-week recovery period (2/sex/group). The wounds were covered with occlusive dressing. The second set of wounds was established since the first set already progressed towards healing and closure by Day 19.

One high dose female was found dead on Day 21. Histopathology evaluation revealed a severe thrombus in the heart (likely the cause of death), which probably was related to an incidental trauma of vessel wall due to repeated bleeding procedures. Slight to well defined erythema and edema were noted in all groups, including control groups (seen at the edge of wounds and in the surrounding areas), while the severity, incidence, and duration increased with dose and dosing frequency. No significant signs were seen in the wounds. The reaction was generally reversible after the recovery period. There were no toxicologically significant treatment-related findings in body weight, ophthalmology, ECG, respiration rate, hematology, clinical chemistry, gross pathology, organ weights, or histopathology evaluation. Microscopically, a slight increase of epidermal hyperplasia or re-epithelialization at the wound edge or adjacent to the wound was noted in all dose groups.

The test article was generally well tolerated in this open-wound dermal toxicity study. The NOAEL was identified as the high dose, 10% EX-02 gel applied at 8 g per day.

5.5.2. Genetic Toxicology

Per the ICH S6(R1) guidance, genetic toxicology studies are not needed for the development of NEXOBRID. Nevertheless, the applicant conducted a standard battery of genotoxicity tests as shown below.

Study 8 Reverse mutation assay using bacteria (*Salmonella typhimurium*) with Debrase (Study# 020994, GLP)

Salmonella typhimurium strains (TA98, TA100, TA102, TA1535, and TA1537) were treated with NEXOBRID powder at a range of concentrations up to 5000 μg/plate, in the presence and absence of S9. No significant increases in revertant colony numbers were noted in any of the bacteria strains at any dose level in the presence or absence of S9. NEXOBRID was not mutagenic under the study conditions.

Study 9 In vitro mammalian chromosome aberration test in Chinese hamster V79 cells with Debrase (Study# 021083, GLP)

Chinese hamster V79 cells were treated with NEXOBRID at concentrations of 0.0158- 15.8 μg/ml for 4 hr without S9, 25-100 μg/ml for 4 hr with S9, and 0.5-5 μg/ml for 20 hr without S9. The doses were limited because at higher concentrations cells became round and loosely attached after treatment and nearly all cells were washed out during the washing procedure.

This is conceivable as the test article is a mixture of proteolytic enzymes. Therefore, this assay appears not appropriate for the evaluation of NEXOBRID. However, the concentration of 100 μg/ml (4 hr with S9) reached acceptable cytotoxicity level (mitotic index of 39%). No increases in the number of cells with chromosomal aberrations were observed. NEXOBRID was not clastogenic under the study conditions.

Study 10 Mammalian micronucleus test of murine bone marrow cells with Debrase (Study# 030911, GLP)

Single oral doses of 0, 500, 1000, and 2000 mg/kg/day NEXOBRID were administered to NMRI mice (5/sex/group). No signs of toxicity were noted. The ratio between immature erythrocytes (polychromatic erythrocytes, PCEs) and mature erythrocytes (normochromatic erythrocytes, NCEs), which is indicative of bone marrow toxicity, was slightly higher in low dose males and females and high dose males. A statistically significant increase in the group mean frequency of micronucleated PCEs was observed in high dose females. The percentage of PCEs with micronuclei was 0.07% and 0.20% in control female and male mice, and 0.26% and 0.31% in high dose female and male mice. The values for high dose mice were within the range of historical control data (male: 0.05-0.38%; female: 0.01-0.30%). The statistical significance was likely due to the low background in control female mice and therefore not considered biologically relevant. No other increases in the percentage of micronucleated cells were noted.

Reviewer's comments:
Oral route is inappropriate for the administration of protein products. Therefore, this study is of little value in genotoxicity assessment. It is not recommended to include the result of this study in the drug label.

5.5.3. Carcinogenicity

Per the ICH S1A guidance, carcinogenicity studies are not needed for the development of NEXOBRID.

5.5.4. Reproductive and Developmental Toxicology

Study 11 Intravenous developmental toxicity study of Debrase powder in rats (Study# SOD00002, GLP)

IV doses of 0 (vehicle: 0.9% saline), 0.5, 1, 4, and 8 mg/kg/day NEXOBRID were administered to pregnant female SD rats (25/group) once daily from gestation days (GD) 7 to 17. Treatment of the 8 mg/kg/day group was stopped on GD 8-10 and sacrificed because of severe injection site reactions (purple/black discoloration and swelling). Severe toxicity was noted at doses ≥ 4 mg/kg/day. Mortality was observed after 2-3 doses in the control (n=1), 1 mg/kg/day (n=2) and 4 mg/kg/day (n=3) dose groups. One additional rat in the 4 mg/kg/day group was sacrificed moribund on GD 15. Infusion site reactions were observed in all dose groups, increasing in severity and incidence with increasing dose. Body weight loss (-2.5 g vs. +4.2 g in control) was seen at GD 10 in the 8 mg/kg/day group.

Three rats in the vehicle control group and one rat in the 1 mg/kg/day group delivered prematurely. Caesarean-section data or litter parameters were not significantly affected by the NEXOBRID treatment. No gross external, soft tissue or skeletal fetal alterations were associated with NEXOBRID treatment up to 4 mg/kg/day. The maternal NOAEL was determined to be 0.5 mg/kg/day (based on mortality) and the developmental NOAEL was determined to be 4 mg/kg/day, under the study conditions. See the table in Section 5.4 for TK information.

Study 12 Intravenous developmental toxicity study of Debrase powder in rabbits (Study# SOD00004, GLP)

IV doses of 0 (vehicle: 0.9% saline), 0.01, 0.05, and 0.1 mg/kg/day NEXOBRID were administered to pregnant female NZW rabbits (20/group) once daily from GD 7 to 19. Mortality was noted at mid dose and high dose. One mid dose rabbit was euthanized on GD 11 and one high dose rabbit was found dead on GD 13. Local irritation at the infusion site occurred in all groups, including the vehicle control. Scab, abrasion, ulceration, and discharge from the ulceration and/or discoloration (red skin or purple) were noted in all dose groups. Discoloration and swelling at the injection sites were seen in all groups including control (no dose-relation). At the end of treatment, a decrease in body weight gain (-38%) was noted at high dose, compared with control.

Caesarean-section data or litter parameters were not significantly affected by the NEXOBRID treatment. No gross external, soft tissue or skeletal fetal alterations were associated with NEXOBRID treatment up to 0.1 mg/kg/day. The maternal NOAEL was determined to be 0.01 mg/kg/day (based on mortality) and the developmental NOAEL was determined to be 0.1 mg/kg/day, under the study conditions. See the table in Section 5.4 for TK information.

Reviewer's comments:
Similar to repeat-dose IV toxicology studies, severe maternal toxicities were noted in these IV embryofetal toxicity studies. The tolerable maternal systemic exposure levels were much lower compared with the maximum human exposure in clinical setting. These studies are considered of limited value in human risk assessment. Considering the nature of this biologic product and the proposed short-term clinical use, the Division has agreed that a fertility study and a pre- and postnatal development study are not necessary for NEXOBRID.

5.5.5. Other Toxicology Studies

Study 13 Test for sensitization (guinea pig maximization test) with Debrase (Study# 021095, GLP)

During the induction phase, female guinea pigs (10 in test group, 5 in control group) were intradermally injected with 0.1% NEXOBRID (diluted in gel vehicle, 3 pairs of injections of 0.1 ml: test article, Freund's Adjuvant complete, and test article + Freund's Adjuvant complete, on Day 0) and topically treated with a patch loaded with 0.5 ml 30% NEXOBRID gel for 48 hours (on

Day 7). On Day 20, the animals were challenged with a patch loaded with 0.5 ml 30% NEXOBRID gel for 24 hrs. Skin reactions were observed at 24, 48, and 72 hours after patch removal. No skin sensitization potential of NEXOBRID gel was noted in this study.

6 Clinical Pharmacology

6.1. Executive Summary

NexoBrid is a complex mixture of a concentrate of proteolytic enzymes enriched in Bromelain extracted from pineapple stems (*Ananas comosus [L.] Merr.*) for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns. The Applicant has indicated that the mechanism of action of NexoBrid is mediated by the proteolytic activity of its enzymes.

- Proposed indication: For eschar removal (debridement) in adults with DPT and/or FT thermal burns.
- Proposed dosing regimens: The Applicant has proposed that NexoBrid Gel should be applied topically for 4 hours to the burn wound at a dose of 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% total body surface area (TBSA) or 5 g NexoBrid powder mixed with 50 g Gel Vehicle/2.5% TBSA . NexoBrid can be applied to an area of up to 15% TBSA in one session. If the wound is greater than 15% TBSA, NexoBrid should be applied in 2 separate sessions but should not exceed application to more than (b) (4)% TBSA .
- Proposed dosage forms/presentations: NexoBrid is to be applied topically using a gel based formulation. NexoBrid is comprised of 2 components: a sterile powder consisting of a concentrate of proteolytic enzymes enriched in Bromelain (50 mL (b) (4) glass vial containing 2 or 5 g sterile lyophilized NexoBrid powder) and a Gel Vehicle (150 mL (b) (4) glass bottle containing 20 or 50 g sterile Gel Vehicle) used for preparation of NexoBrid Gel. The NexoBrid powder and the Gel Vehicle are mixed to obtain NexoBrid Gel in a final concentration of (b) (4) g/g, at the patient's bedside ≤15 minutes prior to topical use.

The key review findings with specific recommendations/comments are summarized below:

Table 1. Key review findings

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from two pivotal Phase 3 studies in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns (MW2010-03-02 and MW2004-11-02).
Dosing regimen	The Applicant has proposed that NexoBrid can be applied to an area of up to 15% TBSA in one session. If the wound is greater than 15% TBSA, NexoBrid should be applied in 2 separate sessions but should not exceed application to more than (b) (4)% TBSA. The proposed regimen was evaluated in the phase 3 trial; however, there is only limited data from patients treated with two topical applications and maximal usage information is also

	very limited at doses above 20 gm per application and TBSA larger than 10%. As a result, the applicant's proposed dosing regimen is <u>not supported by the available data from the clinical studies.</u> If the Applicant desires the labeling currently proposed, they will need to conduct a new maximal use study designed to address the systemic safety of their product and support the proposed dosing regimens. In particular, the Applicant must ensure they study adequate numbers of patients treated with two applications of the product who have %TBSA within the upper range and are treated with doses within the upper range to support systemic safety and desired labeling. If the Applicant desires to proceed with labeling in accordance with the completed maximal use study, then labeling will be restrictive in terms of number of applications, %TBSA and total dosing.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization based on intrinsic or extrinsic factors is not required for this product.
Assessment of Pharmacokinetics	Pharmacokinetics of NexoBrid was evaluated in patients in one phase 2 study (MW2008-09-03) and one phase 3 study (MW2010-03-02). We noted inconsistencies in the PK data collected in the phase 2 study due to changes in the bioanalytical assay and site. Across both studies, there is limited exposure information for use of NexoBrid at doses above 20 gm per application. Further, limited exposure data are available to support the second application of the product as there are very few subjects who received the second dose. Based on the limited PK data, the estimated systemic half-life of this product is ~ 12 hours and separation between first and second application is important to avoid any potential accumulation. The Applicant has not provided a clear rationale for the interval between the first application and the second application. If the duration between the first and second application is shorter than 48 hours there may be potential for higher systemic exposure due to accumulation.
Labeling	The dosing regimen section in the labeling section needs to be revised per Applicant's final decision to conduct a new maximal use study or continue with the completed maximal use study. The limitations of the completed maximal use study and the impact on labeling was conveyed to the Applicant at

	the late cycle meeting. The review team also has specific content and formatting change recommendations under section 2 and section 12.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in Phase 2 study with PK assessment and in the Phase 3 clinical trials.
Immunogenicity	The pivotal clinical study, DETECT (2010-03-02), included immunogenicity testing of samples collected prior to and at different time points following NexoBrid treatment. ADA incidence was high at baseline (40.3%, 25/62) and post treatment (93.5%, 58/62). However, no apparent relationship was observed between maximum post-treatment antibody titer and either the total dose of NexoBrid (grams applied) or %TBSA treated. Based on the available data, immunogenicity does not appear to impact efficacy and safety of this topical product.
Drug interaction	No clinical drug interaction studies were conducted by the Applicant. As the product is intended for topical application for a short treatment period, the potential for systemic drug interaction is not expected to be significant.

6.1.1. Recommendations

From a Clinical Pharmacology standpoint, this BLA is acceptable to support the approval of NexoBrid (Bromelain) for eschar removal (debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns provided that the Applicant and the Agency come to an agreement on the dosing regimen and labeling for the proposed product. If the Applicant plans to seek the dosing regimen as proposed in the current BLA, they need to conduct an additional maximal use study to address the systemic safety of their product and support the proposed dosing regimen.

6.1.2. Post-Marketing Requirements and Commitment (PMR/PMC)

A PMR/PMC is not proposed in this review cycle. If the Applicant wants to pursue the proposed dosing regimen, they would need to conduct a new maximal use study designed to address the systemic safety of their product and support the proposed dosing regimens. In particular, the Applicant must ensure that an adequate number of patients in the upper range of the % TBSA are enrolled and treated with two applications of the product at doses that reflect the upper range of amounts anticipated to be used in the clinic. This was conveyed to the Applicant at the late cycle meeting.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

<table>
<tr><td>Mechanism of Action</td><td>The effects of NexoBrid's active pharmaceutical ingredient is mediated by the proteolytic activity of the mixture of enzymes that selectively debride the eschar or denatured collagen.</td></tr>
<tr><td>PK Parameters</td><td>Pharmacokinetics of NexoBrid was evaluated in patients in one phase 2 study (MW2008-09-03) and one phase 3 study (MW2010-03-02).

Following topical application of NexoBrid to burn wounds, systemic exposure of bromelain was observed through 48 hours post dose. Bromelain serum exposure increases proportionally with dose. Median Tmax values ranged between 2.0 and 4.0 hours (during the duration of treatment application). Mean elimination half-life values ranged between 12 and 17 hours.
The tables below summarize PK parameters (mean ± SD) from MW2008-09-03 and MW2010-03-02 studies analyzed by the same assay and analytical facility ((b) (4) Site).

<table>
<tr><th>Treatment</th><th>Study ID</th><th>N</th><th>Tmax
Median (range) (h)</th><th>Cmax
(ng/mL)</th><th>AUClast
(h*ng/mL)</th></tr>
<tr><td rowspan="3">First Application</td><td>MW2008-09-03</td><td>13</td><td>4.0 (0 50 - 4.1)</td><td>800 ± 640</td><td>2760 ± 2870</td></tr>
<tr><td>MW2010-03-02</td><td>21</td><td>4.0 (0 50 - 12)</td><td>200 ± 184</td><td>2500 ± 2330</td></tr>
<tr><td>Combined</td><td>34</td><td>4.0 (0 50 - 12)</td><td>429 ± 507</td><td>2600 ± 2510</td></tr>
<tr><td rowspan="3">Second Application</td><td>MW2008-09-03</td><td>12</td><td>4.0 (0 50 - 4.2)</td><td>782 ± 711</td><td>10600 ±1 2500</td></tr>
<tr><td>MW2010-03-02</td><td>1</td><td>4.0</td><td>183</td><td>6010</td></tr>
<tr><td>Combined</td><td>13</td><td>4.0 (0 50 - 4.2)</td><td>736 ± 701</td><td>10300 ± 12100</td></tr>
</table>
</td></tr>
<tr><td>Bioanalytical methods</td><td>The Applicant used a validated sandwich electrochemiluminescence (ECL) immunoassay based on immunorecognition of NexoBrid active ingredient proteins by affinity-purified rabbit polyclonal anti-NexoBrid antibodies. The assay primarily monitors levels of stem bromelain which is the major component in NexoBrid and believed to be responsible for its mechanism of action. Two different analytical sites (b) (4) were used by the sponsor for the maximal use study MW2008-09-03 and the results across these two sites were not consistent which was ascribed to changes in the critical reagents (rabbit anti-NexoBrid polyclonal antibodies) used in the assays. PK samples from Phase 3 were analyzed at the (b) (4) site using the updated bioanalytical assay. Since the Applicant has not conducted cross-validation between the two assays, PK data from the</td></tr>
</table>

	(b) (4) site was primarily used for the assessment of maximal usage and PK characterization.
Labeling	The dosing regimen section in the labeling section needs to be revised per Applicant's final decision whether they plan to conduct a new maximal use study or decide to continue with the completed maximal use study. The limitations of the completed maximal use study and the impact on labeling was conveyed to the Applicant at the late cycle meeting. The review team also has specific content and formatting change recommendations under section 2 and section 12.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in Phase 2 PK study and Phase 3 clinical trials.
Drug-drug interactions	The sponsor conducted an in vitro study to evaluate the ability of NexoBrid to inhibit the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) in human liver microsomes and human hepatocytes. According to this study NexoBrid can inhibit the metabolism of CYP2C8 substrates (IC50=30 µg/mL). However, the clinical significance of this observation is unclear and the sponsor did not conduct any clinical drug interaction studies. However, since the product is intended for topical application for a short treatment period, the potential for systemic drug interaction is not expected to be significant.
Immunogenicity	The pivotal clinical study, DETECT (2010-03-02), included immunogenicity testing of samples collected prior to and at different time points following NexoBrid treatment. ADA incidence was high at baseline (40.3%, 25/62) and post treatment (93.5%, 58/62). However, no apparent relationship was observed between maximum post-treatment antibody titer and either the total dose of NexoBrid (grams applied) or %TBSA treated. Based on the available data immunogenicity does not appear to impact efficacy and safety of this topical product.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosing regimen is 2 g of NexoBrid per 1% TBSA of an adult which can be administered using either 2g NexoBrid powder mixed with 20g Gel Vehicle per 1% TBSA of an adult, or 5g NexoBrid powder mixed with 50g Gel Vehicle per 2.5% TBSA of an adult. The Applicant has proposed that NexoBrid can be applied to an area of up to 15% TBSA in one session. If the wound is greater than 15% TBSA, NexoBrid should be applied in 2 separate sessions but should not exceed application to more than (b) (4)% TBSA.

While the proposed regimen was evaluated in the phase 3 trial(s) and in prior Phase 2 dose ranging studies, there is only limited data from patients treated with two topical applications. Furthermore, systemic exposure data under maximal use conditions is also very limited at doses above 20 gm per application and mean % TBSA of 10%. The Applicant has also not specified the time interval between the first and second treatment. In the two studies where the Applicant collected PK information, the duration between the first and second treatment ranges from 4 hours to 26.33 hours. However, considering the limited maximal use data and potential for accumulation it would be preferable to have a longer duration between the first and second treatment.

As a result, the dosing regimen as proposed by the Applicant in the product label is not supported by the available data from the clinical studies. See additional discussion under Section 6.1 "Key review findings".

Therapeutic Individualization

Therapeutic individualization was not evaluated in this BLA.

Outstanding Issues

There are no outstanding issues that would preclude the approval of the product from a Clinical Pharmacology perspective, however, the Applicant and the Agency must come to an agreement on the dosing regimen for the proposed product.

If the Applicant desires to get the labeling as proposed they would need to conduct an additional maximal use study to address the systemic safety of their product. In the new maximal use study, the Applicant must ensure adequate number of patients treated with two applications of the product who are have %BSA within the upper range of % TBSA and are treated with doses that reflect the amounts used for the higher range of %TBSA. If the Applicant plans to use the current completed PK study, then the resulting labeling will be restrictive in terms of number of doses, % TBSA and total dose of the drug. This was conveyed to the Applicant at the late cycle meeting.

6.3. Comprehensive Clinical Pharmacology Review

The applicant has provided results from 8 clinical studies as a part of the clinical development program for NexoBrid under this BLA submission:

- Two Phase 3 studies: MW2010-03-02 and MW2004-11-02
- Four completed Phase 2 studies: MW2002-04-01, MW2005-10-05, MW2008-09-03, MW2001-10-03
- Two completed supportive safety studies: MW2012-01-02 and 35-98-910

However, assessment of pharmacokinetics was conducted only in studies MW2008-09-03 and MW2010-03-02. The clinical pharmacology review will primarily focus on the results from these studies.

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	The mechanism of action of NexoBrid's active pharmaceutical ingredient is mediated by the proteolytic activity of the mixture of enzymes that selectively debride the eschar or denatured collagen.
Dose finding	The sponsor conducted a dose-ranging clinical study (MW2001-10-03) evaluating 3 different doses of NexoBrid 1, 2, or 4 g were mixed with 20 g Gel Vehicle and applied per 1% TBSA. While similar efficacy was observed for the 3 doses of NexoBrid; the 2 g dose was chosen over the 1 g dose as it may efficacious treatment in more severe or difficult to treat burns than those of the patients in this study.
General Information	
Bioanalysis	To monitor the systemic levels of NexoBrid, the Applicant used a validated sandwich electrochemiluminescence (ECL) immunoassay based on immunorecognition of NexoBrid active ingredient proteins by affinity-purified rabbit polyclonal anti-NexoBrid antibodies. The assay primarily monitors levels of stem bromelain which is the major component in NexoBrid and believed to be responsible for its mechanism of action. Two different analytical sites (b) (4) (b) (4)) were used by the sponsor for the maximal use study MW2008-09-03 and the results across these two sites were not consistent which was ascribed to a change in the critical reagent (rabbit anti-NexoBrid polyclonal antibodies) used in the assay. PK samples from Phase 3 were analyzed at the (b) (4) site using the updated bioanalytical assay. Since the Applicant has not conducted cross-validation between the two assays, exposure data from the (b) (4) site was primarily used for PK characterization and maximal use assessment. NexoBrid is a botanical drug product and consists of more than one chemical constituent and therefore the Applicant's approach to monitor only the major constituent of the drug product (stem bromelain) is acceptable.
PK model	The Applicant has not conducted any PK modeling and simulation analysis.

Heathy subjects vs patients	PK assessment in healthy subjects was not conducted.
Drug exposure at steady state	Not applicable as this is a single dose treatment with the option of a second dose only if needed.
Dose proportionality	Systemic exposures of NexoBrid increased in a dose related manner with higher topical dose being associated with higher Cmax and AUC. Conclusions with regard to dose linearity cannot be made due to limited PK data and the fact that topical dosing is not fixed (i.e. depends on TBSA).
ADME	
Absorption	NexoBrid appears to be rapidly absorbed, with median Tmax values between 2.0 and 4.0 hours. Following the second application of the product, greater than 2-fold increase in the values of Cmax and AUC0-4 was observed in some subjects.
Distribution	Not assessed
Elimination	The mean elimination half-life of bromelain ranged between 12 and 17 hours.
Metabolism	Bromelain is expected to be metabolized into small peptides by catabolic pathways.
Excretion	The excretion of NexoBrid has not been studied.
Drug interaction	Results from in-vitro studies in human liver microsomes and human hepatocytes indicate that NexoBrid can inhibit the metabolism of CYP2C8 substrates (IC50=30 μg/mL). However, the clinical significance of this observation is unclear and the sponsor didn't conduct any clinical drug interaction studies. As the product is intended for topical application for a short treatment period, the potential for systemic drug interaction is not expected to be significant.
Immunogenicity	
Incidence	The overall incidence of antibodies against NexoBrid was high with 40.3% of patients (25/62) in the NexoBrid treatment arm having a positive ADA result at baseline and incidence of treatment-emergent ADA rising to 93.5% (58/62).
Impact on PK	There was no obvious relationship between ADA titer and the systemic exposure of NexoBrid.
Impact on efficacy	Since this is a topical product applied at the target site (i.e. skin), the impact of immunogenicity on efficacy is unlikely. The data shows that

	there was no obvious relationship between lack of NexoBrid efficacy and baseline ADA titer was observed.
Impact on injection site reactions	No clear relationship was observed between the presence of ADA pre-treatment and hypersensitivity reaction.

[Insert text here]

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The clinical pharmacology studies in this BLA were primarily intended to provide maximal exposure data to inform the systemic safety of this product. Results from the two phase 3 studies (MW2010-03-02 and MW2004-11-02) provide pivotal evidence of efficacy for the proposed indication. Refer to Section 7 for additional details.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen as proposed by the applicant is not acceptable. See Section 6.1 for additional discussion.

The Applicant has proposed that NexoBrid can be applied to an area of up to 15% TBSA in one session. If the wound is greater than 15% TBSA, NexoBrid should be applied in 2 separate sessions but should not exceed application to more than (b) (4) % TBSA (maximum total dose of (b) (4) gm of NexoBrid).

The proposed regimen was evaluated in the phase 3 trial; however, there are only limited data from patients treated with two topical applications and maximal usage information is also very limited at doses above 20 gm per application. The Applicant has not specified the time interval between the first and second treatment which is a concern due to limited maximal use data and potential for accumulation (discussed further below).

An information request (IR) was sent to the sponsor on 11th December 2020 requesting a listing of patients that needed a second application in studies MW2008-09-03 and MW2010-03-02 along with the duration between the first and second treatments. The Applicant's response (dated 18th December 2020) indicated that only 19 subjects across the two studies were exposed to a second application of NexoBrid (Table 2). Fourteen of the 19 subjects were from the Phase 2 study MW2008-09-03 and 5 subjects were from the pivotal Phase 3 study MW2010-03-02. In these subjects the duration of time between the first application and second application of NexoBrid ranged from 4 hours to 26.33 hours.

Table 2. Listing of patients treated with a second application of NexoBrid in studies MW2008-09-03 and MW2010-03-02.

Study Identifier	Subject Identifier	Total Number of Target Wounds	Total Body Surface Area (% TBSA) of TWs	First application date/time	Second application date/time	Duration (Hours)
MW2008-09-03	(b) (6)	3	25		(b) (6)	4
		2	5			4.7
		3	12.5			23
		4	14.449999			22.83
		5	11			26.33
		5	34			23.75
		2	15			14.95
		2	24			4.5
		2	23.5			22.83
		4	26			4.47
		3	14			21.5
		3	19			21.83
		3	29			15.25
		2	17			17.75
MW2010-03-02		2	13.5			22.92
		2	9.5			13.25
		1	5			17.8
		2	5.25			16.75
		3	21.1			21

Of the subjects exposed to a second application of the product only two subjects (subject # (b) (6) and (b) (6)) were treated with the (b) (4) total dose of 60 g and only a limited number of subjects were treated at doses greater than 20 g per application. This does not allow for a conclusive assessment of the safety of the (b) (4) dosing regimen particularly at the higher range of the (b) (4) doses.

The Applicant has provided maximal usage data in support of the proposed dosing regimen from studies MW2008-09-03 and MW2010-03-02. The doses of NexoBrid evaluated ranged from 3 g to 36 gm per application with the maximum total dose of 60 gm over two applications. The Applicant assessed the systemic exposure of NexoBrid in both studies (MW2008-09-03 and MW2010-03-02). However, there are concerns about the quality of the PK data submitted by the Applicant to support their proposed labeling and inform the systemic safety of their product.

Blood samples for PK assessment from study MW2008-09-03 were analyzed using a validated sandwich electrochemiluminescence (ECL) immunoassay at 2 bioanalytical analysis sites. Samplers for the first 23 patients were analyzed at (b) (4) and for the remaining 13 patients at the (b) (4) site). Also a validated method was used at each site, differences were observed in the exposure values between the 2 analysis sites with higher systemic exposures for patients from the (b) (4) analysis site compared to the (b) (4) analysis site (Table 3 and Table 4). We also noted that some samples in both studies (MW 2008-09-03 and MW 2010-03-02) were analyzed outside of the

long-term stability time period established in the bioanalytical assay validation report for the assay for measurement of bromelain in human serum. Two IRs were sent to the Applicant regarding the bioanalytical methodologies on 11th December 2020 and 12th February 2021 asking for clarification on the discrepancy in data across the two bioanalytical sites and for the reanalysis of PK data by omitting samples that were stored beyond the established sample stability period. In their response dated 18th February the Applicant provided updated PK analysis for study MW 2008-09-03 excluding the data from samples that were outside of the established long-term stability time period. Similarly, the Applicant indicated that PK data from samples from study MW 2010-03-02 that were stored beyond the established sample stability period were omitted from the main analysis and presented separately as an exploratory analysis.

Table 3. Summary of PK results in NexoBbrid treated patients in study MW 2008-09-03 ((b) (4) analysis site)

Number of Treatments	T_{max} Median (range) (h)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4}/Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last}/ Dose (h*ng/mL/g)
	Mean ± SD						
1 (N=22)	2.0 (0.90 – 4.2)	5870±4570	444±351	15800±12200	1170±854	38300±39800	2810±2500
2 (N=2)	4.0	9140	826	20000	1770	95300	8790

AUC_{last}=area under the curve until last measurable time-point, AUC_{0-4}=area under the concentration-time curve from time zero to time 4h, C_{max}=maximum observed concentration, T_{max}=time at which the maximum concentration was observed

Table 4. Summary of PK results in NexoBrid treated patients in study MW 2008-09-03 ((b) (4) analysis site)

Number of Treatments	T_{max} Median (range) (h)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4}/Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last}/Dose (h*ng/mL/g)
1 (N=13)	4.0 (0.50 - 4.1)	800±640	44.7±36.6	1930±648	103±48.8[a]	2760±2870	149±147
2 (N=12)	4.0 (0.50 - 4.2)	782±711	41.8±33.0	2130±1570	120±115	10600±12500	575±605

AUC_{last}=area under the curve until last measurable time-point, AUC_{0-4}=area under the concentration-time curve from time zero to time 4h, C_{max}=maximum observed concentration, T_{max}=time at which the maximum concentration was observed

[a] – N=8

Table 5. Summary of PK results in NexoBrid treated patients in study MW 2010-03-02 ((b) (4) analysis site)

Number of Treatments	T_{max} Median (range) (h)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4} /Dose (h*ng/mL/g)	AUC_{0-24} (h*ng/mL)	AUC_{0-24}/ Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last} /Dose (h*ng/mL/g)
First (n=21)	4.0 (0.50 - 12)	200±184	16.4±11.9	516±546	39.8±29.7	2030±1790 (n=20)	178±144 (n=20)	2500±2330	215±202
Second (n=1)	4.0	183	15.0	618	50.6	3020	248	6010	492

AUC_{last}=area under the curve until last measurable time-point, AUC_{0-4}=area under the concentration-time curve from time zero to time 4h, AUC_{0-24}=area under the concentration-time curve from time zero to time 24h, C_{max}=maximum observed concentration, T_{max}=time at which the maximum concentration was observed

Regarding the inconsistency in data between the two analytical sites, the Applicant indicated that while the assay was conceptually the same across the two sites, cross-validation was not conducted due to non-availability of QC samples, out of stability patient samples and the introduction of new critical reagents (labelled anti-NexoBrid antibodies). The Applicant indicated that the validation results with the assay procedure at the (b) (4) site confirmed that accuracy and precision remained practically the same, and the standard and quantitation ranges are comparable (see appendix for additional details about the analytical assay). However, the absence of cross-validation data makes it difficult to reconcile the inconsistency in the systemic exposure information from samples analyzed at the (b) (4) site and the (b) (4) site. Therefore, PK information for NexoBrid from the two sites are analyzed separately (Table 3 and Table 4).

Overall, results from studies MW 2008-09-03 and MW 2010-03-02 (Table 5) indicate that there is systemic absorption of NexoBrid following topical administration with quantifiable serum concentrations through 48 hours post application. NexoBrid appears to be rapidly absorbed following topical application, with median Tmax values between 2.0 and 4.0 hours (Table 3, 4 and 5). Mean elimination half-life values ranged between 12 and 17 hours which indicates potential for accumulation if there is inadequate separation between first and second applications.

Table 6 compares the dose normalized Cmax between the first application of NexoBrid and the second application of NexoBrid from the Phase 2 study MW 2008-09-03. Results suggest that accumulation can be varied and can be greater than 2-fold even when there is ~ 22 hour interval between the first and second application. However, it must be noted that these results are from a limited number of subjects (14) and the duration between the first and second application is not consistent which makes it difficult to draw any concrete conclusions about the potential for accumulation after the second application. In the Phase 3 study MW 2010-03-02, only 5 subjects received a second application of NexoBrid and PK data was available from only one of them.

Table 6. Summary of dose normalized Cmax ratios for patients who were treated with two applications of NexoBrid in study MW 2008-09-03 ((b) (4) analysis site)

Duration (hrs)	Subject ID	Analysis Site	Duration	C_{max} (ng/mL)			C_{max} /Dose		
				Treatment 1	Treatment 2	Ratio	Treatment 1	Treatment 2	Ratio
<12	(b) (6)	(b) (4)	5.50	222	190	0.856	22.2	19.0	0.856
			4.50	469	645	1.38	19.5	32.3	1.65
			4.50	627	865	1.38	26.1	33.3	1.27
		N	3	3	3	3	3	3	3
		Mean	4.83	439	567	1.20	22.6	28.2	1.26
		SD	0.577	204	344	0.301	3.32	7.96	0.397
		CV%	11.9	46.5	60.8	25.0	14.7	28.3	31.5
≥12	(b) (6)	(b) (4)	22.8	319	860	2.70	17.7	33.1	1.87
			22.8	259	459	1.77	16.2	32.8	2.03
			26.3	597	483	0.809	59.7	40.3	0.674
			24.0	1770	2930	1.66	70.8	83.7	1.18
			15.0	412	289	0.701	41.2	20.6	0.501
			24.0	818	467	0.571	40.9	18.0	0.439
			22.0	600	605	1.01	40.0	24.2	0.605
			15.0	862	806	0.935	23.9	33.6	1.40
			17.5	2440	786	0.322	153	131	0.859
		N	9	9	9	9	9	9	9
		Mean	21.0	897	854	1.16	51.4	46.4	1.06
		SD	4.15	734	802	0.745	42.0	37.2	0.593
		CV%	19.7	81.7	93.9	64.0	81.7	80.3	55.8

The subject from the (b) (4) analysis site ((b) (6) duration of 9.5 hours) was excluded from summarization; however the C_{max} and dose normalized C_{max} ratios were both 0.770

Due to the forementioned limitations of available data, the Applicant will need to conduct an additional maximal use study to assess the safety and systemic exposure of their product, if they plan to recommend the dosing regimen in the proposed labeling submitted in this BLA. In the new study, the Applicant needs to ensure inclusion of an adequate number of patients treated with two applications of the product who are have %TBSA within the upper range of % TBSA and are treated with doses that reflect the upper end of the proposed dosing regimen.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Not applicable

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Since NexoBrid is intended for topical application for a short treatment period of 1-2 applications, the potential for systemic drug interaction is not expected to be significant.

The Applicant conducted an in vitro study to evaluate the ability of NexoBrid to inhibit the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) in human liver microsomes and human hepatocytes, with the aim of ascertaining the potential of NexoBrid to inhibit the metabolism of concomitantly administered drugs. Results from these in-vitro studies suggested that NexoBrid can inhibit the metabolism of CYP2C8 substrates (IC50=30 µg/mL). However, the clinical significance of this observation is unclear and the sponsor did not conduct any clinical studies to assess drug interaction potential with CYPs or transporters. Furthermore, the Application did not explain the relevance of the in-vitro findings in the context of the systemic exposures observed in the clinic. An IR was sent on 12th December, 2020, asking for additional clarification about the clinical significance of the in-vitro results. In their response dated 18th December, 2020, the Applicant indicated that NexoBrid primarily consists of proteolytic enzymes that are considered to be therapeutic proteins (TP). Therefore, NexoBrid does not fall into any of the scenarios where evaluation of DDI /transporter mediated DDI potential would be warranted per the draft guidance for drug interaction assessment for TPs (Drug-Drug Interaction Assessment for Therapeutic Proteins. Guidance for Industry, FDA August 2020). We concur with the Applicant's response that evaluation of DDI /transporter mediated DDI potential for NexoBrid for the proposed indication is not warranted.

What is the overall incidence of immunogenicity to NexoBrid? What is the impact of immunogenicity on PK and Efficacy?

The pivotal clinical study MW2010-03-02 included immunogenicity testing of samples collected prior to and at different times following NexoBrid treatment (baseline, Day 28, Day 56, 6 months, and 24 months). The overall incidence of antibodies against NexoBrid was high with 40.3% of patients (25/62) in the NexoBrid treatment arm having a positive ADA result at baseline. The incidence of treatment-emergent antibodies was 93.5% (58/62), which included 62.1% (36/58) subjects who were negative at baseline and 37.9% (22/58) who had at least a four-fold increase post-treatment (Table 7). The treatment-emergent ADA titer peaked at the 4-week post-treatment time point (Table 8).

Table 7. Baseline ADA Prevalence and treatment-emergent ADA Incidence (ADA evaluable population)

Category	NexoBrid Treatment Arm
Number of patients with samples	68
Number of patients in ADA evaluable population	62
ADA Prevalence Pre-treatment	
Number of patients with positive ADA result in pre-treatment sample	25
% of ADA evaluable population	40.3%
Treatment-emergent ADA Positive	
Number of patients meeting definition of treatment-induced or treatment-boosted	58
% of ADA evaluable population	93.5%

ADA = anti-drug antibodies
Note: Only 1 patient (b) (6) was negative at baseline and at 1-week post-treatment (no other post-treatment samples available); 3 other patients did not meet the definitions of "treatment-induced" or "treatment-boosted", namely Spatients (b) (6) had same titer pre- and post-dose; Spatient (b) (6) was positive at baseline but negative post-dose.

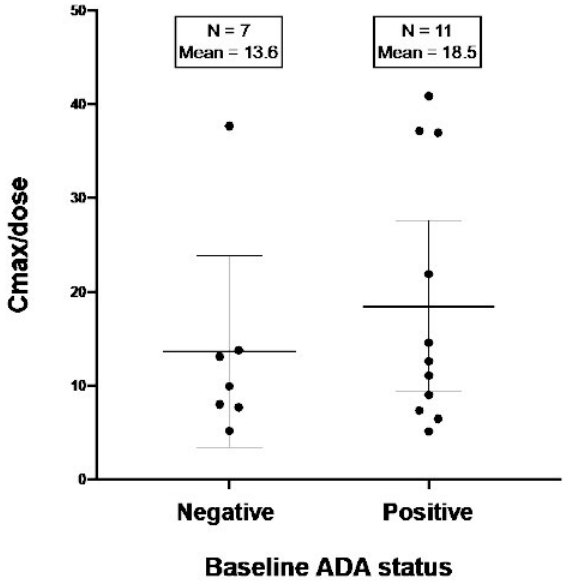
Table 8: ADA titer vs time for patients from study MW2010-03-02

	ADA Titer At Sampling Time Prior to or Following Treatment					
Statistic	Pre-treatment	1-Week Post-treatment	4-Week Post-treatment	8-Week Post-treatment	6-Month Post-treatment	24-Month Post-treatment
Number of patients with result	62	23	52	45	47	21
Minimum	1	1	80	50	50	50
25% percentile	1	10	1250	1250	1250	250
Median	1	50	6250	1250	1250	250
75% percentile	182.5	6250	31250	31250	6250	6250
Maximum	31250	156250	781250	156250	156250	31250
Geometric mean	10.5	118.2	4819	4217	1805	677.1

ADA = anti-drug antibodies
Note: Patients with a Negative ADA result were assigned as titer=1
Source: Bioanalytical report 151093AMES_MYI
GraphPad Prism version 8.2.1 for macOS

Figure 1 illustrates the relationship between dose-adjusted Cmax and dose-adjusted AUC_{0-4h} to baseline ADA status. Results indicate that dose-adjusted Cmax and dose-adjusted AUC_{0-4h} appear to be slightly higher for ADA-positive patients at baseline compared to ADA negative at baseline. However, due to the limited number of data points and the high variability a definitive conclusion cannot be reached on the relationship between baseline ADA status and the PK of NexoBrid.

Figure 1. Dose-adjusted Cmax vs Baseline ADA Status (ADA Evaluable Population)



ADA = anti-drug antibodies, C_{max} = maximum observed concentration, occurring at T_{max}
Source: MW2010-03-02
Graph drawn & descriptive statistics calculated using GraphPad Prism version 8.2.1 for macOS.

There was no apparent relationship between maximum post-treatment antibody titer and either the total dose of NexoBrid (grams applied) or %TBSA treated.

Since NexoBrid is a topical product and the product is administered in one or two 4-hour applications to severe burn patients, efficacy is not expected to be influenced by either the baseline or post-treatment ADA positive/negative status or titer as the drug is applied directly to the target site (i.e. skin). In the ADA evaluable population (25 subjects), there was no obvious relationship between lack of NexoBrid efficacy and baseline ADA titer. Of the 25 patients with ADA-positive results at baseline in the ADA evaluable population and only 3 ([redacted] (b) (6)) failed to reach the efficacy endpoint of complete eschar removal suggesting the lack of an obvious relationship between efficacy (complete eschar removal) and baseline or post-treatment ADA titer. Similarly no clear relationship could be established between the presence of ADA pre-treatment and hypersensitivity reaction.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The clinical development program consists of 8 studies, all of which were multicenter and multinational.

The Applicant is principally relying on the 2 Phase 3 studies, to provide the evidence of efficacy:

- 2010-03-02 (2010 or 03-02) or DETECT and
- 2004-11-02 (2004 or 11-02).

The Applicant is relying on 6 of the 8 studies to support the safety of NexoBrid in the target population. Of those 6 studies, the Applicant is principally relying on the Phase 3 studies, 2010 and 2004, for evidence of the safety of NexoBrid (see Section 8.2.1 for additional discussion of the safety database).

The Applicant is not relying on study 2012-01-02 or study 35-98-910 to support efficacy or safety because of the designs of those studies (See section 8.2.1 for additional details).

The Applicant cites the following reasons for considering the data from non-U.S. sites to apply to the U.S. population:

- No clinically meaningful differences in efficacy results were noted when the data were analyzed by race.
- There were “few” differences (not otherwise described) in target wounds between subjects at U.S. and non-U.S. sites.
- The incidence of surgical excision in the Phase 3 studies suggested that surgical SOC is the standard method for eschar removal across regions and differences relating to excision are not likely to affect data interpretation.

Listing of Clinical Trials Relevant to this BLA

Type of Study	**Study Identifier**	**Location of Study Report**	**Objectives of the Study**	**Study Design and Type of Control**	**Test Products; Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
Safety and Efficacy	MW2010-03-02	Module 5.3.5.1	To demonstrate the efficacy of enzymatic eschar removal with NexoBrid by providing complete eschar removal as compared with Gel Vehicle. To demonstrate the efficacy of enzymatic eschar removal with NexoBrid by providing earlier complete eschar removal, reduction in patients' surgical burden, and its related blood loss as compared to SOC. To assess the safety of NexoBrid compared to SOC, Including demonstration that treatment with NexoBrid does not cause an unacceptable level of harm on wound closure outcome and long-term outcomes of cosmesis and function.	Phase 3, Multicenter, Randomized, Assessor blinded study including 3 arms: NexoBrid, SOC, Gel Vehicle in a ratio of 3:3:1 Controlled (SOC and Gel Vehicle)	**NexoBrid:** 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% TBSA or 5 g NexoBrid powder mixed with 50 g Gel/2.5% TBSA, topically, maximum of 2 applications per wound. **Gel Vehicle:** 20 g/1% TBSA or 50 g/2.5% TBSA, topically, maximum of 2 applications per wound. **SOC:** Included surgical and/or nonsurgical eschar removal procedures	**NexoBrid**: M/F: 49/26 **SOC**: M/F: 59/16 **Gel Vehicle:** M/F: 15/10	Adults ≥18 years of age hospitalized in burn units with DPT and/or FT burns (≥3% to ≤30% TBSA)	4 hours per application	Ongoing; Acute Phase and 12-month Follow-up Period are complete, while the 24-month Follow-up Period is ongoing. Final CSR (Acute and 12-month long-term follow-up)

Type of Study	**Study Identifier**	**Location of Study Report**	**Objectives of the Study**	**Study Design and Type of Control**	**Test Products; Dosage Regimen; Route of Administration**	**Number of Subjects**	**Healthy Subjects or Diagnosis of Patients**	**Duration of Treatment**	**Study Status; Type of Report**
Safety and Efficacy	MW2004-11-02	Module 5.3.5.1	To evaluate the safety and enzymatic debriding efficacy of NexoBrid in hospitalized patients with DPT and/or full thickness thermal burns of 5%-30% TBSA, but with total burn wounds of no more than 30% TBSA and to compare NexoBrid to SOC.	Phase 3, Multicenter, Open label, Randomized study including 2 arms: NexoBrid and SOC in a ratio of 1:1 Controlled (SOC)	**NexoBrid:** 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% TBSA or 5 g NexoBrid powder mixed with 50 g Gel Vehicle/2.5% TBSA, topically, maximum of 2 applications per wound. **SOC:** Included surgical and/or nonsurgical eschar removal procedures	**NexoBrid**: M/F: 54/21 **SOC**: M/F: 61/20 **NexoBrid (for training and safety assessments)**: M/F: 23/3	Adults and children (ages 4 to 55 years), hospitalized in burn units with DPT and/or FT burns (5% to ≤30% TBSA)	4 hours per application	Completed; Final CSR
Safety and Exploratory Efficacy	MW2005-10-05	Module 5.3.5.1	To evaluate the safety (and exploratory efficacy) of NexoBrid, Gel Vehicle, and SOC in DPT and FT thermal burns of 1%-5% TBSA.	Phase 2, Single center, Open label, Randomized study including 3 arms: NexoBrid, SOC, Gel Vehicle in a ratio of 1:1:1 Controlled (SOC and Gel Vehicle)	**NexoBrid:** 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% TBSA or 5 g NexoBrid powder mixed with 50 g Gel/2.5% TBSA, topically, maximum of 2 applications per wound.	**NexoBrid:** M/F: 9/1 **Gel Vehicle:** M/F: 9/1 **SOC:** M/F: 8/3	Adults 18 to 65 years of age hospitalized in burn units with DPT and/or FT burns (≥1% to ≤10% TBSA)	4 hours per application	Completed; Final CSR

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
					Gel Vehicle: 20 g/1% TBSA or 50 g/2.5% TBSA, topically, maximum of 2 applications per wound. **SOC:** Included surgical and/or nonsurgical eschar removal procedures.				
Safety and Efficacy	MW2002-04-01	Module 5.3.5.1	To evaluate the safety and enzymatic debriding efficacy of NexoBrid in hospitalized subjects with DPT and FT thermal burns (2%-15% TBSA); To compare NexoBrid to SOC; To examine any possible deleterious effects of Gel Vehicle on wound healing	Phase 2, Multicenter, parallel, Observer-blinded, Prospective, Randomized study including 3 arms: NexoBrid; Gel Vehicle, and SOC in a ratio of 2:1:1 Controlled (SOC and Gel Vehicle)	**NexoBrid:** 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% TBSA, topically, single treatment. **Gel Vehicle:** 20 g/1% TBSA, topically, single treatment. **SOC**: Included surgical and/or nonsurgical eschar removal procedures.	**NexoBrid:** M/F: 54/19 **Gel Vehicle:** M/F: 25/11 **SOC:** M/F: 28/10	Adult patients (18 to 70 years) with DPT or FT burns ranging from $\geq$2% to $\leq$15% TBSA, but with no more than 30% TBSA burns in total.	4 hours per application	Completed; Final CSR
Dose Ranging Study	MW2001-10-03	Module 5.3.4.2	To compare the efficacy and safety of 3 NexoBrid doses when used to	Phase 2, Multicenter, Open label, Observer	**NexoBrid:** 1, 2, or 4 g NexoBrid powder mixed with 20 g Gel	**NexoBrid 1 g:** M/F: 4/2	Adults (18 to 70 years) hospitalized in burn units	4 hours per application	Completed; Final CSR

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
			enzymatically debride partial deep dermal or FT burns in hospitalized patients.	blinded, Randomized, dose-ranging study including 3 arms: NexoBrid 1, 2, or 4 g in a ratio of 1:1:1	Vehicle/1% TBSA, topically, maximum of 2 applications per wound.	**NexoBrid 2 g:** M/F: 4/3 **NexoBrid 4 g:** M/F: 4/3	with partial deep dermal and/or FT burns ranging from 1% to 15% TBSA.		
Safety, PK, exploratory efficacy	MW2008-09-03	Module 5.3.5.2	To evaluate the safety and efficacy (exploratory) of NexoBrid in hospitalized subjects with PT (mid and deep dermal) and or FT thermal burns. To explore NexoBrid absorption as measured by PK analysis.	Phase 2, Multicenter, Single-arm, Open label study	**NexoBrid:** 2 g NexoBrid powder mixed with 20 g Gel Vehicle/1% TBSA, topically, a maximum of 2 applications per wound.	**NexoBrid:** M/F: 27/9	Children and adults between 4 and 70 years of age, hospitalized with PT (mid and deep dermal) and/or FT burns ranging from 4% to 30% TBSA, but no more than 30% TBSA burns in total. Did not include facial, perineal or genital wounds.	4 hours per application	Completed; Final CSR

7.2. Review Strategy

The safety review will focus on "Cohort 2," which was the focus of the safety analyses in the application. Cohort 2 consists of pooled data from the 2 Phase 3 studies: 2010 and 2004. See Section 8.2.1 for a more detailed description of the safety database.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study MW2010-03-02 (DETECT)

Trial Design

Study MW2010-03-02 (2010) is a randomized, vehicle- and standard of care (SOC)-controlled, assessor-blinded study to evaluate the efficacy and safety of NexoBrid in subjects with thermal burns. Subjects were enrolled from 2015 to 2019. The study enrolled subjects 18 years of age and older hospitalized with thermal burns caused by fire/flame, scalds, or contact. Burns were classified as deep partial thickness (DPT), full thickness (FT), or superficial partial thickness (SPT). Subjects could have a maximum total burn area of ≤ 30% total body surface area (TBSA) of SPT, DPT and/or FT wounds. Separated burn areas were classified as target wounds (TWs) defined as a DPT and/or FT wound ≥0.5% TBSA that do not include facial, perineal, or genital wounds. Subjects could have one or more TWs. All TWs were treated per the randomized treatment arm.

The study periods included an eschar removal stage, a wound closure stage, and a follow-up stage where subjects were followed for 24 months to assess wound cosmesis, function, and scarring. Subjects randomized to SOC were treated per the investigator's judgment until the eschar was removed. Subjects randomized to NexoBrid or vehicle gel were treated using the topical treatment process on TWs up to a maximum TBSA of 15%. If >50 to <95% of eschar was removed following the first application of topical treatment, the subject was to be treated with a second application of topical treatment. In addition, if the subject had >15% TBSA burn area, two treatments would be planned to treat all TWs while treating no more than 15% TBSA per treatment session. If eschar remained after the one or two topical treatments, the remaining eschar was removed using surgical or non-surgical SOC methods as rescue treatment.

The amount of blinding was limited due to the differences in the treatment regimens. The study utilized blinded assessors for certain assessments. Because NexoBrid and vehicle gel need to be prepared just prior to application and have differences in preparation instructions and final appearance (i.e. NexoBrid is gold while vehicle is clear), the treating investigator would not be blinded to treatment. An assessor blinded to whether a subject was treated with NexoBrid or vehicle was to evaluate eschar removal following the topical treatment. If feasible, the blinded assessor was also assigned to evaluate eschar removal for subjects on the SOC arm but would not have been blinded to treatment for subjects on the SOC arm. Weekly evaluations for wound closure and long-term follow-up assessments for cosmesis and function were to be done by a second blinded assessor blinded to all treatment arms.

Subjects were enrolled under three amendments to the protocol (Amendments 8, 9, and 11; no subjects were enrolled under Amendment 10). The inclusion criteria and

randomization/stratification method differed under the three amendments. Most subjects (70%) were enrolled under Amendment 11. One key difference is that under Amendments 8 and 9, subjects could have a maximum burn area of 15%. while under Amendment 11 subjects could have a maximum burn area of 30%. Another key difference is that subjects under Amendment 8 were allocated using a minimization algorithm, while subjects under Amendments 9 and 11 were allocated using block randomization. The stratification factors also differed in each amendment, but were based on total burn area, wound depth, and center. Other factors such as the allowable age range, the minimum TBSA for TWs, and allowable amount of SPT burns also varied across amendments.

The inclusion criteria under the three amendments is as follows:

- Amendment 8 (February 22, 2015) [21 subjects] and Amendment 9 (August 12, 2015) [32 subjects] – Subjects enrolled May 2015 – October 2016
    - Age 18 – 70 years
    - Total burn area ≥ 3% DPT and / or FT
    - Total burn area ≤ 15% TBSA; SPT, DPT and/or FT in depth
    - At least one wound is ≥1% TBSA (DPT and/or FT and does not include facial, perineal, or genital wounds)
- Amendment 11 (June 22, 2016) [122 subjects]– Subjects enrolled October 2016 – June 2018
    - Age ≥18 years
    - Total burn area ≥ 3% DPT and / or FT
    - Total burn area ≤ 30% TBSA; SPT, DPT and/or FT in depth
    - At least one wound is ≥0.5% TBSA (DPT and/or FT and does not include facial, perineal, or genital wounds)
    - SPT areas that cannot be demarcated from DPT and FT areas should be less than 50% of the % TBSA of the target wound

The randomization method and stratification factors under the three amendments were as follows:

- Amendment 8 (February 22, 2015) [21 subjects] – Subjects enrolled May 2015 – March 2016 Subjects were allocated to treatment using the method of minimization and three stratification factors. For the minimization method, a score for each treatment group was calculated for a new subject based on the new subject's strata and the number of subjects already allocated to each treatment. The subject would be allocated to the treatment with the smallest score for the given strata. If there was a tie between the scores for two treatments, randomization was used to allocate the subject. The algorithm was run through a central site. The stratification factors were
    - Total burn area TBSA (≥3% to ≤9% vs. >9% to ≤15%)
    - Wound depth (All TWs are FT, Mixed TWs (FT and DPT and proportion of SPT <20%), Mixed TWs (FT and DPT and proportion of SPT ≥20%), All TWs are DPT and proportion of SPT ≥20%)
    - Center
- Amendment 9 (August 12, 2015) – Subjects enrolled March 2016 – October 2016

Subjects were randomized using block randomization and the following stratification factors.
    - Wound depth (All TWs are FT, Mixed TWs (FT and DPT), All TWs are DPT
    - Center
- Amendment 11 (June 22, 2016) – Subjects enrolled October 2016 – June 2018
Subjects were randomized using block randomization and the following stratification factors.
    - Total burn area TBSA (≤15%, >15%)
    - Wound depth (All TWs are FT, Mixed TWs (FT and DPT), All TWs are DPT)
    - Center group based on SOC practice (Non-surgical, Mixed, Surgical, West, East). US sites were assigned to the non-surgical, mixed, and surgical groups based on usual SOC practice, and non-US sites were assigned to the West or East groups. The West group included sites in Belgium, Germany, Israel, Italy, and Georgia. The East group included sites in the Czech Republic and Romania.

Note that the 'center group' stratification factor was defined in Amendment 11 of the protocol, and that it is not clear when centers were classified as primarily using non-surgical, mixed, or surgical SOC. Some centers that enrolled subjects under Amendment 11 also enrolled subjects under Amendments 8 and 9, however, some centers only enrolled subjects under Amendment 11, and thus could not have been classified based on prior experience within Study 2010. Thus, it is unclear whether the applicant used information internal or external to the ongoing study to define a center's stratum classification. It is also not clear why Georgia is classified in the West group instead of the East group.

All DPT and FT burns that met the inclusion criteria were defined as target wounds and were to be treated with study treatment per the randomized treatment arm. Subjects were randomized to NexoBrid gel, SOC, and vehicle gel in a 3:3:1 ratio. Subjects assigned to NexoBrid or gel vehicle were treated in the same manner. NexoBrid or vehicle were to be applied to no more than 15% TBSA per treatment session (though some discretion was permitted by the investigator to treat areas up to 18% TBSA). Subjects in the SOC arm were treated per the investigator's usual practice and clinical judgment using surgical and non-surgical eschar removal procedures. Surgical procedures included tangential, minor, avulsion, Versajet, and dermabrasion excisions. Non-surgical procedures included the application of collagenase ointment, antimicrobial solutions, ointments/creams, and or silver dressings. SOC procedures could be completed as needed until complete debridement.

The NexoBrid and vehicle gel procedure consisted of

- wound preparation (surrounding the treatment area with Vaseline ointment adhesive barrier and sprinkling sterile isotonic sodium chloride solution on the wound to keep it moist)
- applying the gel product to the wound area(s) (≤15% TBSA) and leaving in place under a dressing for 4 hours
- removing dissolved eschar from the wound with a sterile blunt-edged instrument (with appropriate preventive analgesia medication)

- applying a dressing soaked in antibacterial solution for 2 hours.

Eschar removal was to be assessed immediately following the 2-hour soaking period. A second treatment session could be performed if the total TW area was >15% TBSA or eschar removal was incomplete after the first treatment session, but at least 50% of eschar was removed (the additional treatment was to be applied only to areas with remaining eschar). The second treatment session could begin immediately, or up to 24 hours later. The eschar removal stage was considered complete when ≥95% of eschar was removed.

Once ≥95% of eschar was removed, wound management was to follow normal standard care such as grafting for full thickness wounds or healing by spontaneous epithelialization for partial thickness areas with viable dermis. Wounds were to be assessed on a weekly basis until all TWs and donor sites are closed. Confirmation of wound closure for each target wound will be performed 2 weeks later. Wound closure was defined as >95% area epithelialized or closed by graft.

Long-term wound assessments will be performed at Months 1, 3, 6, 12, 18, and 24 from the wound closure confirmatory visit. Maintenance of wound closure will be assessed at Months 1 and 3. A blinded assessor (blinded to all treatment arms) will conduct cosmesis assessments at each visit.

The applicant conducted a database lock after all subjects completed the Month 12 visit. Data from the Month 18 and Month 24 assessments are not included in the submitted study report.

Study Endpoints

The primary efficacy endpoint was the incidence of eschar removal (≥95%) at the end of the topical treatment soaking period for NexoBrid versus gel vehicle. If two applications of the product were used, the assessment was based on the end of the soaking period after the second application. The endpoint was assessed on the subject level over all TWs.

The study evaluated three secondary efficacy endpoints. All of the secondary endpoints were comparisons between NexoBrid and SOC.

1. Incidence of surgical eschar removal (tangential/minor/avulsion/Versajet, and/or dermabrasion excision).
2. Time to eschar removal.
3. Actual blood loss during the eschar removal procedures.

The study also included safety endpoints designed to assess whether NexoBrid treatment had detrimental effects relative to SOC for outcomes related to wound closure and cosmesis and function. The safety endpoints were comparisons between NexoBrid and SOC.

1. Time to wound closure (wound-level assessment).
2. Modified Vancouver Scar Scale (MVSS) averaged over TWs at Month 12. MVSS will

also be assessed at Month 24. MVSS at Month 24 is not included in this study report.

Wound closure is defined as >95% area epithelialized or closed by graft. The MVSS evaluates cosmesis based on pigmentation, pliability, height, vascularity, pain, and pruritus each scored on a scale from 0 to 2, 0 to 3, or 0 to 5 for each TW. Total scores per TW range from 0 to 18 with a score of 0 representing normal skin (Table 1).

Table 1 – Modified Vancouver Scar Scale

	Pigmentation	Pliability	Height	Vascularity	Pain	Pruritus
0	Normal	Normal	Flat	Normal	None	None
1	Hypopigmented	Supple – flexible with minimal resistance	< 2 mm	Pink	Occasional	Occasional
2	Mixed	Yielding – giving way to pressure	2 to 5 mm	Red	Requiring medication	Requiring medication
3	Hyperpigmented	Firm – inflexible/ not easily moved/ resistant to manual pressure	> 5 mm	Purple		
4		Banding-rope-like tissue that blanches with extension of the scar				
5		Contracture-permanent shortening of scar, producing deformity or distortion				

Source: pg. 45 of the statistical analysis plan.

Additional exploratory endpoints include

1. Percent wound area surgically excised for eschar removal
2. Patient and Observer Scar Assessment Scale (POSAS) for cosmesis and function
3. Incidence of surgical escharotomy procedures in circumferential extremities target wounds
4. Incidence of reduction in interstitial/compartment pressure in circumferential extremity wounds (measured immediately following eschar removal)
5. Incidence of surgically harvested donor site wounds
6. Percent area surgically harvested donor site wounds
7. Blood loss following eschar removal procedures based on changes in hematocrit
8. MVSS and POSAS on donor site scars
9. PK evaluation
10. Autograft related parameters

11. Duration of hospitalization
12. Further functionality evaluations using the QuickDASH questionnaire, Lower Extremity Functional Scale (LEFS), Range of Motion (ROM) measurements, EQ5D health questionnaire, and Burn Specific Health Scale (BHSH-B).

Statistical Analysis Plan

The full analysis set (FAS) population is defined as all subjects randomized into the trial. The per protocol (PP) population includes all subjects who fulfill all inclusion/exclusion criteria and do not have major protocol violations. The safety analysis set includes all subjects who received a treatment and uses the actual treatment received. The FAS population will be used for all primary and secondary endpoints and the time to wound closure safety endpoint. The safety analysis set will be used for the MVSS endpoints.

The primary efficacy endpoint of incidence of eschar removal at the end of the topical treatment soaking procedure (NexoBrid versus vehicle gel) is analyzed with Fisher's exact test. The odds ratio and 95% confidence interval will be estimated using exact methods. Little missing data is expected for this endpoint as it evaluated immediately following the treatment process among subjects treated with NexoBrid or gel vehicle. However, subjects with missing data for this endpoint will be considered as not achieving eschar removal.

The secondary endpoint of incidence of surgical eschar removal (NexoBrid versus SOC) is analyzed with logistic regression with terms for treatment, TW depth (all FT, mixed, all DPT), total %TBSA per subject, and number of TWs (1, 2, ≥3). The odds ratio will be estimated along with the 95% confidence interval. If possible, the analysis will be repeated with center added to the model. Subjects with missing data will be considered as having surgical excision. As sensitivity analyses, an observed-case analysis and imputing subjects with missing data as not having surgical excision will be conducted.

The secondary endpoint of time to eschar removal (NexoBrid versus SOC) is defined as time from randomization until eschar removal has been achieved on all TWs. For subjects who do not reach complete eschar removal, time will be censored at the last non-missing assessment (typically the last debridement procedure). Medians will be calculated from Kaplan-Meier estimates. Treatment groups will be compared using a Cox regression model adjusted for treatment, TW depth (all FT, mixed, all DPT), total %TBSA per subject, center group, and number of TWs (1, 2, ≥3). The center groups are defined as Non-surgical, Mixed, Surgical, West, or East. US sites are classified as Non-surgical, Mixed, or Surgical. Non-US sites are classified as West or East. The applicant will assess whether the proportional hazards assumption appears to hold by including an interaction term for time since randomization and treatment group. If the coefficient is not significant at the 0.05 level, then Cox regression would be used, otherwise a generalized Wilcoxon-Gehan test will be performed.

Blood loss (BL) for NexoBrid versus SOC will be calculated for each subject and each procedure

based on the subject's weight (in kg), pre- and post-procedure hemoglobin levels (Hb_{before}, Hb_{after}), and total volume of whole blood (V_{WB}) and packed red blood cells (V_{PC}) transfused. The formula is as follows (see T. McCullough et al., "Estimated blood loss underestimates calculated blood loss during radical retropubic prostatectomy," Urol Int, vol. 72, no. 1, pp. 13-6, 2004)

$$BL = \frac{70 \cdot Weight \cdot (Hb_{before} - Hb_{after})}{(Hb_{before} + Hb_{after})/2} + V_{WB} + \frac{5}{3}V_{PC}$$

BL will be summed over all procedures carried out to remove eschar (surgical and non-surgical, including NexoBrid and vehicle gel.) Hemoglobin is to be measured immediately before each procedure and 4 hours after completion. The amount of blood transfused during this time period will also be included. BL will also be calculated using the hemoglobin assessment prior to the first procedure and the hemoglobin assessment after the last eschar removal procedure, treating the eschar removal as one continuous procedure. As a fairly high proportion of missing data is expected for this endpoint, the BL calculation leading to the least amount of missing data will be considered the primary analysis.

The analysis method for BL will depend on a test for the normality of the data. If the Shapiro-Wilk test is not rejected at 0.005 level of significance, then the data will be analyzed using a t-test. If the test is rejected, the data will be analyzed using a Mann-Whitney test.

Missing data for the blood loss endpoint will be handled with multiple imputation. The imputation will either be done using the t-test or the Mann-Whitney test, depending on the outcome of the Shapiro-Wilk test on the observed cases. If the parametric model is used, a linear regression model will be fit with terms for wound area, wound depth, and course of debridement (only non-surgical SOC, non-surgical SOC followed by surgical, only surgical, only NexoBrid, NexoBrid followed by non-surgical SOC followed by surgical, NexoBrid followed by surgical, only vehicle gel, vehicle gel followed by non-surgical SOC followed by surgical, vehicle gel followed by surgical) to the set of subjects with complete data for these variables in each treatment group separately. Missing data will be imputed m=25 times by adding a random normal variate with mean 0 and standard deviation equal to the residual standard deviation from the linear model fitted to the complete data set. If the non-parametric model is used, predictive mean matching will be used. Random draws from the five nearest neighbors for each missing value and five multiply imputed datasets will be used. Each dataset will be analyzed with the t-test or Mann-Whitney test and the results will be integrated using Rubin's rules.

The primary and three secondary endpoints will be analyzed in sequential order to control for multiplicity.

The safety endpoints were time to wound closure and MVSS at Month 12 and Month 24 for NexoBrid versus SOC. Wound closure was defined as ≥95% closure with closure confirmed two weeks later. Because the safety endpoints are designed to assess whether NexoBrid has a detrimental effect relative to SOC, the applicant specified a non-inferiority margins for time to wound closure and MVSS score. The margin for time to wound closure was 7 days and the margin for MVSS at the two timepoints was 1.9 units. The protocol stated that the justification

for the 7-day margin for time to wound closure is as follows.

- In the previously-conducted Study MW2004-11-02, the mean time to wound closure on the SOC arm was 27 days and the 95th percentile was 64 days.
- The applicant states, although they did not have studies on the time to wound closure for a placebo, the "worst case scenario" for the mean time to wound closure on the placebo might be comparable to the 95th percentile for SOC. The applicant then proposed that 64-27=37 (95th percentile – mean) was an estimate of M1 (the effect of the standard treatment against placebo), and that preserving 80% of the M1 effect may lead to a reasonable M2 (the largest clinically acceptable difference). Thus, they propose 0.2*37=7.4, rounded to 7 as the margin. They also posit that a difference of 7 days would have no clinical significance on patient mobilization and return to a pre-injury lifestyle, as rehabilitation can take weeks or months after wounds close. The applicant also noted that complications such as infections, were not an issue in previous studies as most infections occurred earlier in the healing course.

The protocol stated that the justification for the 1.9 unit margin for MVSS is

- In Study MW2004-11-02, the mean MVSS score on the SOC arm was 3.83 and the maximum possible score on the MVSS scale is 18.
- The treatment difference between the mean on the SOC arm and the maximum possible score is 18 - 3.83 = 14.17 and lower bound for 95% confidence interval of the difference is 13.42 (proposed estimate of M1). Preserving 80% of the M1 effect leads to 0.2*13.42=2.7 as the proposed estimate for M2. A survey of burn experts conducted by the applicant stated that a difference of no more than 2 units would not be considered clinically meaningful. Thus, the applicant selected 1.9 as the margin for the MVSS endpoints.

Reviewer Comment
The applicant noted that they did not have data from previous studies available to estimate the time to wound closure or MVSS score on the vehicle arm. The applicant attempted to justify that outcomes on a vehicle gel would be comparable to the 'worse case scenarios' on the SOC arm (i.e. the 95th percentile for time to wound closure on subjects treated with SOC and the worst possible score on the ordinal MVSS score). However, these are not plausible assumptions for how subjects treated with a vehicle gel might respond. Subjects with burns may be treated with a variety of regimens to remove eschar, however, standard of care dictates that if one method is not working adequately, other methods would be initiated. Thus, if subjects were treated with an ineffective vehicle gel, once it was determined that the placebo was not working, other non-surgical or surgical methods would be initiated. Thus, treatment with vehicle might cause a brief delay before other more effective eschar removal methods would be initiated. However, assuming that all vehicle subjects have the worst possible outcomes is not reasonable. Thus, the M1 and M2 calculations by the sponsor are not justifiable, and the proposed margins can only be supportable to the extent that they truly represent clinical judgement on no clinically meaningful differences.

Time to wound closure will be analyzed either with a marginal Cox regression model with robust sandwich estimator or with an accelerated failure time (AFT) model, depending on the

results of a test regarding the proportional hazards assumption. The analyses will be conducted on the wound level and the model will take into account the clusters of wounds within a subject. To incorporate the non-inferiority margin into the analyses, the observed wound closure times on the SOC arm will be transformed by adding a constant of 7 days to each observation. The transformed SOC data will be used to conduct hypothesis tests. The applicant will assess whether the proportional hazards assumption appears to hold by conducting a Cox regression model with terms for treatment, TW depth, %TBSA for the TW, number of TWs and an interaction term for time since randomization and treatment group. If the coefficient for the interaction term is not significant at the 0.05 level, then a Cox regression model would be used. If the test for the proportional hazards assumption is not significant, the data will be analyzed with a marginal Cox regression model with a robust sandwich estimator, with terms for treatment, TW depth, %TBSA for the TW, and number of TWs. If the proportional hazards assumption is not appropriate, an accelerated failure time model with shared frailty will be used. The accelerated failure time model will include terms for treatment, percent wound SPT area, percent wound DPT area, %TBSA, number of TWs, and center group. The model will also include a random effect for subject. Missing data will be censored.

MVSS scores will be assessed at Months 1, 3, 6, 12, 18, and 24 from the wound closure confirmatory visit for each target wound and averaged over the subject. MVSS scores will be analyzed using the safety analysis set (actual treatment) rather than the FAS. The NexoBrid and SOC arms will be compared at each timepoint (Month 12 and Month 24) using a linear model with terms for treatment, wound depth, %TBSA, number of TWs. Missing data will be handled with a single imputation method that fits a linear regression model using MVSS values at earlier timepoints and stratification factors. In particular, separate linear models for each treatment will be fit for subjects whose last MVSS assessment was at Month 1, 3, or 6. A random variate with mean 0 and standard deviation equal to the residual standard deviation from the linear model will be added to the predicted value. A similar imputation will be conducted for the Month 24 analysis. Note that the applicant conducted a database lock following the Month 12 assessments and Month 24 endpoint are not included in this submission.

Reviewer Comment
Rather than construct confidence intervals for the parameter of interest for the time to wound closure, the applicant has proposed transforming the collected data on the SOC arm by adding the value of corresponding non-inferiority bound (i.e. 7 days) and conducting a hypothesis test. Note that if the data transformation is based on adding a constant to the observations in one treatment arm, then the hypothesis test results and the confidence interval comparisons will only be equivalent when the parameter of interest is a treatment difference ($\theta_T - \theta_C$) and the test is for a shift in distributions. This is clearly not the case for time to event endpoints, where Cox regression assumes that the hazards are proportional, and the accelerated failure time model assumes the survival functions differ by an acceleration factor on the time scale. Thus, "adding a constant" to all of the observations on one treatment arm, does not create a hypothesis test that would correspond to the confidence interval of a parameter of interest for time-to-event endpoints, and the transformation potentially obscures any real relationship between the treatment arms that might exist. Calculating appropriate confidence intervals on the non-

transformed data will preserve any real relationships within the data. In addition, as noted above, the proposed non-inferiority margins do not have strong justifications and using transformed data in a hypothesis test would not permit a user to compare a confidence interval to an alternate margin. Additionally, the specified margins for the time to event endpoint are not on the same scale as the proposed confidence intervals and cannot be directly interpreted.

Protocol Amendments

Subjects were enrolled under three amendments (Amendments 8, 9, and 11). Differences in randomization methods, stratification factors, and inclusion criteria among these amendments are discussed in the Study Design section above. These changes to the protocol were in response to FDA's comments on elements of the study design.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that, "All studies conformed to International Council for Harmonisation (ICH) guidelines on Good Clinical Practice" (Section 1.2.1 of the Clinical Overview). However, the clinical inspections found that study 2010 was not conducted in accordance with current GCP standards. See Section 4.1.

Financial Disclosure

The Applicant considered the following to be covered studies:

- MW2002-04-01: 25 Principal Investigators
- MW2004-11-02: 33 Principal Investigators
- MW2010-02-03: 30 Principal Investigators

The Applicant certified that they had not entered into any financial arrangement with any of the investigators.

Patient Disposition

Study 2010 enrolled 175 subjects, 75 randomized to NexoBrid, 75 randomized to SOC and 25 randomized to vehicle gel. All 75 subjects randomized to NexoBrid were treated with NexoBrid. On the vehicle gel arm, 24 out of 25 subjects were treated with vehicle gel and 1 was not treated. On the SOC arm, 68 out of 75 subjects were treated with SOC, 5 were not treated, and 2 were treated with NexoBrid. The Acute Phase was defined as from randomization to the Month 3 follow-up visit after the wound closure confirmatory visit. The 12-month follow-up period includes follow-up through Month 12. A higher proportion of subjects randomized to the

SOC arm were never treated than on the topical treatment arms. As subjects and investigators could not be blinded to the assignment of topical treatment versus SOC, the decision to not initiate treatment could be due to the randomized treatment assignment. Four of the 5 subjects withdrew consent prior to initiating treatment, and one was found to have not met the screening criteria immediately after randomization. During the treatment and follow-up stages, discontinuation rates and reasons for discontinuing the study were fairly balanced across treatment arms. Two subjects on the NexoBrid arm died during the study, one during the Acute Phase and one during the 12-month follow-up period. See Table 2.

Table 2 – Disposition of Subjects in Study 2010

	NexoBrid	SOC	Vehicle
Randomized	75	75	25
Treated as randomized	75	68	24
Not treated	0	5 (7%)	1 (4%)
Treated with wrong treatment	0	2[a]	0
Completed Acute Phase	67 (89%)	63 (84%)	23 (92%)
Discontinued during Acute Phase	8 (11%)	7 (9%)	1 (4%)
Death	1 (1%)	0	0
Lost to follow-up	6 (8%)	5 (7%)	1 (4%)
Withdrawal by subject	1 (1%)	2 (3%)	0
Completed 12-month follow-up period	57 (76%)	58 (77%)	20 (80%)
Discontinued during 12-month follow-up period	10 (13%)	5 (7%)	3 (12%)
Death	1 (1%)	0	0
Lost to follow-up	7 (9%)	5 (7%)	3 (12%)
Withdrawal by subject	2 (3%)	0	0

[a] Two subjects randomized to SOC were treated with NexoBrid
Source: pg. 71 of the study report for Study 2010 and reviewer analysis.

Protocol Violations/Deviations

Twelve subjects were identified by the applicant as having major protocol violations, including withdrawal of consent prior to treatment, not meeting inclusion/exclusion criteria, being treated with the incorrect treatment, failing to follow topical treatment instructions, and not having eschar removal assessment performed due to loss to follow-up or withdrawal of consent. Most of the violations were for subjects on the SOC arm due to withdrawal of consent prior to initiating treatment or subjects who received the incorrect treatment. See Table 3.

Table 3 – Protocol Violations (I-ITT)

Protocol Deviations	NexoBrid N=75	SOC N=75	Vehicle N=25
Subject not treated/withdrew consent		4	1
Subject not treated/failed inclusion/exclusion criteria		1	

Subject treated/ failed inclusion/exclusion criteria	1	
Subject treated with incorrect treatment	2	
Topical treatment instructions not followed		1
Eschar removal assessment not performed	1	1

Source: pg. 74-75 of the study report for Study 2010 and reviewer analysis.

Demographic Characteristics

The baseline demographics were generally balanced across treatment arms. The mean age was approximately 41 years. A higher proportion of subjects were male than female, and the SOC arm had a higher proportion of males than the NexoBrid or vehicle arms. The majority of subjects were White, followed by Black or African-American, Asian, and other. The majority of subjects were not Hispanic or Latino. Fifty-six percent of subjects were enrolled in the US. See Table 4.

Table 4 – Demographic Characteristics in Study 2010

	NexoBrid N=75	SOC N=75	Vehicle N=25
Age (years)			
Mean	41.3	40.9	40.7
Range	18-75	18-72	18-70
18-64 years	69 (92%)	69 (92%)	21 (84%)
65+ years	6 (8%)	6 (8%)	4 (16%)
Gender			
Female	26 (35%)	16 (21%)	10 (40%)
Male	49 (65%)	59 (79%)	15 (60%)
Race			
Asian	1 (1%)	1 (1%)	0
Black or African-American	8 (11%)	13 (17%)	3 (12%)
White	61 (81%)	59 (79%)	21 (84%)
Other	5 (7%)	2 (3%)	1 (4%)
Ethnicity			
Not Hispanic or Latino	61 (81%)	67 (89%)	17 (68%)
Hispanic or Latino	14 (19%)	8 (11%)	8 (32%)
Region			
US	42 (56%)	42 (56%)	14 (56%)
Rest of World[a]	33 (44%)	33 (44%)	11 (44%)

[a] Romania, Italy, Georgia, Czech Republic, Belgium, Germany, Israel
Percentages may not sum to 100% due to rounding
Source: pg. 77 of Study Report 2010 and reviewer analysis.

Other Baseline Characteristics

The burn wound characteristics of percent TBSA, number of target wounds, and TW depth were generally consistent across treatment arms. Total burn area refers to all SPT, DPT, and FT burn areas and subjects were to have ≤30% TBSA total burn area. Target wounds were identified as continuous burn areas ≥0.5% TBSA (DPT or FT) (not including facial, perineal, or genital wounds). SPT areas that cannot be demarcated from DPT and FT areas can be included in a TW but must be <50% of the %TBSA of a TW. The TWs represent the areas treated with randomized treatment. Most subjects had ≤15% TBSA for the total burn area, and all but two subjects had TW area ≤15% TBSA. Most subjects also had 1 or 2 target wounds and all DPT or mixed DPT/FT burns. See Table 5.

Table 5 – Wound Characteristics in Study 2010

	NexoBrid N=75	SOC N=75	Vehicle N=25
Total burn area[a], %TBSA			
≤15%	67 (89%)	69 (92%)	24 (96%)
>15%	8 (11%)	6 (8%)	1 (4%)
Mean (SD)	9.0 (5.2)	8.3 (4.2)	8.9 (3.6)
Target wound area[b], %TBSA			
≤15%	74 (99%)	75 (100%)	24 (96%)
>15%	1 (1%)	0 (0%)	1 (4%)
Mean (SD)	6.3 (3.7)	5.9 (3.1)	6.5 (3.6)
Number of TWs			
1	41 (55%)	35 (47%)	13 (52%)
2	20 (27%)	29 (39%)	6 (24%)
≥3	14 (19%)	11 (15%)	6 (24%)
TW Depth			
All DPT	34 (45%)	36 (48%)	12 (48%)
Mixed	39 (52%)	35 (47%)	12 (48%)
All FT	2 (3%)	4 (5%)	1 (4%)

[a] A subject's total burn area should be ≤30% TBSA (SPT, DPT, or FT)
[b] TWs are continuous burn areas ≥0.5% TBSA (DPT or FT) (not including facial, perineal, or genital wounds). SPT areas that cannot be demarcated from DPT and FT areas must be <50% of the %TBSA of a TW.
SD=Standard deviation
Percentages may not sum to 100% due to rounding
Source: reviewer analysis.

SOC treatment encompasses a variety of surgical and non-surgical methods. The investigator's decision to begin with either a surgical or non-surgical method is likely impacted by both wound characteristics and general SOC preferences of the treating investigator or institution. Table 6 presents the strata factors by the planned initial treatment (non-surgical or surgical) for

subjects in the SOC arm (among subjects for whom an initial treatment was planned) to investigate any relationships between stratification factors and the initial treatment modality. Five subjects discontinued the study before treatment was initiated. Approximately two-thirds of subjects were initially treated with non-surgical methods, and one-third with surgical methods. The groups most likely to be treated initially with surgical methods include subjects with all FT wounds and subjects at centers classified (as a stratification factor in Amendment 11) as preferring surgical SOC.

Table 6 – Investigator Choice of First Treatment in the SOC Arm by Strata

	SOC Treated Subjects (N=70)	
	Nonsurgical N=46 (66%)	Surgical N= 24 (34%)
TW Depth		
All DPT	26 (81%)	6 (19%)
Mixed	19 (56%)	15 (44%)
All FT	1 (25%)	3 (75%)
Total burn area[a], %TBSA		
≤15%	42 (65%)	23 (35%)
>15%	4 (80%)	1 (20%)
Center Group		
Non-surgical	6 (60%)	4 (40%)
Mixed	11 (73%)	4 (27%)
Surgical	3 (21%)	11 (79%)
West	14 (74%)	5 (26%)
East	12 (100%)	0 (0%)
Number of TWs		
1	21 (66%)	11 (34%)
2	18 (67%)	9 (33%)
≥3	7 (63%)	4 (36%)

[a] Total burn area of SPT, DPT, or FT
Source: reviewer analysis.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the incidence of eschar removal at the end of the topical treatment soaking period for NexoBrid versus gel vehicle. Eschar was considered removed if ≥95% was removed. If two topical treatment applications were used, the assessment was based on the end of the soaking period after the second application. The endpoint was assessed on the subject level over all TWs. The applicant used Fisher's exact test to calculate the p-value and exact methods to calculate a confidence interval for the odds ratio. This reviewer also calculated the risk difference and used exact methods to calculate a confidence interval for the risk difference.

All subjects on the NexoBrid arm and all but one subject on the vehicle arm (who withdrew consent and was not treated) had observed data at the end of the topical treatment soaking period. The vehicle subject with missing data was treated as not achieving eschar removal. The reviewer conducted a sensitivity analysis that treats missing data in the least favorable way, that is imputing subjects with missing data as achieving eschar removal for the NexoBrid arm and not achieving eschar removal on the vehicle arm.

NexoBrid was more effective than vehicle in removing eschar by the end of the topical treatment soaking period. The results for the sensitivity analysis were similar to the primary analysis, as only one subject on the vehicle arm had missing data for this endpoint. See Table 7.

Table 7 – Incidence of Eschar Removal at the End of the Topical Treatment Period

	NexoBrid N=75	Vehicle N=25	Odds Ratio 95% CI p-value	Risk Difference 95% CI
Primary analysis (FAS)[a]	70 (93.3%)	1 (4.0%)	288.28 (35.5, >999.9) <0.001	89.3% (73.6%, 96.2%)
Sensitivity analysis[b]	70 (93.3%)	2 (8.0%)	141.4 (25.4, >999.9) <0.001	85.3% (68.4%, 94.2%)

[a]Missing data imputed as not achieving eschar removal.
[b]Missing data imputed as not achieving eschar removal for the NexoBrid arm and achieving eschar removal on the vehicle arm. Note that all subjects on the NexoBrid arm had observed data.
Source: pg. 86 of Study Report 2010 and reviewer analysis.

NexoBrid or vehicle gel could be applied a second time if either the TW area was >15% TBSA (and two treatments were needed to apply the topical treatment to all TWs because a maximum of 15% TBSA (±3% TBSA) could be treated within one session), or if most, but not all (≥50% but <95%), of the eschar was removed following the first application. Note that only one subject in the NexoBrid had two topical treatments planned in order to treat all TWs due to >15% TBSA. One vehicle subject had 18% TBSA, but all TWs were treated in the initial treatment because the TW area was within 3% of 15% TBSA. Among the 75 NexoBrid subjects, after the first treatment application 67 (89.3%) were classified as 'eschar removal complete.' Of the remaining 8 subjects,

- 1 subject had %TBSA > 15% and received two treatments to different sets of TWs due to the large TBSA. This subject had complete eschar removal after the second treatment (each TW was treated once).
- 2 subjects had complete eschar removal after a repeat NexoBrid treatment to the initially treated TWs.

- 2 subjects received a second NexoBrid treatment to the initially treated TWs but still did not achieve complete eschar removal and therefore also received additional surgical or non-surgical treatment for eschar removal.
- 3 subjects proceeded directly to additional surgical or non-surgical treatment and did not receive a second NexoBrid treatment because <50% of eschar was removed in the first treatment.

Among the 25 subjects randomized to vehicle, 1 subject was never treated, 1 subject had complete eschar removal after one treatment, and the remaining 23 subjects proceeded directly to additional surgical or non-surgical treatment following the first treatment and did not receive a second gel vehicle treatment.

To further describe the amount of eschar remaining after the first treatment, Table 8 presents the percent of eschar remaining after the first topical treatment. Subjects had 1 to 4 TWs. Eschar removal was assessed by TW. After one treatment, 97% of NexoBrid subjects had <50% of eschar remaining on target wounds compared to 8% of subjects treated with vehicle.

Table 8 – Maximum Percent of Eschar Remaining among Target Wounds after First Topical Treatment

Percent Remaining	Subject Status	NexoBrid N=75	Vehicle N=25
Subjects with ≤15% TBSA of Target Wounds (2nd application can be done if eschar removal is incomplete and <50% of eschar remains)			
0	Eschar removal complete	46 (61%)	0 (0%)
1-5%	Eschar removal complete	21 (29%)	1 (4%)
6-49%	Eligible for 2nd application[a]	5 (7%)	1 (4%)
50-100%	Not eligible for 2nd application	2 (3%)	22 (88%)[b]
Missing	Not treated	--	1 (4%)
Subjects with >15% TBSA of Target Wounds (2 applications planned)			
1-5%	Eschar removal complete after 2nd application	1 (1%)	--

[a] Note one subject in each arm proceeded to surgical or non-surgical treatment rather than have a second topical treatment application

[b] One subject on the vehicle arm had 18% TBSA target wound area at baseline, but all TWs were treated during the first application

Data Quality and Integrity

Five investigative sites in Study 2010 were investigated. Two sites were inspected prior to the completion of the study and three sites were inspected during the BLA review. The Office of Scientific Investigations identified several issues which lead to significant concerns related to the conduct of the study and the reliability of the assessment of the primary endpoint (complete eschar removal) and the assessment of wound closure. The concerns related to the unblinding of blinded assessors, use of photographs to assess eschar removal and wound closure, and lack of documented training of the blinded assessors. Thus, they concluded that the study should be interpreted with the understanding that assessments of key endpoints may not have fully utilized a blinded assessor.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints compared NexoBrid to SOC regarding the incidence of excision for eschar removal, time to eschar removal, and blood loss.

Incidence of Eschar Removal
For the incidence of excision for eschar removal, the primary analysis method was logistic regression with terms for treatment, TW depth (all FT, mixed, all DPT), total %TBSA per subject, and number of TWs (1, 2, ≥3). Missing data was handled by imputing values that imply an excision occurred for either treatment arm. This reviewer also calculated the risk difference and used the method from Ge, et al (2011)[22] to calculate a confidence interval for the risk difference.

All subjects on the NexoBrid arm and all but 6 subjects on the SOC arm had observed data regarding excisions for eschar removal. In the primary analysis, subjects with missing data were imputed as having an excision. The reviewer also conducted a sensitivity analysis that treats missing data in the least favorable way, that is missing data are imputed as having an excision for the NexoBrid arm and not having an excision on the SOC arm.

Fewer subjects on the NexoBrid arm had surgical excisions on the NexoBrid arm than the SOC arm. The results of the sensitivity analysis were similar to the primary analysis. See Table 9.

[22] Ge M, Durham LK, and Meyer DR. Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug Information Journal 2011;45:481-493

Table 9 – Incidence of Excision for Eschar Removal

	NexoBrid N=75	SOC N=75	Odds Ratio 95% CI p-value	Risk Difference 95% CI
Primary analysis (FAS)[a]	3 (4.0%)	54 (72.0%)	0.011 (0.003, 0.044) <0.001	-67.4% (-78.2%, -56.6%)
Sensitivity analysis[b]	3 (4.0%)	48 (64.0%)	0.015 (0.004, 0.060) <0.001	-59.4% (-70.5%, -48.4%)

[a]Missing data imputed as having an excision.
[b]Missing data imputed as having an excision for the NexoBrid arm and not having an excision on the SOC arm. Note that all subjects on the NexoBrid arm had observed data.
Source: pg. 88 of Study Report 2010 and reviewer analysis.

Time to Eschar Removal
The second secondary endpoint was time to complete eschar removal, where complete eschar removal was defined as ≥95% removed for all TWs on a subject. For subjects who do not reach complete eschar removal, time was censored at the last non-missing assessment (typically the last debridement procedure).

All subjects in the NexoBrid arm were followed until eschar removal was complete (no censored observations). Five subjects on the SOC arm never initiated treatment and were censored at time 0. One additional subject on the SOC arm withdrew consent after initiating non-surgical treatment and was censored approximately 18 hours (0.75 days) after randomization. All other subjects on the SOC arm were followed through the eschar removal stage. Note that because the patient population is hospitalized patients, subjects who discontinued the study prior to completing eschar removal, would likely continue to receive similar standard of care within the same hospital as those who remain in the study. Thus, assuming that subjects on the SOC arm who discontinue the study and are censored would have a similar treatment course to those remaining in the study may be reasonable.

Median times to eschar removal were calculated from Kaplan-Meier estimates. Treatment groups were to be compared either using a Cox regression model or a generalized Wilcoxon-Gehan test, depending on the applicant's assessment as to whether the proportional hazards assumption was reasonable. The applicant assessed the validity of the proportional hazards assumption by including an interaction term for time since randomization and treatment group in the Cox model. When this analysis was conducted, the p-value for the interaction term was <0.0001. Thus, the applicant rejected the proportional hazards assumption and analyzed the endpoint with a generalized Wilcoxon-Gehan test, adjusted for treatment, TW depth (all FT, mixed, all DPT), total %TBSA per subject, center group, and number of TWs (1, 2, **≥3).** The center groups are defined as Non-surgical, Mixed, Surgical, West, East. The results from the Wilcoxon-Gehan test are presented in Table 10. The median time to eschar removal

was approximately 1 day on the NexoBrid arm and 3.8 days on the SOC arm and the difference between the survival functions was statistically significant. The survival curves for NexoBrid versus SOC are presented in

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Figure 1.

Table 10 – Time to Eschar Removal

	NexoBrid N=75	SOC N=75	Test Statistic[a] p-value
Median (days) (FAS)	1.02	3.83	23.14 <0.0001

[a] Wilcoxon-Gehan test

Source: pg. 90 of Study Report 2010 and reviewer analysis.

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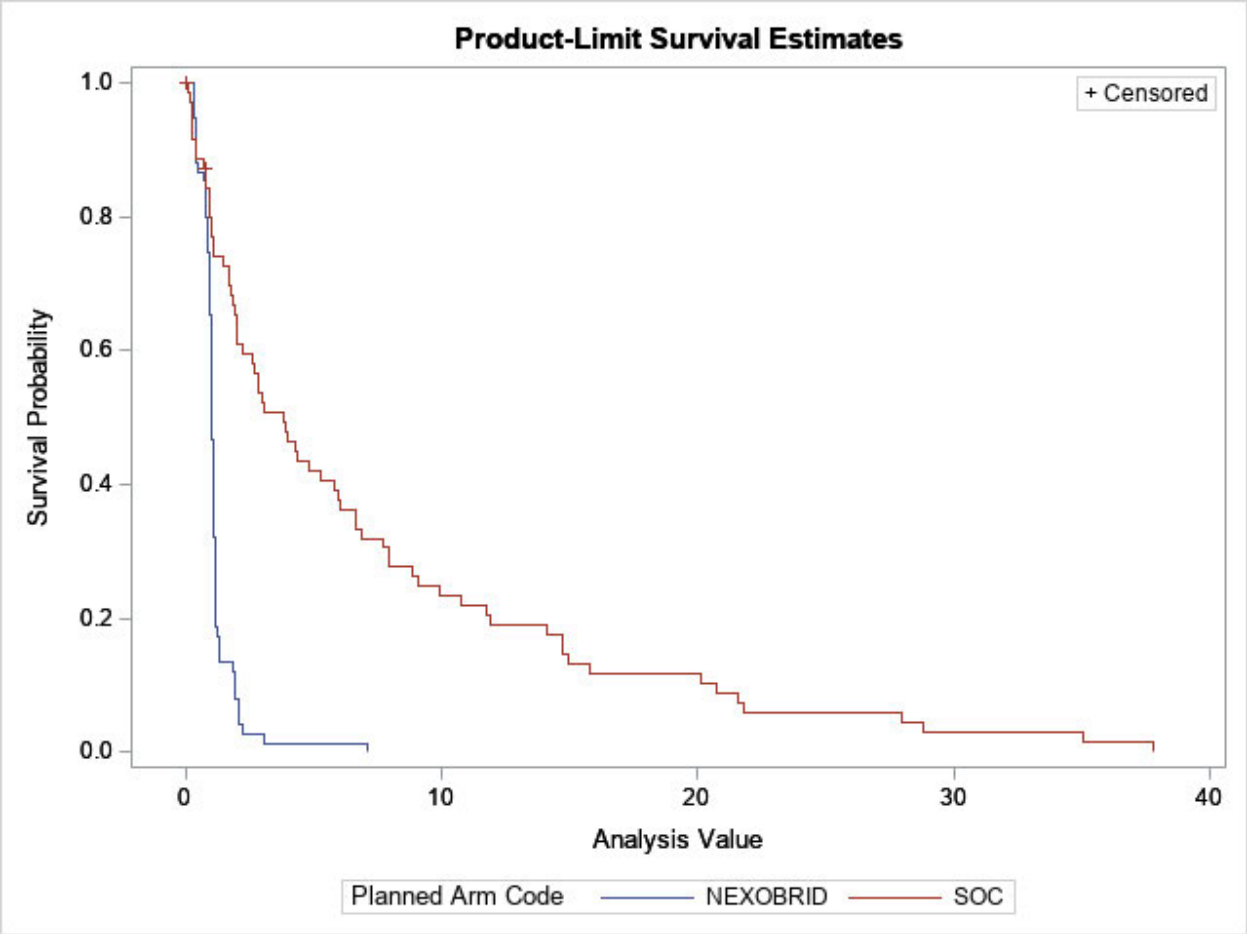
Figure 1 – Time to Eschar Removal



Note: time is expressed in days.
Source: Reviewer analysis.

The analysis model included four factors: TW depth, total burn area %TBSA, center group, and number of TWs. To assess the impact of each of these factors, subgroup analyses for the median time to eschar removal were conducted. The median time to eschar removal for subjects treated with NexoBrid was approximately 1 day in all subgroups reflecting that 93% of subjects on the NexoBrid arm did not require supplemental procedures to remove eschar. However, the time to eschar removal in the SOC arm appears to vary across TW depth, total burn area, and center classification (representing differences in stated SOC practices). The impact of the number of TWs does not appear to be as important a factor in the time to eschar removal. See Table 11.

Table 11 – Median Time (Days) to Eschar Removal by Strata

	NexoBrid N=75	SOC N=75
TW Depth		
All DPT	0.993 (N=34)	6.650 (N=36)
Mixed	1.056 (N=39)	2.574 (N=35)
All FT	1.107 (N=2)	0.834 (N=4)
Total burn area[a], %TBSA		
≤15%	1.012 (N=67)	3.037 (N=69)
>15%	1.066 (N=8)	5.990 (N=6)
Center Group		
Non-surgical	0.966 (N=14)	3.434 (N=11)
Mixed	0.995 (N=14)	2.689 (N=16)
Surgical	1.020 (N=14)	1.527 (N=15)
West	1.075 (N=17)	4.810 (N=21)
East	1.099 (N=16)	7.913 (N=12)
Number of TWs		
1	0.989 (N=41)	3.828 (N=35)
2	1.016 (N=20)	3.935 (N=29)
≥3	1.139 (N=14)	2.836 (N=11)

[a] Total burn area of SPT, DPT, or FT
Source: reviewer analysis.

Blood Loss Related to Eschar Removal
The third secondary endpoint was blood loss related to eschar removal. Blood loss is calculated using the subject's weight, pre- and post-procedure hemoglobin levels, and total volume of whole blood and packed red blood cells transfused during the procedure. (See the Statistical Analysis Plan section for the formula.) Hemoglobin is to be measured immediately before each procedure and 4 hours after completion. Subjects had from one to three separate eschar removal procedures (NexoBrid, vehicle gel, non-surgical procedure or surgical procedure). Subjects could have two treatments of the same type (e.g. two NexoBrid procedures or two surgical procedures) or have treatments of different types. The Statistical Analysis Plan included two proposals for calculating blood loss, depending on the amount of missing data for the endpoint. Either the calculated blood loss was to be computed for each eschar removal procedure and then summed over all procedures or the calculated blood loss would use the hemoglobin assessment prior to the first procedure and the assessment after the last eschar removal procedure, treating the eschar removal as one continuous procedure. The calculation leading to the least amount of missing data was to be considered the primary analysis. Missing data for the blood loss endpoint was handled with multiple imputation.

Note that NexoBrid and surgical procedures are relatively short procedures that generally will have pre- and post-procedure hemoglobin levels taken hours apart. However, non-surgical SOC treatments may be continued for days or weeks. Thus, the pre- and post-procedure hemoglobin levels for these treatments could be taken days or weeks apart. The formula used to calculate blood loss was developed for use with surgical procedures, and the applicant has not provided

information to support whether the formula is suitable for interpreting hemoglobin changes across days or weeks or whether the applicant's proposal to combine blood loss estimates across multiple procedures by either summing the estimates from the individual procedures or estimating the total blood loss by using just the beginning and ending hemoglobin levels are useful representations of the clinical impact to a subject.

The analysis using just the hemoglobin assessment prior to the first eschar removal procedure and the assessment after the last eschar removal procedure had fewer missing observations than the analysis using the per-procedure hemoglobin values, thus the applicant considers the "continuous procedure" assessment as the primary analysis. The "continuous procedure (pre-first to post-last)" analysis had 20% missing data for NexoBrid and 51% for SOC and the "sum over procedures" analysis had 23% missing data for NexoBrid and 63% for SOC. However, the amount of missing data was substantial under both calculations. Non-surgical procedures had particularly high rates of missing data, perhaps because it was more difficult to predict when the non-surgical treatment would end and schedule labs for 4 hours after the treatment ended. On the SOC arm, the differences in the amount of missing data between the two ways of calculating blood loss is driven by subjects whose first treatment was non-surgical and whose second treatment was surgical, presumably because hemoglobin values were more likely to missing following non-surgical treatment, but observed following surgical treatment. Nine subjects who had missing hemoglobin assessments following the initial non-surgical procedure did have hemoglobin assessments following the second surgical procedure. Even though using the pre-first procedure and post-last procedure hemoglobin values for the calculation of blood loss leads to slightly less missing data, there may be issues with trying to interpret blood loss based on the pre-first procedure and post-last procedure hemoglobin values because there may be other intervening events that impact hemoglobin levels over days or weeks. Table 12 presents the amount of missing hemoglobin data by procedure and overall treatment course.

Table 12 – Amount of Missing Hemoglobin Data during Eschar Removal Stage

	NexoBrid N=75	SOC N=75
First Procedure	N=75	N=75
NexoBrid	14/75 (16%)	2/2[a] (100%)
Non-surgical	--	31/44 (70%)
Surgical	--	9/24 (38%)
Not treated	--	5/5 (100%)
Total	14/75 (16%)	47/75 (63%)
Second Procedure	N=8	N=26
NexoBrid	2/5 (40%)	--
Non-surgical	2/2 (100%)	1/1 (100%)
Surgical	0/1 (0%)	4/25 (16%)
Total	4/8 (50%)	5/26 (19%)
Third Procedure	N=3	N=2
Non-surgical	0/1 (0%)	--
Surgical	1/2 (50%)	2/2 (100%)
Total	1/3 (33%)	2/2 (100%)
Sum across Procedures	17/75 (23%)	47/75 (63%)
Treatment Course		
NexoBrid	13/70 (19%)	2/2 (100%)
NexoBrid - Non-Surgical	1/2 (50%)	--
NexoBrid - Surgical	0/2 (0%)	--
NexoBrid – Non-Surgical - Surgical	1/1 (100%)	--
Non-Surgical	--	13/20 (65%)
Non-Surgical - Surgical	--	9/24 (38%)
Surgical	--	8/23 (35%)
Surgical - Non-Surgical - Surgical	--	1/1 (100%)
Not treated	--	5/5 (100%)
Pre-First to Post-Last Procedure	15/75 (20%)	38/75 (51%)

Source: reviewer analysis

The summary statistics calculated from the observed cases for both methods of calculating blood loss (using the pre-first and post-last procedure hemoglobin values and summing the values across all individual procedures) are presented in Table 13. The calculated values for the blood loss are similar across the two calculation methods, though, the amount of missing data is high, limiting the utility of the observed case estimates. The variability is large relative to the mean values, and the variability is larger on the SOC arm than the NexoBrid arm. Note that under this calculation method that 'negative blood loss' values are possible (theoretically equaling 'blood gain') if the post-procedure hemoglobin values are higher than the pre-procedure values. For the NexoBrid arm mean blood loss in the observed-case analysis is approximately 14 mL, with a standard deviation of approximately 512 mL. Both the mean and standard deviation on the SOC arm were higher (mean of 815 mL and standard deviation of

1020 mL).

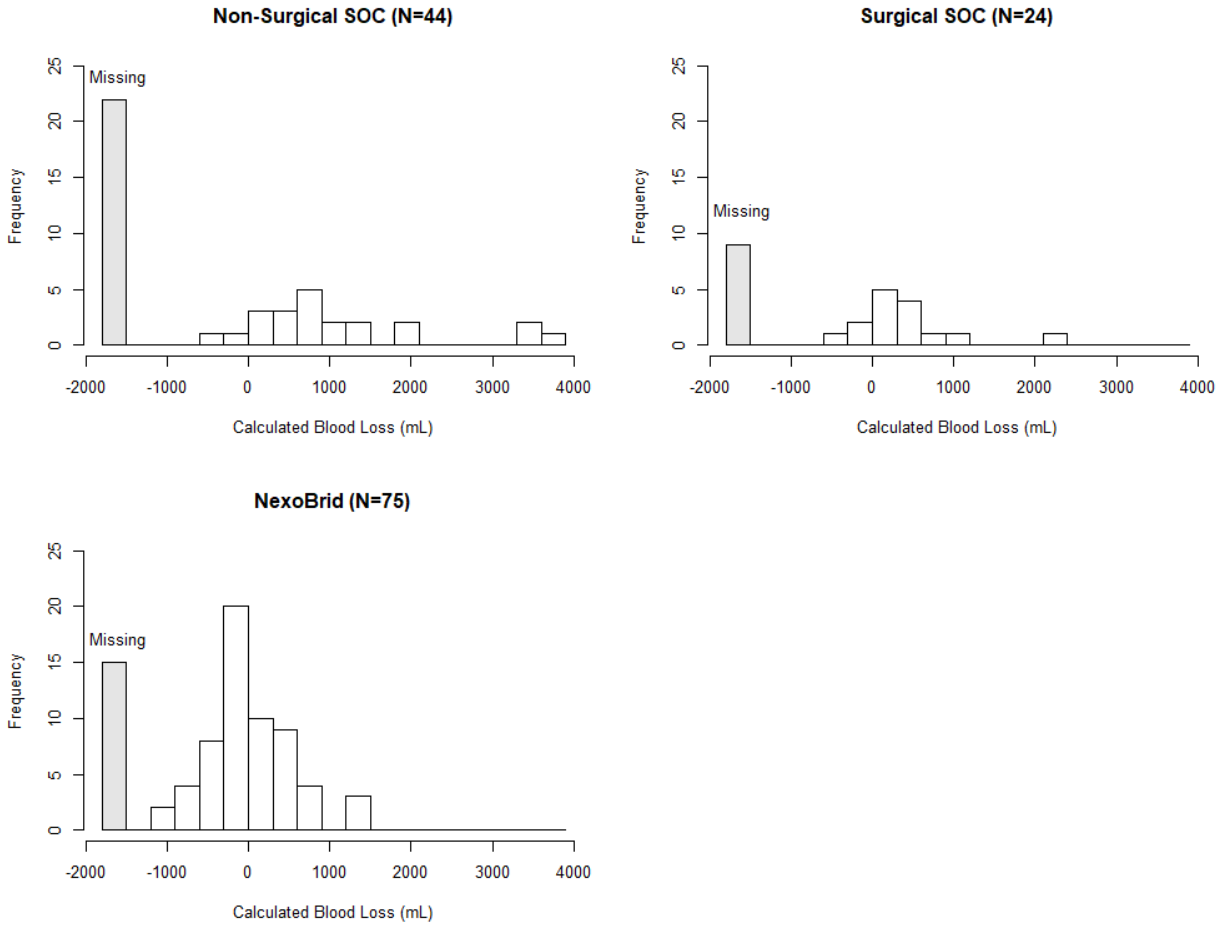
Table 13 – Calculated Blood Loss Summary Statistics (Observed Cases)

	NexoBrid N=75	SOC N=75
Pre-First to Post-Last Procedure	N=60	N=37
Mean (SD)	14.17 (512.40)	814.51 (1020.32)
Min, Max	-956.76, 1425.29	-452.03, 3620.43
Sum over Procedures	N=58	N=28
Mean (SD)	-12.59 (496.52)	679.97 (1009.09)
Min, Max	-1162.70, 1529.86	-452.03, 3682.85

SD=Standard deviation
Source: pg. 93 and 193 of Study Report 2010 and reviewer analysis.

The calculated blood loss values using the pre-first to post-last procedure hemoglobin values are presented in Figure 2, with the subjects on the SOC arm grouped by their first eschar removal procedure (non-surgical or surgical). Subjects with missing data are included in the bar on the left of each plot. Among subjects randomized to the SOC arm, 2 subjects who received NexoBrid and 5 subjects who did not receive any treatment are not represented.

Figure 2 – Calculated Blood Loss during Eschar Removal Stage (Pre-First to Post-Last Procedure) by First Procedure Type



Note: SOC plots do not include 2 subjects who received NexoBrid and 5 subjects who did not receive any treatment.
Source: Reviewer analysis.

Three subjects (1 subject on the NexoBrid arm and 2 subjects on the SOC arm) received blood transfusions during the eschar removal period. The amount of blood products transfused is included in the calculation of blood lost for these subjects. An additional 7 subjects (3 subjects on the NexoBrid arm and 4 subjects on the SOC arm) received blood transfusions within one week after the end of the eschar removal period.

For the inferential analyses, the data was to be analyzed with either a parametric or non-parametric procedure depending on the results of a Shapiro-Wilks test. Because the Shapiro-Wilk test for normality was rejected at 0.005 level of significance, the data was analyzed using a Wilcoxon-Mann-Whitney test rather than a t-test. The applicant handled missing data using multiple imputation with predictive mean matching using random draws from the five nearest neighbors for each missing value and five multiply imputed datasets. The multiple imputation

used wound area, wound depth, and course of debridement (only non-surgical SOC, non-surgical SOC followed by surgical, only surgical, only NexoBrid, NexoBrid followed by non-surgical SOC followed by surgical, NexoBrid followed by surgical, only vehicle gel, vehicle gel followed by non-surgical SOC followed by surgical, vehicle gel followed by surgical) in the model for each treatment group separately.

The applicant presents the results using the hemoglobin assessments prior to the first eschar removal procedure and the assessment after the last eschar removal procedure, because this analysis had fewer missing observations. The results of the Mann-Whitney test for this assessment was statistically significant with a test statistic of 24.11 and a p-value of <0.0001. The results for the analysis summing blood loss over procedures were similar with a test statistic of 21.05 and a p-value of <0.00001. Although the applicant attempted to impute missing data using data from subjects with comparable characteristics, because approximately half of the subjects on the SOC arm had missing data, the results of this analysis may be difficult to interpret. Thus while the point estimates based on observed data and inferential analyses based on imputed data indicate that the amount of blood loss due to eschar removal for subjects treated with NexoBrid may be lower than for subjects treated with SOC, the large amount of missing data and concerns with interpreting the blood loss calculations over potentially lengthy eschar removal treatment periods make it difficult to interpret the results of this endpoint and translate it to clinical benefit for the subjects.

Additional Endpoints – Safety Endpoints

To assess whether NexoBrid was detrimental relative to SOC in terms of time to wound closure and long-term cosmesis, the study included three safety endpoints: time to wound closure and cosmesis at Month 12 and Month 24 evaluated using the MVSS. MVSS at Month 24 is not included in this submission as the database lock was before all subjects completed their Month 24 visit. To rule out a certain level of detrimental effects, the safety endpoints were designed with non-inferiority comparisons of NexoBrid to SOC.

Time to Wound Closure

Time to wound closure was assessed for NexoBrid versus SOC. The primary analysis proposed by the applicant was to conduct the analysis at the wound level using a clustered analysis method. Wound closure was assessed weekly following the eschar removal stage. Closure was defined as ≥95% skin re-epithelialization without drainage or dressing requirements. Closure was to be confirmed 2 weeks later.

Median times to wound closure were calculated from Kaplan-Meier estimates. Time to wound closure was to be evaluated with either a marginal Cox regression model or an accelerated failure time model with shared frailty. The proportional hazards assumption was evaluated by conducting a statistical test for the time-treatment interaction in the Cox model analysis. The applicant rejected the proportional hazards assumption, because the coefficient of the time-treatment interaction was significant at the 0.05 level (p <0.0001). Thus, the applicant analyzed

the data with an accelerated failure time model that includes terms for treatment, wound depth, %TBSA, number of TWs, and time by treatment interaction and a random effect for subject. Missing data is censored.

The median time to ≥95% wound closure on the per wound analysis was 27 days on the NexoBrid arm and 28 days on the SOC arm (Table 14). However, while the statistical test may take into account the clustering within subjects and take into account important subject- and treatment-related factors, the Kaplan-Meier estimates of the medians do not. During protocol development, the Agency recommended that the applicant evaluate time to 100% wound closure on a per subject analysis, as this analysis would be more clinically meaningful than defining wound closure as ≥95% closure. The Agency made these recommendations because time to closure of the last TW and complete (100%) closure may be more representative of when patients can resume more normal activities than when the 'typical wound' is closed. However, the applicant continued to define the main analysis on the wound level and using the ≥95% wound closure definition. Supportive analyses based on the by-subject estimates are also included in Table 14. An additional analysis defining wound closure as 100% closure is also included. Note that because a subject's follow-up schedule was switched from weekly visits to visits at Months 1, 3, 6, 12 after wound closure (≥95%) was confirmed at a 2-week follow-up visit, not all subjects who had assessments of ≥95% closure have assessments when 100% closure was observed. Thus, there is a greater amount of censored observations in the 100% closure analysis. The time to wound closure on the per-subject analysis was 31 versus 36 days for ≥95% and 38 versus 52 days for the ≥100% analysis. The analysis for the 100% closure, by-subject analysis has over 52-68% missing data in the two arms, and thus the estimates may not be reliable. Therefore, conclusions about wound closure based on ≥95% closure may be more interpretable, even if the analyses are less clinically meaningful. The median time to wound closure was smaller on the NexoBrid arm than the SOC arm for all three analyses.

The survival curves for NexoBrid versus SOC for per-wound analysis are presented in

Figure 3 and the survival curves for the per subject analysis are presented in Figure 4.

Table 14 – Time to Wound Closure

	NexoBrid N=75	SOC N=75
Per-Wound Analysis ≥95% wound closure	N=128 Wounds	N=129 Wounds
Median (days)	27	28
95% Confidence interval	(22, 33)	(24, 37)
Censored observations	35 (27%)	49 (38%)
Per-Subject Analysis ≥95% wound closure	N=75	N=75
Median (days)	31	36
95% Confidence interval	(23, 36)	(27, 41)
Censored observations	21 (28%)	30 (40%)
Per-Subject Analysis ≥100% wound closure	N=75	N=75
Median (days)	38	52
95% Confidence interval	(31, 46)	(39, NA)
Censored observations	39 (52%)	51 (68%)

NA = not available
Source: pg. 121 of Study Report 2010 and reviewer analysis.

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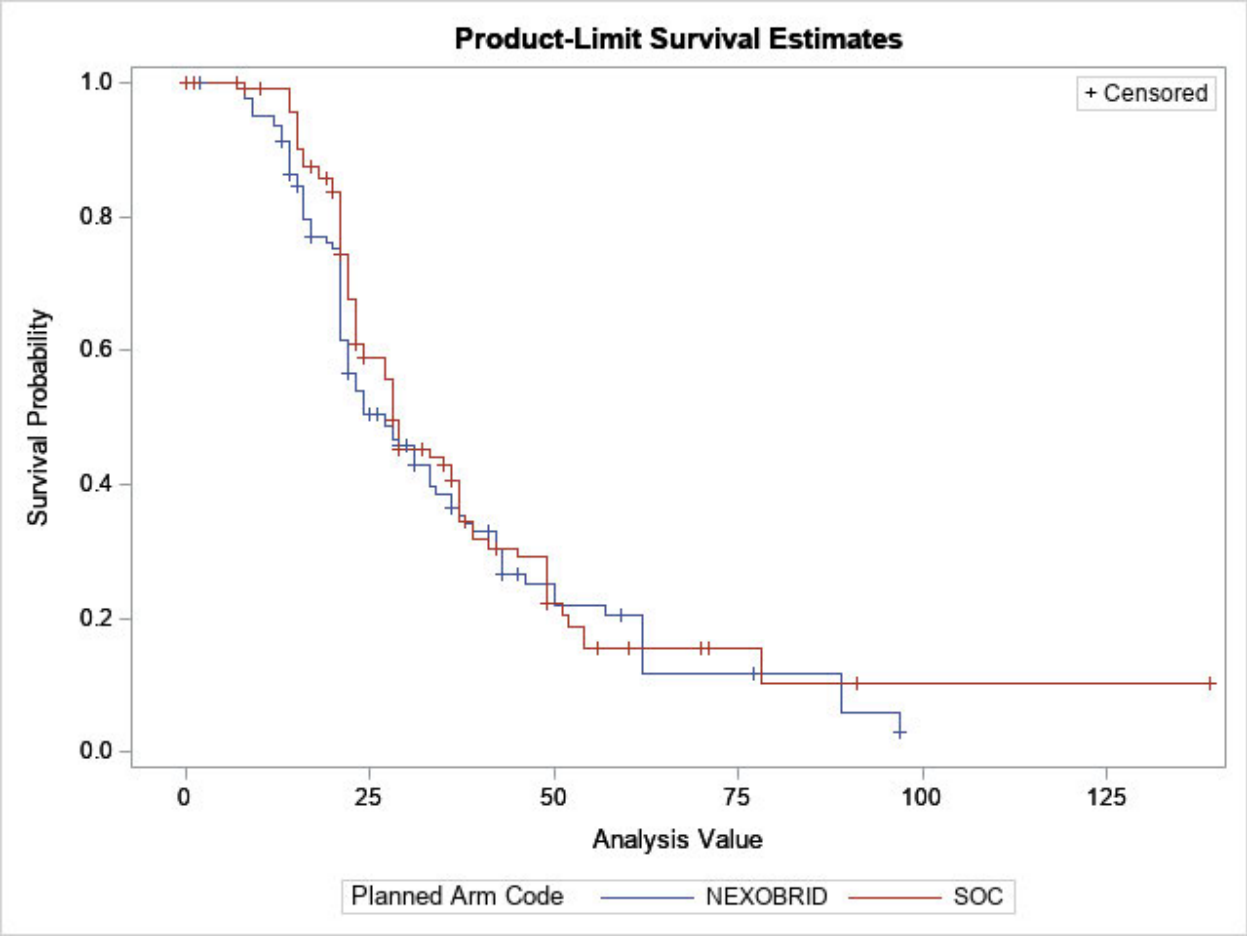
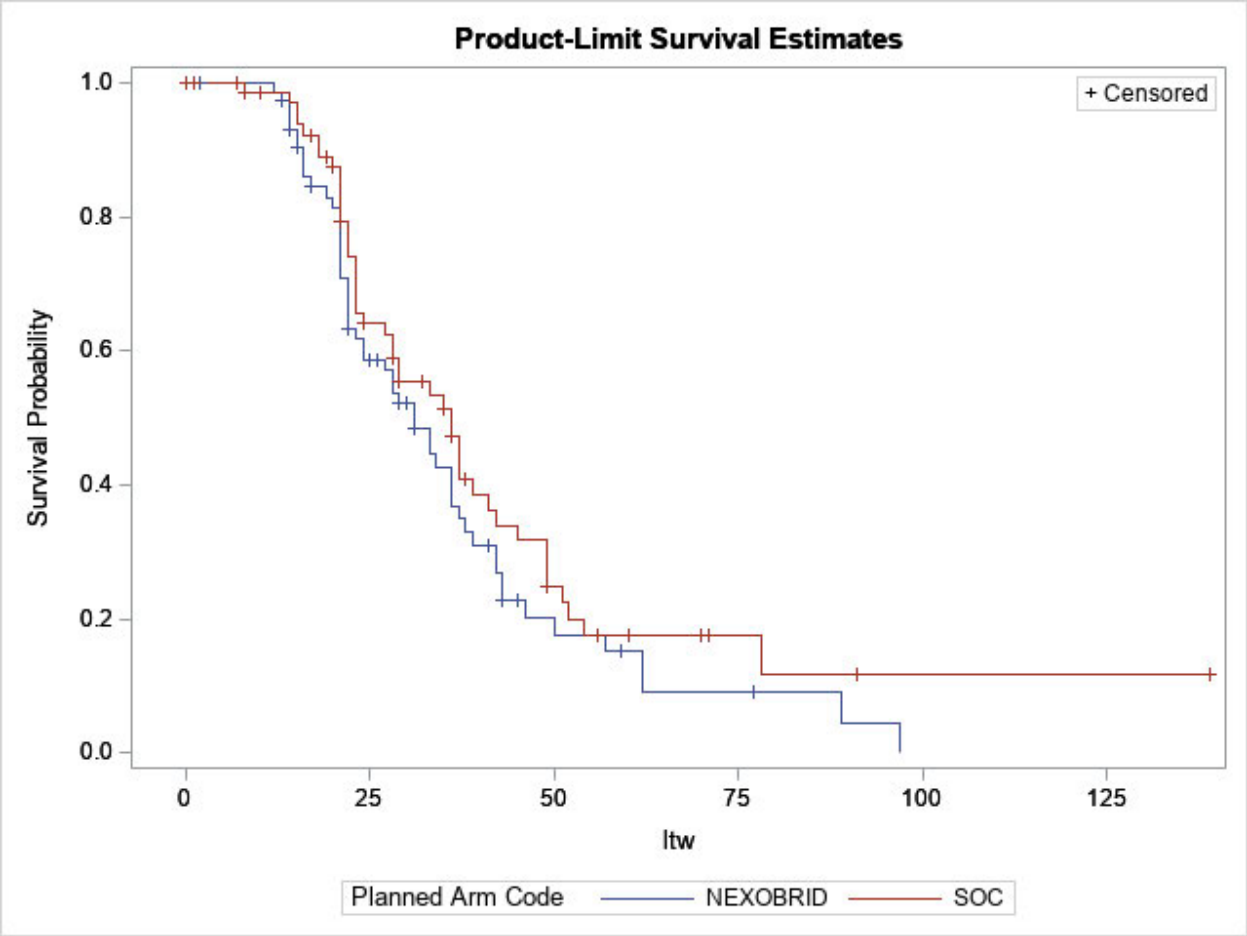
Figure 3 – Time to **≥95%** Wound Closure (Per Wound Analysis)



Source: reviewer analysis

Figure 4 - Time to **≥95%** Wound Closure (Per Subject Analysis)



Source: reviewer analysis

As noted in the Statistical Analysis Plan section above, the applicant attempted to incorporate the proposed non-inferiority margin of days into hypothesis tests for the time to wound closure endpoint by adding a constant of 7 days to each observation on the SOC arm. Because the hypotheses for time to event endpoints are based on the hazard ratio and not the treatment difference, such a transformation for the data on the SOC arm does not lead to a hypothesis test that would be appropriate for the question of interest. Similarly, the prespecified non-inferiority margin is not directly relevant for the proposed hypotheses, because the pre-specified non-inferiority margin is on the 'treatment difference' scale and would not be directly applicable to test statistics (such as the hazard ratio) from time-to-event analysis methods. Therefore, it may be difficult to interpret the analyses pre-specified in the protocol for the time to wound closure endpoint. The applicant followed the procedures from the protocol and reported an estimate for the acceleration factor for the AFT model. However, because the use of the transformed data is not appropriate for such methods, this analysis is not interpretable and does not lead to additional insight into the time to wound closure between the two treatment arms.

This reviewer considered whether the protocol-specified analyses could be implemented on the data as observed, rather than adding a constant of 7 to each SOC observation. However, although the applicant attempted to assess the assumptions needed for the proportional hazards assumption, the protocol assumes that an AFT model would be a suitable model if the proportional hazards assumption is not satisfied. However, the AFT model assumes that t the covariates act multiplicatively (proportionally) with respect to the survival time. The AFT model also needs to have a specified parametric model for the control survival function. The SAP did not include justification that an AFT model would be appropriate or full pre-specification of the details needed to implement such a model (such as the underlying parametric model for the survival function). The applicant also did not provide a proposal for handling subjects with 0 values for the follow-up time (i.e. subjects who withdrew from the study before receiving randomized treatment) that cause errors in the analysis because the analysis involves taking logarithms of the event/follow-up times. Therefore, there are also challenges with implementing and interpreting the proposed model on the observed data, as it is not clear that assumptions are met or that the models were adequately pre-specified. Thus, the impact of the prespecified covariates will be investigated through subgroup analysis on the estimated medians, rather than trying to identify a model that can be appropriately used for an inferential analysis. See Table 15. Many of the subgroups are small, and time to wound closure is variable across subgroups so it is difficult to determine if any of the covariates have an impact on the time to wound closure.

Table 15 - Time to **≥95%** Wound Closure (Per Subject Analysis) by Stratification Factors

Median (95% Confidence Interval)	NexoBrid N=75	SOC N=75
Center Group		
Non-surgical	N=14 21 (19, 33)	N=11 30 (15, 54)
Mixed	N=11 50 (28, 62)	N=16 33 (20, NA)
Surgical	N=14 31 (22, NA)	N=15 52 (27, NA)
West	N=17 37 (21, 43)	N=21 28.5 (23, 37)
East	N=16 16 (14, 36)	N=12 28 (8, NA)
Number of TWs		
1	N=41 31 (22, 36)	N-35 41 (28, 52)
2	N=20 25.5 (16, 50)	N=29 33 (22, 39)
≥3	N=14	N=11

	36 (21, 43)	27 (21, 49)
TW Depth		
All DPT	N=34	N=36
	31 (21, 37)	29 (23, 45)
Mixed or All FT	N=41	N=39
	31 (24, 42)	36 (24, 54)

NA = not available
Source: reviewer analysis.

Subjects were evaluated 1 month and 3 months after the wound closure confirmation visit (two weeks after the last TW achieved closure). Sixty-six subjects (88%) on the NexoBrid arm and 62 subjects (83%) on the SOC arm had assessments of ≥95% wound closure confirmed two weeks later on all TWs. One NexoBrid subject died prior to achieving wound closure and other subjects had missing closure assessments on at least one target wound. All of these subjects with observed wound closure who returned for the 1-month follow-up visit maintained closure, though some subjects did not return for the follow-up visit. Similarly, most subjects who returned for the 3-month follow-up visit maintained closure, though 1 subject on the NexoBrid arm and 2 subjects on the SOC arm did not maintain wound closure, and some additional subjects did not return for assessment. The amount of missing data was slightly higher on the SOC arm. See Table 16.

Table 16 – Maintenance of Wound Closure

	NexoBrid N=75	SOC N=75
≥95% wound closure confirmed 2 weeks later		
Yes	66 (88%)	62 (83%)
Missing	9 (12%)	13 (17%)
Wound closure maintained after 1 month		
Yes	61 (81%)	56 (75%)
No	0	0
Missing	14 (19%)	19 (25%)
Wound Closure maintained after 3 months		
Yes	54 (72%)	52 (69%)
No	1 (1%)	2 (3%)
Missing	20 (27%)	21 (28%)

Source: pg. 2231 of Study Report 2010 and reviewer analysis.

Modified Vancouver Score Scale
Cosmesis of the TWs was assessed using the MVSS at Months 1, 3, 6, and 12. It was also planned to be assessed at Months 18 and 24, but these results are not included in the current submission. MVSS at Month 12 was one of the key safety endpoints. The MVSS evaluates cosmesis based on pigmentation, pliability, height, vascularity, pain, and pruritus each scored

on a scale from 0 to 2, 0 to 3, or 0 to 5 for each TW. Total scores per TW range from 0 to 18 with a score of 0 representing normal skin. The SAP noted that MVSS at Month 12 would be analyzed using the safety analysis set rather than the FAS. The safety analysis set excludes the 5 subjects randomized to SOC who were never treated; in addition, the 2 subjects randomized to SOC but treated with NexoBrid are included in the NexoBrid arm. MVSS scores are assessed per wound and averaged over the TWs per subject for the analysis. The analysis method is a linear model with terms for treatment, wound depth, %TBSA, number of TWs. Missing data was imputed using a single imputation regression method with random variate added (see the Statistical Analysis Plan section above). Note that while the clinical study report describes the missing data handling method as a multiple imputation method, the method described in the SAP and used in the presented analyses is a single imputation method. The MVSS scores were lower on the NexoBrid arm than the SOC arm and the upper bound of the confidence interval was -0.48, which was less than the pre-specified non-inferiority margin of 1.9. See Table 17. The results were also consistent across subgroups for center group, number of TWs, and TW depth (Table 18). However, the applicant did not provide information supporting that the MVSS was fit for purpose. Thus, while the results were more favorable on the NexoBrid arm than the SOC arm, due to limited information on the properties of the MVSS, the information may not be suitable for labeling.

Table 17 – Modified Vancouver Score Scale (MVSS) at Month 12 (safety analysis set)

	NexoBrid N=77	SOC N=68	Risk Difference 95% CI
Min, Max	0, 10	0, 11.43	
Mean (SD)	3.70 (2.10)	5.08 (3.11)	
LS Means	4.23	5.59	-1.36 (-2.24, -0.48)

SD=Standard deviation; LS = Least squares, CI=Confidence interval
Source: pg. 129 of Study Report 2010 and reviewer analysis.

Table 18 - Modified Vancouver Score Scale (MVSS) at Month 12 by stratification factors(safety analysis set)

Mean (SD)	NexoBrid N=77	SOC N=68
Center Group		
Non-surgical	N=14 4.18 (1.50)	N=10 6.10 (2.87)
Mixed	N=14 3.83 (2.75)	N=15 7.54 (2.40)
Surgical	N=14 3.26 (1.85)	N=14 4.65 (2.63)
West	N=17 2.57 (2.47)	N=19 2.88 (3.01)
East	N=18 4.63 (1.17)	N=10 5.21 (2.31)
Number of TWs		
1	N=42 3.76 (2.34)	N=31 4.96 (3.53)
2	N=20 3.25 (1.58)	N=27 5.16 (2.80)
≥3	N=15 4.13 (2.03)	N=10 5.22 (2.76)
TW Depth		
All DPT	N=35 3.82 (2.03)	N=31 5.46 (2.68)
Mixed or All FT	N=42 3.60 (2.18)	N=37 4.75 (3.43)

SD=Standard deviation
Source: reviewer analysis.

8.1.3. Study MW2004-11-02

Trial Design

Study MW2004-11-02 (2004) is a randomized, open-label, SOC-controlled study to evaluate the efficacy and safety of NexoBrid in subjects with thermal burns. Subjects were enrolled from 2006 to 2010. Study 2004 was designed primarily with input from the European Medicines Agency (EMA). Study 2004 is reviewed as a supportive study to the primary Study 2010.

Study 2004 enrolled subjects 4 to 55 years of age and older hospitalized with thermal burns caused by fire/flame, scalds, or contact. Subjects were to have 5-30% TBSA of DPT or FT wounds, with at least one DPT and/or FT wound ≥2% TBSA. At least 50% of the DPT and/or FT

burn wound area is to be intended for surgical debridement. Total burn wound area is to be ≤30% TBSA. All TWs were treated per the randomized treatment arm.

The first subject at each site was designated as a training subject and treated with NexoBrid. Subsequently enrolled subjects were randomized to NexoBrid or SOC in a 1:1 ratio. Randomization was stratified by %TBSA (≤15% vs. >15%) within each site. No blinding procedures were implemented; the study was fully open-label. All DPT and FT wounds were treated with randomized treatment. Following debridement, subjects were followed weekly for wound closure. After wound closure, subjects were followed for 3 months. If a subject had >15% TBSA burn area, NexoBrid was applied in two separate sessions. In case of partial debridement after the first NexoBrid application, treatment could be repeated no later than 48 hours after the first debridement.

Study Endpoints

The co-primary efficacy endpoints are (1) the percent treated wound excised (by tangential/minor/ Versajet excision) or dermabraded, in first surgery and (2) the percent treated wound autografted for deep partial wounds. Although the protocol originally intended for the excision endpoint to be evaluated in all treated wounds and the autografting endpoint to be evaluated on DPT wounds, based on recommendations from EMA in 2008, the applicant modified the analysis to exclude wounds that were entirely full thickness or have full thickness areas, so that comparable populations would be evaluated for both primary endpoints. The excision endpoint in all treated wound was evaluated as a secondary endpoint. The applicant states that full thickness wounds generally require grafting due to lack of dermal remnants, so the exclusion of FT wounds from the grafting endpoint would exclude wounds expected to need grafting regardless of treatment.

The secondary endpoints were

- Percent treated wound excised (by tangential/minor/Versajet excision) or dermabraded, in first surgery for all wounds
- Time to complete wound closure
- Time to eschar removal (defined as ≥90% eschar removed)
- Blood loss (change in hemoglobin and hematocrit from pre- to post-treatment assessments)

This review will not evaluate the secondary endpoints of time to eschar removal and blood loss as these endpoints are not needed to support the results for Study 2010 and they were not included in the efficacy hierarchy.

Statistical Analysis Plan

The Intent-to-Treat (ITT) population included all randomized subjects. The modified ITT (mITT) population included all randomized subjects with at least one wound that was entirely DPT, as

evaluated in the pre-debridement assessment. The co-primary endpoints (percent treated wound excised and percent treated wound autografted) were evaluated in the mITT population using a per-wound analysis. The secondary endpoints were evaluated in the ITT population. Percent treated wound excised (all subjects) was conducted per wound. Time to wound closure, time to eschar removal, and blood loss were conducted per subject.

The percent treated wound excised (DPT wounds), percent treated wound autografted (DPT wounds), and percent treated wound excised (all wounds) endpoints were included in the multiplicity-controlled hierarchy and were analyzed in the order listed. The other secondary endpoints were not included in the hierarchy.

The co-primary endpoints of percent wound excised and percent wound autografted and the secondary endpoint of percent wound excised (all wounds) are analyzed on the wound level. The analysis method was repeated measures ANOVA with terms for treatment, and baseline %TBSA stratum level with subject as a random effect. The compound symmetric variance structure was used. For the ANOVA analyses, the normality assumption was tested using the Shapiro-Wilk test on the residuals. The statistical analysis plan (SAP) stated that if the "model assumption fails, appropriate transform (such as square-root transform or log transform on the analyzed variables will be used instead" (pg 23 of the SAP). However, the SAP does not specify criteria for determining whether the "model assumption failed" or how an "appropriate transform" would be selected. The applicant used the square-root transform on the dependent variable for these analyses, but did not provide a justification for this decision.

The time to event endpoints were analyzed with a log-rank test with the medians estimated with the Kaplan-Meier method. Hazard ratios were estimated with a Cox regression model.

Multiplicity was controlled for the two co-primary endpoints (percent wound excised and percent wound autografted in DPT wounds) and the first secondary endpoint of percent wound excised in all wounds, by analyzing these three endpoints sequentially in the order listed.

Missing values in wound measurements was imputed using LOCF.

An interim analysis was planned after 152 subjects completed the study. The interim analysis had early stopping rules for futility and efficacy. The rules were:

a. Stop the study for efficacy if the p-value for %wound excised < 0.02 and the p-value for %wound autografted < 0.02;
b. Stop the study for futility if both p-values for %wound excised and for %wound autografted >0.5;
c. Otherwise the study will be continued.

Critical values adjusted with the Fleming, Harrington, and O'Brien[23] boundary were used for the co-primary endpoints using critical values of 2.33 (two-sided significance level=0.02) at the interim analysis and critical values of 2.045 (two-sided significance level=0.0408) at the final analysis for each endpoint.

The study was stopped after the interim analysis and 156 subjects were randomized into the study.

Protocol Amendments

Subjects were initially enrolled under Amendment 1 of the protocol. The protocol was amended several times after subject enrollment began in February 2006. The key study elements that were modified in these amendments are as follows. Originally the protocol had the following endpoints:

- Primary: percent treated wound excised (tangential and/or minor excision) in first surgery. Secondary: time to complete wound closure and percent treated wound autografted.
  Amendment 2 (dated 1/7/2008) added additional permitted surgical debridement methods (Versajet and dermabrasion). Amendment 3 (dated 10/2/2008) reorganized the endpoints to include co-primary endpoints and add an additional secondary endpoint (changes italicized):
- Co-primary: percent treated wound excised (by tangential/ minor/*Versajet/ dermabrasion*) in first surgery *and percent treated wound autografted of DPT wounds*. Secondary: time to complete wound closure, time to eschar removal, and *blood loss*. Amendment 4 dated 5/15/2009 modified the population included in the analysis of the percent treated wound excised primary endpoint to include only DPT wounds so that both co-primary endpoints would be analyzed on DPT wounds. Percent treated wound excised in all treated wounds was added as a key secondary endpoint within the multiplicity control hierarchy.

8.1.4. Study Results (Study 2004)

Patient Disposition

Study 2004 enrolled 182 subjects. The first subject enrolled at each site was a training subject and was treated with NexoBrid. The study enrolled 26 training subjects and 156 subjects who were randomized to either NexoBrid or SOC. Approximately 21% of subjects discontinued the study prior to complete wound closure. The most common reasons for study discontinuation

[23] Controlled Clinical Trials 1984; 5:348-61

were loss to follow-up and non-compliance with the protocol. There was one death on each treatment arm. See Table 19.

Table 19 – Disposition of Subjects in Study 2004

	Training (NexoBrid)	NexoBrid	SOC
Enrolled subjects	26	75	81
Completed study	17 (65%)	64 (85%)	63 (78%)
Reasons for premature termination			
Randomized, but did not receive study drug[a]	--	1 (1%)	--
Lost to follow-up	5 (19%)	6 (8%)	9 (11%)
Non-compliance with protocol	4 (15%)	3 (4%)	7 (9%)
Death	--	1 (1%)	1 (1%)
Other	--	--	1 (1%)

[a] One subject randomized to NexoBrid was not treated because the Medical Director determined that the subject's %TBSA was >30%.
Source: pg. 76 of the study report for Study 2004 and reviewer analysis.

Protocol Violations/Deviations

Two subjects were not treated according to the protocol. One subject randomized to NexoBrid was not treated because the Medical Director determined the subject's %TBSA was >30%. This subject was discontinued from the study without treatment. One subject was randomized to SOC, but the investigator believed that "the subject's poor condition would not allow him to survive SOC treatment (surgical excisions or lengthy non-surgical treatments) but that early eschar removal could save his life." (pg 77 of the Study Report for Study 2004). This subject completed the study.

Demographic Characteristics

The baseline demographics were generally balanced across treatment arms. The mean age was approximately 30 years and the age range was 4 to 55 years. Approximately 20% of subjects were <18 years of age. Note that the study report describes age group categories as ≤18 years and >18 years, but the categories actually correspond to <18 years and ≥18 years (i.e. 18-year-olds are included in the adult group). A higher proportion of subjects were male than female. The majority of subjects were White, followed by Black, Asian, and other. The study was conducted outside the US in Europe, Australia, Brazil, India, and Israel. See Table 20.

Table 20 – Demographic Characteristics in Study 2004 (ITT)

	NexoBrid N=75	SOC N=81
Age (years)		

Mean	31.6	29.3
Range	4 - 55	5 – 55
4-17 years	15 (20%)	16 (20%)
18-55 years	60 (80%)	65 (80%)
Gender		
Female	21 (28%)	20 (25%)
Male	54 (72%)	61 (75%)
Race		
White	63 (84%)	65 (80%)
Black	4 (5%)	5 (6%)
Asian	5 (7%)	3 (4%)
Other	3 (4%)	8 (10%)
Region		
Western Europe[a]	31 (41%)	36 (44%)
Eastern Europe[b]	17 (23%)	18 (22%)
Brazil	12 (16%)	15 (19%)
Rest of World[c]	15 (20%)	12 (15%)

[a] Germany, France, United Kingdom
[b] Poland, Romania, Slovakia
[c] Australia, India, Israel
Percentages may not sum to 100% due to rounding
Source: pg. 81 of Study Report 2004 and reviewer analysis.

Other Baseline Characteristics

The burn wound characteristics of %TBSA, number of target wounds, and whether wounds had a DPT component were generally consistent across treatment arms. See Table 21.

Table 21 – Wound Characteristics in Study 2004

	NexoBrid N=75	SOC N=81
Total burn area[a], %TBSA		
≤15%	48 (64%)	52 (64%)
>15%	27 (36%)	29 (36%)
Mean (SD)	11.3 (4.9)	11.0 (5.4)
Number of TWs		
1	21 (28%)	29 (36%)
2	31 (41%)	26 (32%)
≥3	23 (31%)	26 (32%)
TW Depth		
DPT component	49 (65%)	48 (59%)
No DPT component	26 (35%)	33 (41%)

SD=Standard deviation
Percentages may not sum to 100% due to rounding

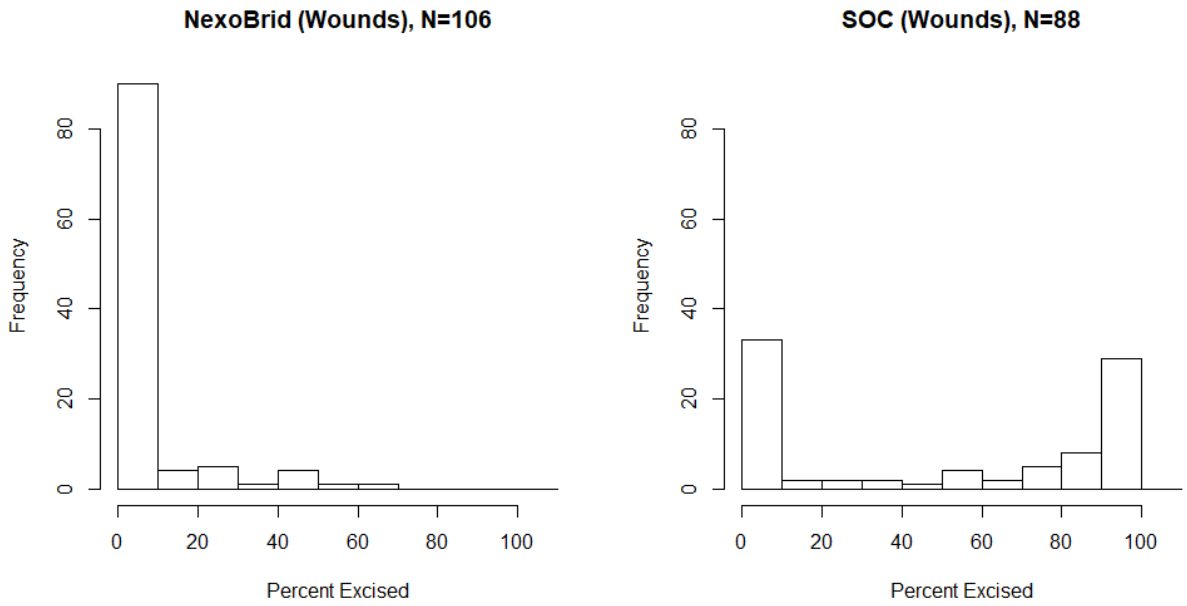
Source: reviewer analysis.

Efficacy Results – Primary Endpoints

The co-primary efficacy endpoints are the percent treated wound excised (by tangential/minor/ Versajet excision) or dermabraded, in first surgery and the percent treated wound autografted of deep partial wounds in randomized subjects with at least one wound that was entirely DPT. The co-primary endpoints are analyzed on the wound level and only for DPT wounds. The analysis method was repeated measures ANOVA with terms for treatment, and baseline %TBSA stratum level with subject as a random effect. The applicant used the square-root transform on the response because of the results of the Shapiro-Wilk test on the residuals did not support the normality assumption. Because the study was stopped after an interim analysis for efficacy, the p-values for the co-primary endpoints were compared to α=0.02. The applicant also presented results for the incidence of excision and autografting (by wound), even though these analyses were not prespecified in the protocol. The study report notes that incidence rates were analyzed using the chi-square test. The applicant's analyses for the incidence rates conducted on the wound level do not take into account the correlation between wounds within a subject. All subjects included in the mITT population (DPT wounds) had observed data for the excision and autografting endpoints. All subjects except for one subject who was randomized to NexoBrid but not treated, had observed data for the excision and autografting endpoints.

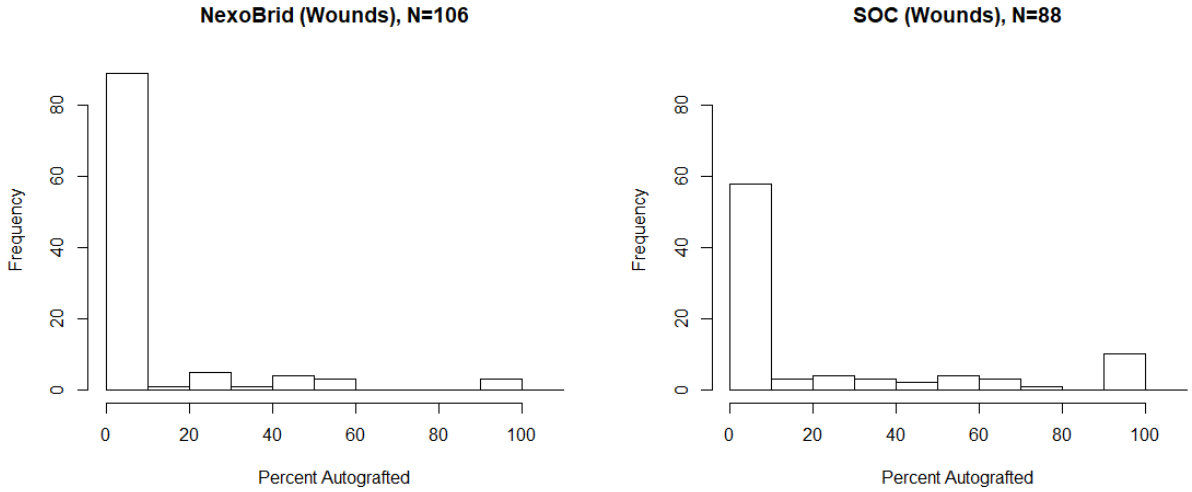
Histograms by treatment group are presented for the percent wound area excised in Figure 5 – Percent Wound Area ExcisedFigure 5 and for the percent wound area autografted in Figure 6. For both endpoints, subjects on the NexoBrid arm are clustered around 0% (no or small areas excised or autografted) with a smaller proportion of subjects with larger wound areas excised or autografted. Subjects on the SOC arm have clusters near 0 and 100% with a smaller of proportion of subjects with excision or autografted areas in between. The extreme shapes of the distributions lead to challenges with interpreting the means and mean differences. The applicant analyzed the square root of the percent wound area excised because of the non-normality of the original scale distribution. However, transformations such as the square root transform would not deal with non-normality due to bimodality or extreme skewness. In addition, because the study is open-label, the calculation of the size of the wound area excised might be more subject to bias based on knowledge of the treatment than whether or not excision was needed. Thus, although the protocol prespecified percent wound area excised as a co-primary endpoint, incidence rates per subject may be more interpretable when comparing the need for excision. Both analyses based on the percent area and incidence rates are presented below for the co-primary endpoints.

Figure 5 – Percent Wound Area Excised



Source: reviewer analysis

Figure 6 – Percent Wound Area Autografted



Source: reviewer analysis

The results of the primary endpoint (percent wound area excised in DPT wounds) and the key secondary endpoint (percent wound area excised in all wounds) are presented in Table 22. Both the confidence intervals based on a model using the dependent variable on the original scale

and a model using the square-root transform (with the bounds transformed back to the original scale) are presented. The applicant presents p-values based on the square-root transform in the study report. The estimates based on the square-root transform differ from the estimates on the original scale, though the conclusions are the same (smaller areas were excised on the NexoBrid arm). Because of the sensitivity of the least squares estimates to the transformation and the skewed and bimodal shapes of the distribution, it is challenging to interpret the results for the percent wound area excised endpoint. Table 22 also presents the results for the key secondary endpoint of percent wound area excised on all wounds (DPT+FT). The results for the DPT wounds and all wounds are similar.

Table 22 –Percent Wound Area Excised (Per Wound Analysis)

	NexoBrid	SOC	p-value	Difference 95% CI
mITT (DPT wounds)	N=49 106 wounds	N=48 88 wounds		
Mean (SD)	5.5 (14.6)	52.0 (44.5)	<0.0001[a] <0.0001[b]	-20.3[a] (-32.3, -11.0) -43.4[b] (-54.0, -32.9)
ITT (All wounds)	N=75 163 wounds	N=81 170 wounds		
Mean (SD)	13.1 (26.9)	56.7 (43.3)	<0.0001[a] <0.0001[b]	-15.6[a] (-24.6, -8.7) -38.5[b] (-48.8, -29.2)

[a] Based on least squares means using the square root transform on the dependent variable (repeated measures ANOVA with terms for treatment, baseline %TBSA stratum, and site)
[b] Based on least squares means using the data on the original scale (repeated measures ANOVA with terms for treatment, baseline %TBSA stratum, and site)
Source: pg. 87 of Study Report 2004 and reviewer analysis.

However, the size of the excision may be less important than whether a subject needed to undergo excision at all. In addition, whether or not excision occurred may be more relevant on the subject level rather than on the wound level. The incidences of excision for the mITT and ITT population at the wound and subject level are presented in Table 23. The applicant presented the per wound analyses in the study report. Fewer subjects needed excision on the NexoBrid arm than the SOC arm.

Table 23 –Incidence of Excision

	NexoBrid	SOC	p-value	Difference (95% CI)
	106 wounds	88 wounds		
mITT (DPT wounds) – Per wound	16/106 (15.1%)	55/88 (62.5%)	<0.0001	-47.4% (-59.1%, -34.3%)
	N=49	N=48		

mITT (DPT wounds) – Per subject	11/49 (22.5%)	37/48 (77.1%)	<0.0001	-54.6% (-71.3%, -38.0%)
	163 wounds	170 wounds		
ITT (All wounds) – Per wound	40/163 (24.5%)	119/170 (70.0%)	<0.0001	-45.5% (-55.0%, 35.9%)
	N=75	N=81		
ITT (All wounds) – Per subject	24/75 (32.0%)	65/81 (80.3%)	<0.0001	-48.3% (-61.9%, 34.6%)

Analyses based on the chi-square test. The per wound analyses do not take correlations within subjects into account.
Source: pg. 87 of Study Report 2004 and reviewer analysis.

The second co-primary endpoint was the percent treated wound autografted of deep partial wounds in subjects with at least one wound that was entirely DPT. The endpoint was analyzed in the same way as the percent wound excised. Similarly to the percent wound excised analysis, the least squares estimates for the treatment difference and confidence interval are sensitive to the transformation used on the dependent variable. See Table 24. In addition, this reviewer could not replicate the applicant's p-value. When applying the transformation and model terms described in the study report and statistical analysis plan, this reviewer got a p-value of 0.0357 rather than the applicant's 0.0054. The applicant did not provide statistical code for calculating the p-value. The applicant did not compute confidence intervals. The reviewer's analysis would not lead to the conclusion of statistically significant results if the p-value were compared with 0.02 due to the interim analysis. The point estimates for the per subject incidence of autografting on DPT wounds are similar to the estimates for the per wound analysis, but the p-value is larger due to the smaller sample size. In summary, while the applicant reported a statistically significant result for the protocol-specified endpoint of percent treated wound autografted on the wound level, this reviewer could not replicate the significant p-value and the percent wound autografted endpoint may be difficult to interpret. The incidence of autografting endpoint does not demonstrate a clear effect, as the applicant's specific methodology was not clear, the per wound analysis does not take into account within-subject correlations, and the per subject analysis does not support an efficacy finding.

Table 24 –Percent Treated Wound Autografted and Incidence of Autografting (mITT – DPT wounds)

	NexoBrid	SOC	p-value	Difference 95% CI
mITT (DPT wounds) – Per wound	N=49 106 wounds	N=48 88 wounds		
Mean (SD)	8.4 (21.3)	21.5 (34.8)	0.0357[a] 0.0250	-1.5[a] (-5.7, -0.007) -11.8[b] (-22.0, -1.5)
Incidence	19/106 (17.9%)	30/88 (34.1%)	0.0099	-16.2% (-28.5%, -3.9%)
mITT (DPT wounds) – Per subject	N-49	N=48		
Incidence	14/49 (28.6%)	22/48 (45.8%)	0.0785	-17.3% (-36.2%, 1.7%)

[a] Based on least squares means using the square root transform on the dependent variable (repeated measures ANOVA with terms for treatment, baseline %TBSA stratum, and site). Note applicant reported a p-value of 0.0054 for this analysis.

[b] Based on least squares means using the data on the original scale (repeated measures ANOVA with terms for treatment, baseline %TBSA stratum, and site)
Source: pg. 87 of Study Report 2004 and reviewer analysis.

Data Quality and Integrity

Because Study 2004 is a supportive study, no clinical inspections were conducted for Study 2004. Study 2004 was a fully open-label study with no blinding due to the significant operational differences between NexoBrid and SOC treatment. Endpoints should be evaluated with consideration to the lack of blinding.

Efficacy Results – Secondary and other relevant endpoints

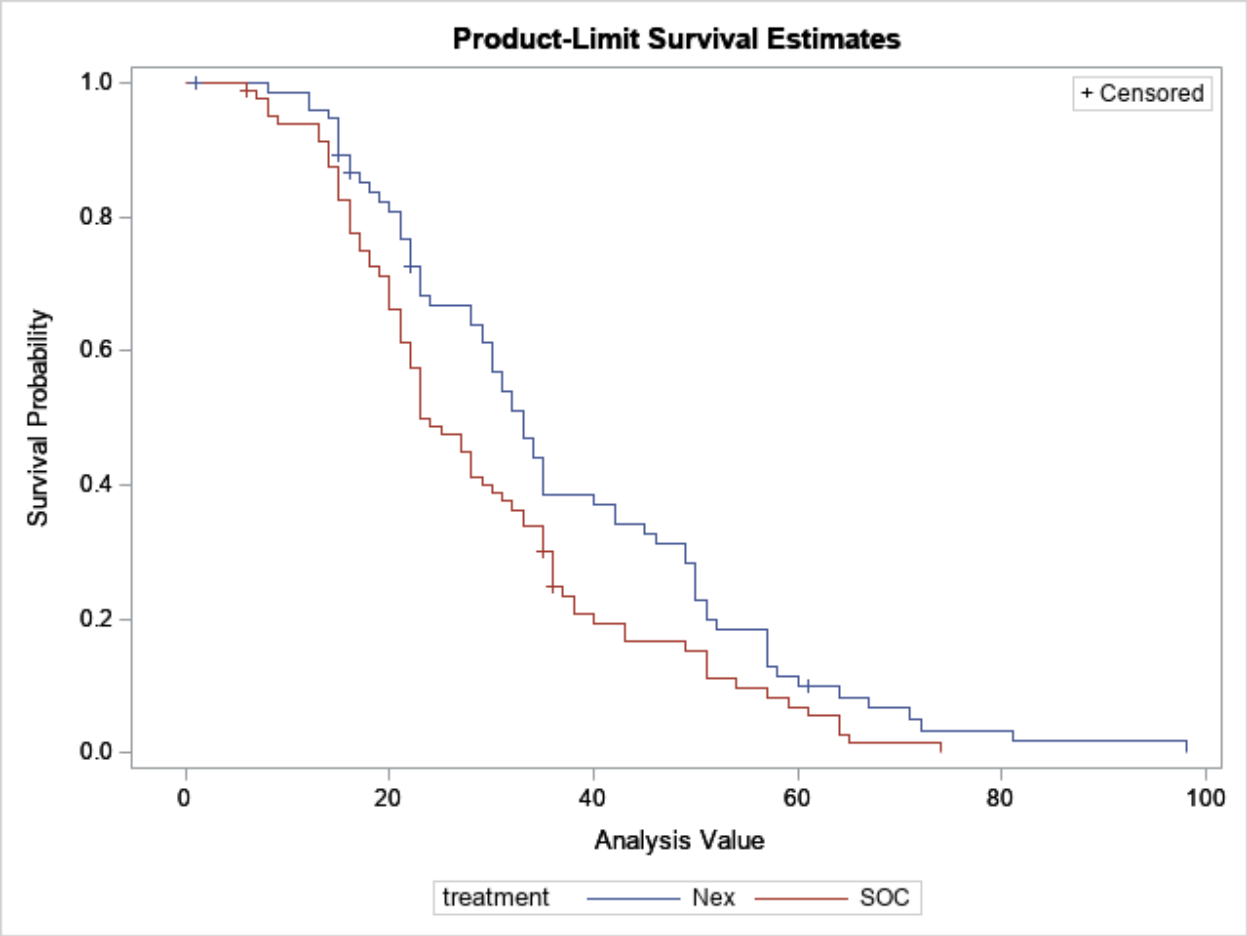
Time to wound closure from the time of informed consent was assessed as a secondary endpoint. The applicant presented results using both complete case and ITT results. The mean and median time to wound closure were presented using a complete case analysis of subjects who remained in the study until all wounds were closed. However, the ITT population (all randomized subjects) was used to calculate the p-value using the log-rank test, censoring subjects with missing data. Time to wound closure (last wound per subject) are summarized in Table 25 and Figure 7. For the ITT analysis, the median time to wound closure of the last wound was 9 days longer on NexoBrid than SOC.

Table 25 – Time to Wound Closure by Subject (Days)

	NexoBrid N=75	SOC N=81
Complete case analysis	N=70	N-78
Mean (SD)	36.2 (18.5)	28.8 (15.6)
Median	32.5	23.0
Range	8-98	6-74
ITT analysis	N=75	N=81
Median (days) 95% Confidence interval Censored observations Log-rank p-value	33 (29, 35) 5 (7%) 0.0187	24 (21, 30) 3 (4%)

Source: pg. 93 of Study Report 2004 and reviewer analysis.

Figure 7 – Time to Wound Closure by Subject



Source: reviewer analysis

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

Study 2010 is the key study supporting the efficacy of NexoBrid, while Study 2004 is supportive. Study 2010 was designed with FDA input after the completion of Study 2004. The study included a vehicle arm for assessing eschar removal and had provisions for using blinded assessors for assessing wound closure and scar assessment, even if these processes were not always followed correctly. Study 2004 was completely open-label and thus it is difficult to assess the impact of bias. In addition, the co-primary endpoints in Study 2004 were based on

assessments of the mean percent of wound excised or autografted, which may be difficult to interpret. In order to support the results of Study 2010, estimates from Study 2004 based on incidence of excision may be more interpretable.

The primary endpoint in Study 2010 was the incidence of eschar removal (≥95%) at the end of the topical treatment soaking period for NexoBrid versus gel vehicle. The key secondary endpoints were incidence of excision for eschar removal, time to eschar removal, and blood loss for NexoBrid versus SOC. The co-primary endpoints in Study 2004 were the percent treated wound excised (by tangential/minor/Versajet excision) or dermabraded, in first surgery and the percent treated wound autografted of deep partial wounds in randomized subjects with at least one wound that was entirely DPT. Among the endpoints comparing NexoBrid to SOC, incidence of excision was evaluated in both studies and demonstrated an effect in each study. The incidence of excision for eschar removal in Studies 2010 and 2004 are presented in Table 26. Although the patient populations and other details of the studies and analyses differed between the two studies, both studies demonstrated an effect on the reduction in incidence of excision for eschar removal for NexoBrid relative to standard of care.

Table 26 – Incidence of Excision for Eschar Removal

	NexoBrid	SOC	Risk Difference 95% CI
Study 2010[a]	3/75 (4.0%)	54/75 (72.0%)	-67.4% (-78.2%, -56.6%)
Study 2004 (DPT wounds)[b]	11/49 (22.5%)	37/48 (77.1%)	-54.6% (-71.3%, -38.0%)
Study 2004 (All wounds)[a]	24/75 (32.0%)	65/81 (80.3%)	-48.3% (-61.9%, 34.6%)

[a] Full Analysis Set (all randomized). Missing data imputed as having an excision.
[b] MITT (DPT wounds)

Secondary and Other Endpoints

Another key consideration is whether NexoBrid extends the time to wound closure relative to standard of care. Wound closure times were comparable in Study 2010 but were slightly longer for subjects treated with NexoBrid in Study 2004. The reasons for the increased time to wound closure for NexoBrid in Study 2004 are not clear. While the times to wound closure are similar across the two studies on the NexoBrid arms, the results for the SOC arms differed across studies and the amount of missing data was much greater in Study 2010. See Table 27. Other secondary endpoints were not consistently evaluated in the two studies and thus are not summarized here.

Table 27 – Time to Wound Closure (per subject)

	NexoBrid	SOC
Study 2010	N=75	N=75
Median (days)	31	36
95% Confidence interval	(23, 36)	(27, 41)

Censored observations	21 (28%)	30 (40%)
Study 2004	N=75	N=81
Median (days)	33	24
95% Confidence interval	(29, 35)	(21, 30)
Censored observations	5 (7%)	3 (4%)

Subpopulations

The incidence of excision rates by demographic subgroups for NexoBrid and SOC are presented in Table 28. The response rates were generally consistent across the demographic subgroups.

Table 28 – Subgroup Analyses for the Incidence of Excision (by Subject) by Demographic Subgroups

	Study 2010		Study 2004	
	NexoBrid N=75	SOC N=75	NexoBrid N=75	SOC N=81
Age (years)				
4-17	--	--	4/15 (27.7%)	13/16 (81.3%)
18-64 years	2/69 (2.9%)	51/69 (73.9%)	20/60 (33.3%)	52/65 (80.0%)
65+ years	1/6 (16.7%)	3/6 (50.0%)	--	--
Gender				
Female	1/26 (3.9%)	11/16 (68.8%)	10/21 (47.6%)	15/20 (75.0%)
Male	2/49 (4.1%)	43/59 (72.9%)	14/54 (25.9%)	50/61 (82.0%)
Race				
Asian	0/1 (0%)	1/1 (100%)	0/5 (0%)	3/3 (100%)
Black or African-American	0/8 (0%)	11/13 (84.6%)	1/4 (25.0%)	3/5 (60.0%)
White	3/61 (4.9%)	41/59 (69.5%)	23/63 (36.5%)	52/65 (80.0%)
Other	0/5 (0%)	1/2 (50.0%)	0/3 (0%)	7/8 (87.5%)
Ethnicity				
Not Hispanic or Latino	2/61 (3.3%)	51/67 (76.1%)	--	--
Hispanic or Latino	1/14 (7.1%)	3/8 (37.5%)	--	--
Region				
US	2/42 (4.8%)	35/42 (83.3%)	--	--
Rest of World	1/33 (3.0%)	19/33 (57.6%)	24/75 (32.0%)	65/81 (80.3%)

Source: reviewer analysis

8.1.6. Review of Safety

8.1.7. Safety Review Approach

The clinical development program consisted of 8 studies (6 Phase 2 studies and 2 Phase 3

studies) in which 467 subjects were treated with NexoBrid, 454 of whom were treated at the 2 grams (g) dose, the dose that the Applicant proposes in labeling.

Note: Per the protocol for study 2010, 2 g or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle (ratio of 1:10) , respectively to obtain sterile NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2 g NexoBrid sterile powder mixed with 20g sterile Gel Vehicle per 1% of TBSA (~ surface of an adult palm) for 4 hours (or 5 g NexoBrid sterile powder mixed with 50g sterile Gel Vehicle per 2.5% of TBSA).

The Applicant defined the safety analysis set as all subjects who received NexoBrid, SOC, or vehicle treatment in the 6 clinical studies.

The Applicant categorized 7 of the 8 studies as "legacy" studies. The legacy studies supported the Marketing Authorization Approval that was submitted to the European Medicines Agency (EMA). The EMA granted marketing authorization on 12/18/2012. Study 2004 is the Phase 3 study that the Applicant submitted to the EMA, and it is one of the Phase 3 studies that the Applicant is relying on to support the BLA.

The main Phase 3 study is MW2010-03-02 (2010 or DETECT). This is the protocol that was the subject of considerable discussion with the Agency (See Section 3.2). Study 2010 is a 24-month study and was ongoing at the time of submission of the BLA. The Applicant included data through 12-months of follow-up in the BLA. The Applicant anticipated the database lock for the 24-month follow-up period to be September 2020.

For the safety analyses, the Applicant included pooled data from 6 of the 8 studies in 2 cohorts:

- Cohort 1: the 2 Phase 3 studies (2010 and 2004) and 4 Phase 2 studies (2001-10-03, 2002-04-01, 2005-10-05, and 2008-09-03)

- Cohort 2: both Phase 3 studies, 2010 and 2004. The Applicant designated Cohort 2 as the primary safety data; it is a subset of Cohort 1.

The Applicant did not include data from the remaining 2 studies in the pooled analyses:

- Study 2012-01-02: No subjects received treatment in this study. It was a follow-up study for long-term assessment of scar and quality of life for subjects enrolled in study 2004.

- Study 35-98-910: This was a retrospective collection of data from hospital records of burn patients.

The Applicant defined 2 study periods in the safety analyses:

- Acute Phase: up to 3 months following wound closure.

- Longer-term: up to 12 months following wound closure and evaluated only in study 2010.

To account for differing durations of follow-up in different studies, the Applicant presented common (>1%) exposure-adjusted incidence rates (EAIR) (in patient-years) by treatment group (Module 5.3.5.3).

This safety review will focus on the primary safety data i.e., Cohort 2, which was the focus of the discussion of safety analyses in the Applicant's submission. Additionally, discussion in the safety review pertains to the Acute Phase, unless otherwise specified, with the following exceptions: deaths and serious adverse events. Generally, the safety review will only discuss comparisons between the NexoBrid and SOC groups for the following reason: Of the 2 Phase 3 studies, only 2010 included a vehicle arm. Therefore, interpretation of the vehicle comparisons from the combined studies is limited because only one study included vehicle, and the number of subjects in the vehicle arm was small relative, to the numbers of subjects in the NexoBrid and SOC arms when the 2 Phase 3 studies are combined.

8.1.8. Review of the Safety Database

Overall Exposure

A total of 454 received NexoBrid treatment at the 2 grams (g) dose, the dose that the Applicant proposes in labeling.

The 2 Phase 3 studies (Cohort 2) provided the primary safety data, with enrollment as follows:

- NexoBrid: n=177
- SOC: n=149
- Gel Vehicle: n= 24

The Applicant intends that NexoBrid may be applied 1 or 2 times to up to (b) (4)% TBSA, for 4 hours per application and that it may be applied to a total of up to (b) (4)% TBSA (in 2 sessions of up to (b) (4) The Applicant intends that NexoBrid be applied at a dose of 2 g NexoBrid per 1% of TBSA. Most subjects in Cohort 2 who were treated with NexoBrid:

- received 1 application of product: 159/177 (90%) and

- had target wounds (TWs) ≤15% TBSA: 158/177 (89%).

The mean (SD) % TBSA of TWs for subjects who received 1 application was 8.7 (4.65) and 13.3 (6.71) for subjects who received 2 applications.

A total of 160 subjects (90%) had exposure data (these data were missing for 17 subjects), and

the mean NexoBrid exposure was 16.6 g. Mean duration of follow-up was ~4 months for subjects in Cohort 2.

Characteristics of the Study Populations Across the Safety Database:

Similar inclusion characteristics of the safety population across the 6 studies included:

- DPT and FT thermal burns caused by fire/flame, scalds or contact
- Total burn area of ≤30% (exceptions: Study 2001-10-03, where total burn area was ≤ 15% and Study 2005-10-05, where total burn area was ≤ 10%).

Similar exclusion characteristics of the safety population across the 6 studies included:

- Smoke inhalation
- History of allergy and/or known sensitivity to pineapples or papain
- Cardiopulmonary disease, severe pre-existing disease which interfered with circulation, immediate life-threating conditions, chronic systemic steroid intake, poorly controlled diabetes
- Treatment of facial, perineal, and/or genital burns with NexoBrid (treatment with NexoBrid for these anatomical locations were not allowed)
- Heavily contaminated burns or pre-existing infections
- Pre-enrollment dressings with silver sulphadiazine (SSD)/silver nitrate (with the exception of Study 2001-10-03)

Baseline demographic and disease characteristics for Cohort 2 are presented in Table 1.

Table 1: Baseline Demographics and Disease Characteristics – Pooled Phase 3 Studies (Cohort 2)*

Analysis Parameter	NexoBrid (N=177)	Standard of Care (N=149)	Placebo Control (Gel Vehicle) (N=24)
Age (years)			
Mean (SD)	36.8 (15.57)	34.6 (15.75)	41.0 (17.65)
Median	36.7	32.1	36.8
Min, Max	4, 76	5, 73	18, 70
Gender, n (%)			
Female	50 (28.2)	33 (22.1)	10 (41.7)
Male	127 (71.8)	116 (77.9)	14 (58.3)
Race, n(%)			
Asian	7 (4.0)	4 (2.7)	0
Black	12 (6.8)	18 (12.1)	3 (12.5)
Caucasian	141 (79.7)	113 (75.8)	20 (83.3)

Middle Eastern	7 (4.0)	4 (2.7)	0
Other	10 (5.6)	10 (6.7)	1 (4.2)

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Analysis Parameter	NexoBrid (N=177)	Standard of Care (N=149)	Placebo Control (Gel Vehicle) (N=24)
Region, n (%)			
US sites	42 (23.7)	39 (26.2)	14 (58.3)
Non-US sites	135 (76.3)	110 (73.8)	10 (41.7)
Etiology, n (%)			
Fire/Flame	111 (62.7)	96 (64.4)	20 (83.3)
Scald	51 (28.8)	39 (26.2)	2 (8.3)
Contact	14 (7.9)	13 (8.7)	2 (8.3)
Other	1 (0.6)	1 (0.7)	0
No. of Target wounds, n (%)			
1	68 (38.4)	60 (40.3)	13 (54.2)
2	61 (34.5)	53 (35.6)	5 (20.8)
≥3	48 (27.1)	36 (24.2)	6 (25.0)
Average No. of TWs			
Mean (SD)	2.0 (1.09)	1.9 (0.98)	1.7 (0.86)
Median	2.0	2.0	1.0
Min, Max	1, 7	1, 6	1, 3
%TBSA of all Wounds			
Mean (SD)	12.0 (6.05)	11.5 (6.39)	8.8 (3.65)
Median	11.0	10.0	8.3
Min, Max	3, 29	3, 30	3, 18
%TBSA of Target Wounds			

Mean (SD)	9.2 (5.07)	8.7 (5.11)	6.4 (3.60)
Median	8.0	7.5	6.3
Min, Max	1, 25	2, 27	2, 18

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Analysis Parameter	NexoBrid (N=177)	Standard of Care (N=149)	Placebo Control (Gel Vehicle) (N=24)
%DPT Area			
Mean (SD)	5.7 (3.73)	4.9 (3.31)	3.6 (1.99)
Median	5.0	4.5	4.0
Min, Max	0, 18	0, 24	0, 7
%SPT Area			
Mean (SD)	1.4 (2.08)	1.7 (2.67)	1.3 (1.88)
Median	0.5	0	0.1
Min, Max	0, 15	0, 13	0, 7
%FT Area			
Mean (SD)	2.1 (3.25)	2.1 (3.74)	1.5 (2.06)
Median	1.0	1.0	0.8
Min, Max	0, 20	0, 27	0, 8

*Source: Table 15 of Summary of Clinical Safety
DPT = deep partial thickness (2nd degree); FT = full thickness (3rd degree); Max = maximum; Min = minimum; SD = standard deviation; SDS = standard deviation score; SPT = superficial partial-thickness (2nd degree); TBSA = total burn surface area; TW = target wound; US = United States

Adequacy of the safety database:

[Insert text here]

The safety database was adequate in size and extent of drug exposures to permit an assessment of the safety of NexoBrid in the target population of adults with DPT and/or FT burns. However, the safety database was not adequate to support the Applicant's proposed dosing regimen, as discussed in Sections 6 and 8.2.11.

8.1.9. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Reasonably applicable clinical evaluations were conducted to assess the safety of NexoBrid, and those evaluations were generally performed at appropriate time(s) during the trial(s). However, see Section 4.1 regarding significant concerns regarding study conduct and data reliability. Those concerns largely pertain to efficacy outcomes, although wound closure was a safety endpoint and is discussed in Section 8.1.2. The OSI audit did not raise specific concerns regarding the safety data.

Categorization of Adverse Events

The Applicant used Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 to align all treatment-emergent adverse events (TEAEs) from the 5 legacy studies included in the pooled data analyses (Cohort 1) with study 2010, the most recently completed study.

The Applicant defined "all adverse events (AEs)" as events that occurred from the time of informed consent through 3 months post wound closure except in Study 2005-10-05 where the timeframe was through 1 month post wound closure.

The investigators determined whether a treatment-emergent adverse event (TEAE) was a general AE or local AE (not target-wound-related and target-wound-related, respectively). The Applicant summarized these categories of AEs separately.
The Applicant summarized TEAEs according to the following categories:

- time of onset:
  - before treatment
  - during the treatment session or within the first 24 hours of treatment
  - during the first week after treatment
  - during Week 2 to Week 4 after treatment
  - during Week 5 to Week 8 after treatment
  - more than 8 weeks after treatment.
- system organ class (SOC)
- preferred term (PT)

Routine Clinical Tests

Laboratory testing included routine chemistry and hematology evaluations. Post-treatment urinalyses were done only in study 2010.

Laboratory specimens were collected at different time points in the clinical development program. In the Phase 3 studies, labs were collected as below:

- study 2010: 4 hours after the end of the procedure for SOC and 4 hours after removal of the topical agent for NexoBrid/Gel Vehicle). In NexoBrid, this referred to the first and second application.

- study 2004: 24 hours after start of debridement n study 2004.

Because of the differences in the collection time points, the Applicant presented test results and analyses at a post-baseline, integrated time point, defined as up to 24 hours after start of treatment (for NexoBrid/Gel this referred to first application and for SOC this referred to post surgery).

The Applicant summarized results using descriptive statistics and categorized results as " abnormal (low)", "normal", and "abnormal (high)" based on the reference normal ranges used in each individual study. For shifts from baseline to abnormal, the Applicant considered the worst outcome in both directions i.e., low/high. A subject could be counted in both categories, if that subject experienced shifts in both directions. The Applicant defined Potentially Clinically Significant (PCS) criteria according to normal ranges for individual studies that provided those ranges.

The Applicant summarized laboratory test results and changes from baseline to the postbaseline integrated time point defined above using descriptive statistics. Laboratory values were categorized as "abnormal (low)", "normal", and "abnormal (high)" based on the reference normal ranges used in each individual study (included in each study report appendix). The Applicant did not include studies that did not have normal ranges provided in the analyses (studies 2001-10-03 and 2008-09-03).

As patients with significant burn injuries might have had abnormal laboratory parameters prior to study treatment, the Applicant considered the change from baseline, as well as the absolute result.

8.1.10. Safety Results

Deaths

The Applicant reported 8 deaths in the clinical development program (cutoff date: (b) (6) 7 in subjects who received NexoBrid and 1 in a subject who received SOC. Seven of the deaths occurred in the NexoBrid group. Six of the deaths occurred in legacy studies, and 2 deaths occurred in study 2010. The Applicant reported no additional deaths in the 4-month Safety Update. A total of 7 deaths occurred during the Acute Period i.e., within 3 months post-wound closure.

Table 2: List of All Deaths that Occurred as of (b) (6)

Patient ID/ Study/ Treatment	Gender/Age	TBSA% of All Wounds TBSA% of All Target Wounds	Preferred Term/ Reported Term	Study Day of Death
(b) (6) DETECT (2010-03-02) *NexoBrid*	Female/ 18 years old	21.1% (all TWs)	Acute respiratory failure/acute respiratory failure	Day 4
(b) (6) DETECT (2010-03-02) *NexoBrid*	Male/ 67 years old	0.5% and 3.5% (all TWs)	Unknown cause	Day 269
(b) (6) (b) (6) / (2004-11-02) *NexoBrid*	Male/ 51 years old	17% (all TWs)	Cardiac arrest/cardiac arrest	Day 21
(b) (6) (b) (6) / (2004-11-02) *Standard of Care*	Male/ 24 years old	11% (all TWs)	Homicide/Murdered	Day 94
(b) (6) (b) (6) / (2002-04-01) *NexoBrid*	Male/ 69 years old	4% (all TWs)	Multiple organ dysfunction failure/Multiorgan failure	Day 70
(b) (6) (b) (6) / (2002-04-01) *NexoBrid*	Male/ 46years old	10% (all TWs)	Respiratory failure/severe respiratory failure with respiratory acidosis	Day 15
(b) (6) (b) (6) / (2002-04-01) *NexoBrid*	Male/ 41years old	12.5% (all TWs)	Aspiration/Aspiration of vomitus into respiratory tract	Day 3
(b) (6) (b) (6) / (2002-04-01) *NexoBrid*	Female/ 21 years old	7% (all TWs)	Tachypnoea/tachypnea	Day 11

*Source: Table 32 Summary of Clinical Safety

Additional information and discussion of the deaths is found in Appendix 19.6.

Serious Adverse Events

The overall percentage of subjects who experienced SAEs in the Phase 3 studies was slighty higher in the NexoBrid arm compared to SOC. There were only single reports of most SAEs. Sepsis and "Wound infection bacterial" were the only 2 SAEs that were reported in more than

one NexoBrid-treated subject, and there were more reports in the NexoBrid arm (5 reports) as compared to SOC (1 report).

Table 3: Summary of Serious TEAEs by System Organ Class and Preferred Term – Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid (N=177, PY=61.89)	Standard of Care (N=149, PY=50.22)	Placebo Control (Gel Vehicle) (N=24, PY=8.62)
System Organ Class Preferred Term	Patients n (%)	Patients n (%)	Patients n (%)
Any Serious TEAEs	15 (8.5)	10 (6.7)	3 (12.5)
Blood and lymphatic system disorders	1 (0.6)	0	0
Disseminated intravascular coagulation	1 (0.6)	0	0
Cardiac disorders	1 (0.6)	0	0
Cardiac arrest	1 (0.6)	0	0
Ear and labyrinth disorders	0	1 (0.7)	0
Tinnitus	0	1 (0.7)	0
General disorders and administration site conditions	0	1 (0.7)	1 (4.2)
Chest pain	0	1 (0.7)	0
Infusion site thrombosis	0	0	1 (4.2)
Immune system disorders	1 (0.6)	0	0
Anaphylactic shock	1 (0.6)	0	0
Infections and infestations	5 (2.8)	4 (2.7)	0
Sepsis	3 (1.7)	1 (0.7)	0
Wound infection bacterial	2 (1.1)	0	0
Osteomyelitis	1 (0.6)	0	0
Urosepsis	1 (0.6)	0	0
Clostridium difficile infection	0	1 (0.7)	0
Septic shock	0	1 (0.7)	0
Wound infection	0	1 (0.7)	0
Injury, poisoning and procedural complications	4 (2.3)	2 (1.3)	0
Scar	1 (0.6)	0	0
Thermal burn	1 (0.6)	0	0
Wound	1 (0.6)	0	0
Wound decomposition	1 (0.6)	1 (0.7)	0

Graft loss	0	1 (0.7)	0
Metabolism and nutrition disorders	0	1 (0.7)	0
Diabetic metabolic decompensation	0	1 (0.7)	0
	NexoBrid (N=177, PY=61.89)	Standard of Care (N=149, PY=50.22)	Placebo Control (Gel Vehicle) (N=24, PY=8.62)
System organ class preferred term	Patients n (%)	Patients n (%)	Patients n (%)
Nervous system disorders	1 (0.6)	0	1 (4.2)
Mental impairment	1 (0.6)	0	0
Seizure	0	0	1 (4.2)
Psychiatric disorders	1 (0.6)	0	0
Acute psychosis	1 (0.6)	0	0
Renal and urinary disorders	0	1 (0.7)	0
Neurogenic bladder	0	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	2 (1.3)	0
Acute respiratory failure	1 (0.6)	0	0
Acute respiratory distress syndrome	0	1 (0.7)	0
Atelectasis	0	1 (0.7)	0
Social circumstances	0	1 (0.7)	0
Homicide	0	1 (0.7)	0
Surgical and medical procedures	2 (1.1)	1 (0.7)	0
Internal fixation of fracture	1 (0.6)	0	0
Therapeutic procedure	1 (0.6)	0	0
Cholecystectomy	0	1 (0.7)	0
Vascular disorders	1 (0.6)	0	1 (4.2)
Deep vein thrombosis	1 (0.6)	0	0
Phlebitis superficial	0	0	1 (4.2)

*Source: Table 33 Summary of Clinical Safety
PY = total patient-years; TEAE = treatment-emergent adverse event

Three SAEs occurred in the vehicle group in Cohort 2:

- Infusion site thrombosis
- Seizure
- Phlebitis superficial

In Cohort 1, the pattern of occurrence of SAEs was similar to what was observed in Cohort 2, with there being only single reports of the majority of SAEs. In Cohort 1:

- 2 more cases of sepsis were added to the tally, and both were in the NexoBrid group, making for 5 reports of in this group in the safety database.

- One additional report of deep vein thrombosis in the NexoBrid group, making for 2 reports in the safety database (none in SOC or vehicle).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant reported that one subject in the safety database discontinued due to a TEAE: A 42 y/o Black male in study 2002-04-01 had a TW burn of 14% TBSA on the posterior trunk. He apparently withdrew within 2 minutes of NexoBrid application due to severe pain and was lost to follow-up. However, narrative information is somewhat unclear, as it describes that he "underwent debridement" with NexoBrid. This subject was enrolled prior to the Applicant's implementation of pain mitigation measures in the clinical development program (see Section 8.2.5.1for additional information on these measures). The information provided regarding this subject suggests significant pain associated with NexoBrid itself. The timeframe from product application to withdrawal (2 minutes) suggests that there is pain inherent to the product and unrelated to procedures for removal of the dissolved eschar.

Overall, the proportions of subjects who completed the Acute Phase in the NexoBrid and SOC groups were similar: 148 subjects (84%) and 126 subjects (85%), respectively. The most common reason for early termination in both groups was "lost to follow-up," and the proportions of subjects who were terminated early for this reason were similar between the NexoBrid and SOC groups. See Table 4.

Table 4. Patient Disposition Acute Phase– Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid (N=177) n (%)	Standard of Care (N=149) n (%)	Placebo Control (Gel Vehicle) (N=24) n (%)
Treated Patients	177	149	24
Patients Completed Acute Phase[a]/Study	148 (83.6)	126 (84.6)	23 (95.8)
Patient Discontinued Study	29 (16.4)	23 (15.4)	1 (4.2)
Reasons for Early Termination			
Death	2 (1.1)	1 (0.7)	0
Lost to Follow-up	18 (10.2)	13 (8.7)	1 (4.2)
Noncompliance with the Protocol	7 (4.0)	7 (4.7)	0
Withdrawal by Patient	2 (1.1)	1 (0.7)	0
Other	0	1 (0.7)	0

*Source: Table 11 Summary of Clinical Safety

Significant Adverse Events

The overall incidence of AEs that investigators graded as severe in Cohort 2, was higher in the NexoBrid group (9.0%) compared to the SOC group (7.0%). The only severe events for which there were multiple reports were:

- Pain: 3 subjects (2%) NexoBrid; 2 subjects (1%) SOC
- Sepsis: 3 subjects (2%) NexoBrid; 2 subjects (1%) SOC (in the SOC group, represents one report of "sepsis", and one report of "septic shock")
- Scar: 2 subjects (1%) NexoBrid; none in the SOC group.

There were single reports of all other severe AEs across treatment groups.

See Section 8.2.4 ("Analysis of Submission-Specific Safety Issues") for discussion of the recognized adverse reactions with NexoBrid treatment.

TEAEs by TBSA

Few subjects had TBSA > 15%: 19 of 177 (11%) in the NexoBrid group and 13 of 149 (9%) in the SOC group (per the Applicant's reporting). In subjects with > 15% TBSA, mean TBSA of wounds was slightly higher in the SOC group (25%) compared to the NexoBrid group (22%), as was the mean TW area: 21% and 19% in the SOC and NexoBrid groups, respectively. In subjects with > 15% TBSA, the incidence of SAEs was notably higher in the NexoBrid group compared to SOC: 26% and 15%, respectively. However, for "any TEAE" in subjects with TBSA > 15% TBSA, the incidence was higher in the SOC group compared to the NexoBrid group: 92% and 79%, respectively. In subjects with < 15% TBSA, the incidence of SAEs was similar between the 2 groups (6% in each group). For "any TEAE" in subjects with < 15% TBSA, the incidence was higher in the NexoBrid group compared to SOC: 61% and 52%, respectively.

Table 5: Overview of the Incidence of TEAEs by %Total Burn Surface Area (≤15% TBSA vs >15% TBSA) by Patient – Pooled Phase 3 Studies (Cohort 2)*

	%TBSA ≤15%			%TBSA >15%		
	NXB N=158	SOC N=136	PBO N=23	NXB N=19	SOC N=13	PBO N=1
Baseline Characteristics						
Mean (SD) %TBSA all Wounds	10.8 (5.13)	10.3 (5.02)	8.4 (3.15)	22 (3.39)	24.8 (3.24)	18.0
Mean (SD) %TBSA TW	8.0 (3.70)	7.5 (3.38)	5.9 (2.68)	19.4 (2.85)	20.9 (3.87)	18.0
Mean (SD) number of TWs	1.9 (1.00)	1.8 (0.91)	1.7 (0.88)	3.2 (1.13)	3.2 (0.90)	2.0

Adverse Events						
Any TEAE	96 (60.8)	71 (52.2)	15 (65.2)	15 (78.9)	12 (92.3)	0
Any Serious TEAE	10 (6.3)	8 (5.9)	3 (13.0)	5 (26.3)	2 (15.4)	0

*Source: Table 49 of Summary of Clinical Safety
NXB=NexoBrid; PBO = placebo control (Gel Vehicle); SD = standard deviation; SOC = standard of care; TBSA = Total Burn Surface Area; TEAE = treatment-emergent adverse event; TW = target wound

TEAEs by Number of NexoBrid Applications

Few subjects received 2 NexoBrid applications: 18 of 177 (10%). The mean % TBSA of TWs was higher for the group that received 2 applications compared to the group that received a single application: 13 (6.71) versus 9 (4.65), respectively. Per Summary of Clinical Safety Table 14.3.1.8.2.1, the 4 SAEs that occurred in subjects who received 2 applications were sepsis, wound decomposition, acute respiratory failure, and deep vein thrombosis. On p. 118 of the SCS, the Applicant states that all 4 of these SAES occurred in one subject. However, SCS Table 51 and ISS Table 14.3.1.8.2.1 indicate that 4 subjects experienced SAEs. Additionally, the subject narratives for the Phase 3 trials do not describe any subject who experienced all 4 of these events. The mean % TBSA of all wounds was higher for subjects in the 2-application group compared to the 1-application group: 17 (7.31) and 12 (5.70), respectively. .

Table 6: Overview of the Incidence of TEAEs by Number of NexoBrid Applications (1 vs 2) by Patient – Pooled Phase 3 Studies (Cohort 2)

	NexoBrid One Application n=159	NexoBrid Two Applications n=18
Baseline Characteristics		
Mean (SD) %TBSA of All Wounds	11.5 (5.70)	16.5 (7.31)
Mean (SD) %TBSA TWs	8.7 (4.65)	13.3 (6.71)
Mean (SD) Number of TWs	2 (1.09)	2.4 (1.04)
Adverse Events		
Any TEAE	96 (60.4)	15 (83.3)
Any Serious TEAE	11 (6.9)	4 (22.2)

*Source: Table 51 of Summary of Clinical Safety
SD = standard deviation; TBSA = Total Burn Surface Area; TEAE = treatment-emergent adverse event; TW = target wound

Endotoxemia

Endotoxin or lipopolysaccharide (LPS) is a component of the outer membrane of Gram-negative

bacteria[24,25] and is released on cell death and lysis.[21] In high amounts, endotoxins may cause pyrogenic reactions, severe inflammatory responses, septic shock, and death.[21] Therefore, individual events suggestive of endotoxemia might be scattered across several different system organ classes. Further, similar clinical manifestations could be associated with the body's response to a severe burn injury itself. Burn patients may be at heightened risk of endotoxin exposure from NexoBrid because the product is applied to an open wound.

MediWound cannot monitor NexoBrid drug substance or drug product for endotoxins because of the botanical nature of the product, (b) (4) (b) (4). During the development program, the Agency advised the Applicant that the manufacturing process should have adequate bioburden control to limit the endotoxin content in the drug product.

Jessica Weintraub, PharmD, a Safety Evaluator in the Division of Pharmacovigilance (DPV) I, evaluated foreign postmarketing safety reports and the literature for adverse events suggestive of endotoxemia or other serious adverse events reported with NexoBrid use. Dr. Weintraub also queried the EMA regarding safety signals currently under evaluation. Dr. Weintraub identified no relevant cases in the FDA Adverse Event Reporting System (FAERS) and found no cases or publications reporting endotoxemia, endotoxic shock, or measurement of endotoxin.

DPV had no recommendations relating to endotoxemia. However, DPV recommended including anaphylaxis and urticaria to the Postmarketing Experience section of the label.

Blood Loss

The Applicant reported that the difference in actual blood loss during eschar removal (ER) was statistically significantly lower in the NexoBrid group versus the SOC group. See Section. 8.11 for issues relating to the blood loss endpoint. Nevertheless, the overall clinical implications of any differences in blood loss between treatment groups during ER are unclear, as blood loss sufficient to require transfusion during ER occurred in ≤ ~5% of subjects in both treatment groups in the pooled Phase 3 studies.

See Table 7 below.

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[24] U.S.Department of Health and Human Services Guidance for Industry. Setting Endotoxin Limits During Development of Investigational Oncology Drugs and Biological Products Guidance for Industry-Draft Guidance, July 2020.

[25] McCulloh RJ, Opal SM. Sepsis, Septic Shock, and Multiple Organ Failure. In: Oropello JM, Pastores SM, Kvetan V. eds. *Critical Care*. McGraw-Hill; Accessed May 7, 2021. https://accessmedicine.mhmedical.com/content.aspx?bookid=1944&sectionid=143518590

Table 7: Subjects Who Received Blood Transfusions – Pooled Phase 3 Studies (Cohort 2)

Time Period Blood Transfusion	NexoBrid (N=177)	Standard of Care (N=149)
Overall	29 (16)	21 (14)
During the ER period	3 (1.7)	8 (5.4)
Within 1 week after the ER period	6 (3.4)	10 (6.1)
Later than 1 week after the ER period	23 (13)	7 (4.7)

* Source: Table 72 of Summary of Clinical Safety

In both Phase 3 studies, an overall higher percentage of subjects in the NexoBrid groups received transfusions. During the ER period and within 1 week of that period, a higher proportion of subjects in the SOC groups received transfusions; however, the percentages in both treatment groups for both of these periods was low (≤ 7%). More than 1 week after the ER period, a higher proportion of subjects in the NexoBrid group in both Phase 3 studies received transfusions, and the highest percentage of subjects who received transfusions during any of the 3 periods was in the NexoBrid group > one week after the ER period (see table below). However, this period may be the least interpretable because it is open-ended through 3 months post-wound closure. Also, the further removed from the eschar procedure, the greater the possibility that the need for transfusion could relate to other factors. However, the proportion of subjects who received transfusions was generally similar for all 3 time periods in the SOC group and notably higher only in the NexoBrid group for the most distant time period from eschar removal. See Table 8 below. Most subjects, irrespective of treatment group, did not require blood transfusions during any of the 3 specified time periods for capturing data on transfusions: during ER, within 1 week after the ER period, and later than 1 week after the ER period.

Table 8: Blood Transfusions –Phase 3 Studies (Cohort 2) – By Study*

Time Period Blood Transfusion	2010-03-02 (2010)		2004-11-02 (2004	
	NexoBrid (N=77)	SOC (N=68)	NexoBrid (N=100)	SOC (N=81)
Overall	9 (11.7)	7 (10.3)	20 (20)	14 (17.3)
During the ER period	1 (1.3)	2 (2.9)	2 (2)	6 (7.4)
Within 1 week after the ER period	3 (3.9)	4 (5.9)	3 (3)	6 (7.4)
More than 1 week after the ER period	7 (9.1)	3 (4.4)	16 (16)	4 (4.9)

*Source: Table 73 of Summary of Clinical Safety

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant defined treatment emergent adverse events (TEAEs) as AEs that occurred after the start of treatment. Acute Phase TEAEs were those AEs that occurred after the start of treatment and up to 3 months after complete wound closure of all treated wounds. TEAEs for the Acute Phase were collected in study 2010. Additionally, some safety data were collected only in study 2010 at 12 and 24 months after complete wound closure. The Applicant plans to submit the 24-month data as a post-approval commitment.

Table 9. Overview of Adverse Events – Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid (N=177) n (%)	Standard of Care (N=149) n (%)	Placebo Control (Gel Vehicle) (N=24) n (%)
Any TEAEs	111 (62.7)	83 (55.7)	15 (62.5)
Mild	53 (29.9)	46 (30.9)	9 (37.5)
Moderate	42 (23.7)	27 (18.1)	3 (12.5)
Severe	16 (9.0)	10 (6.7)	3 (12.5)
Serious TEAEs (SAEs)	15 (8.5)	10 (6.7)	3 (12.5)
Treatment-related TEAEs	14 (7.9)	NA	0
TEAEs leading to early discontinuation	0	0	0
TEAEs leading to death	2 (1.1)	1 (0.7)	0

*Source: Table 18 Summary of Clinical Safety
NA = not assessed; SAE = serious adverse event; TEAE = treatment-emergent adverse event

TEAEs were most frequently reported in the Infections and infestations system organ class for both the NexoBrid and SOC groups, 23.2% and 19.5%, respectively. For both treatment groups, Wound infection was the most frequently reported preferred term (PT) in this system organ class and was reported with similar frequency in both treatment groups: NexoBrid- 9 subjects (5.1%) and SOC- 7 subjects (4.7%). Events were next most frequently reported in the Skin and subcutaneous tissue disorders system organ class: NexoBrid- 20.9% and SOC- 16.8%. For both treatment groups, Pruritus was the most frequently reported PT in this system organ class and was reported with a higher frequency in the NexoBrid- 27 subjects (15.3%) compared to SOC- 19 subjects (12.8%). Also, Pruritus was the overall most frequently reported PT in both treatment groups.

Table 10: TEAEs by System Organ Class and Preferred Term in ≥ 2 Subjects in NexoBrid or SOC Treatment Arm - Pooled Phase 3 Studies (Cohort 2)*

System Organ Class Preferred Term	NexoBrid (N=177, PY=61.89)	Standard of Care (N=149, PY=50.22)
Any TEAEs, n (%)	111 (62.7)	83 (55.7)
Blood and lymphatic system disorders	15 (8.5)	13 (8.7)
Anemia	11 (6.2)	8 (5.4)
Leukocytosis	3 (1.7)	1 (0.7)
Thrombocytosis	1 (0.6)	3 (2.0)
Hemorrhagic anemia	0	2 (1.3)
Cardiac disorders	6 (3.4)	2 (1.3)
Tachycardia	5 (2.8)	0
~~Sinus tachycardia~~	0	1 (0.7)
Gastrointestinal disorders	24 (13.6)	16 (10.7)
Nausea	10 (5.6)	4 (2.7)
Vomiting	9 (5.1)	4 (2.7)
Constipation	5 (2.8)	7 (4.7)
Diarrhea	4 (2.3)	1 (0.7)
General disorders and administration site conditions	34 (19.2)	25 (16.8)
Pyrexia	21 (11.9)	13 (8.7)
Pain	7 (4.0)	6 (4.0)
Hyperthermia	5 (2.8)	4 (2.7)
Hypothermia	2 (1.1)	1 (0.7)
Hepatobiliary disorders	2 (1.1)	0
Hepatic function abnormal	2 (1.1)	0
Immune system disorders	4 (2.3)	1 (0.7)
Drug hypersensitivity	2 (1.1)	0

System Organ Class Preferred Term	NexoBrid (N=177, PY=61.89)	Standard of Care (N=149, PY=50.22)

Infections and infestations	41 (23.2)	29 (19.5)
Wound infection	9 (5.1)	7 (4.7)
Urinary tract infection	7 (4.0)	1 (0.7)
Infection	4 (2.3)	2 (1.3)
Sepsis	4 (2.3)	1 (0.7)
Wound infection bacterial	4 (2.3)	4 (2.7)
Bacteremia	2 (1.1)	0
Folliculitis	2 (1.1)	1 (0.7)
Pneumonia	1 (0.6)	3 (2.0)
Sinusitis	0	2 (1.3)
Injury, poisoning and procedural complications	27 (15.3)	14 (9.4)
Wound complication	5 (2.8)	2 (1.3)
Skin graft failure	4 (2.3)	1 (0.7)
Graft loss	3 (1.7)	3 (2.0)
Wound decomposition	3 (1.7)	2 (1.3)
Anemia postoperative	2 (1.1)	1 (0.7)
Scar	2 (1.1)	0
Subcutaneous hematoma	2 (1.1)	0
Thermal burn	2 (1.1)	0
Wound	2 (1.1)	1 (0.7)
Metabolism and nutrition disorders	8 (4.5)	6 (4.0)
Hypoalbuminemia	2 (1.1)	1 (0.7)
Hyperglycemia	1 (0.6)	3 (2.0)

System Organ Class Preferred Term	NexoBrid (N=177, PY=61.89)	Standard of Care (N=149, PY=50.22)
Musculoskeletal and connective tissue disorders	8 (4.5)	7 (4.7)

Pain in extremity	3 (1.7)	0
Joint range of motion decreased	2 (1.1)	4 (2.7)
Nervous system disorders	10 (5.6)	7 (4.7)
Headache	5 (2.8)	6 (4.0)
Seizure	2 (1.1)	0
Psychiatric disorders	15 (8.5)	11 (7.4)
Insomnia	8 (4.5)	6 (4.0)
Anxiety	2 (1.1)	1 (0.7)
Renal and urinary disorders	6 (3.4)	4 (2.7)
Dysuria	1 (0.6)	2 (1.3)
Skin and subcutaneous tissue disorders	37 (20.9)	25 (16.8)
Pruritus	27 (15.3)	19 (12.8)
Rash	6 (3.4)	0
Decubitus ulcer	2 (1.1)	0
Vascular disorders	9 (5.1)	7 (4.7)
Hypertension	3 (1.7)	1 (0.7)
Hypotension	3 (1.7)	1 (0.7)
Hemorrhage	0	2 (1.3)

*Source: Table 21 Summary of Clinical Safety
PY = patient-years; TEAEs = treatment-emergent adverse events

Local Target Wound (TW)-Related TEAEs

Overall, 63 subjects (36%) in the NexoBrid group and 45 subjects (30%) experienced local TEAEs that were related to the TW. Generally, there were single reports of most events. Events were most commonly reported in the Skin and subcutaneous tissue disorders system organ class: 27 subjects (15%) in the NexoBrid group and 18 subjects (12%) in the SOC group. The most common TEAE in this SOC in both treatment groups was Pruritus: 22 subjects (12%) in the NexoBrid group and 14 subjects (9%) in the SOC group. Events for which there were multiple reports in either treatment group are presented in Table 11.

Table 11: Local Target Wound (TW) Related TEAEs*

System Organ Class Preferred Term	NexoBrid (N=177, PY=61.89)	Standard of Care (N=149, PY=50.22)
Any Local TW-Related TEAEs, n (%)	63 (35.6)	45 (30.2)
General disorders and administration site conditions	3 (2)	1 (1)
Pain	3 (1.7)	1 (0.7)

Infections and infestations	18 (10.2)	15 (10.1)
Wound infection	8 (4.5)	6 (4.0)
Wound infection bacterial	3 (1.7)	4 (2.7)
Injury, poisoning and procedural complications	23 (13.0)	13 (8.7)
Wound complication	5 (2.8)	2 (1.3)
Skin graft failure	4 (2.3)	1 (0.7)
Graft loss	3 (1.7)	3 (2.0)
Wound decomposition	3 (1.7)	2 (1.3)
Scar	2 (1.1)	0
Subcutaneous hematoma	2 (1.1)	0
Wound	2 (1.1)	1 (0.7)
Musculoskeletal and connective tissue disorders	4 (2.3)	5 (3.4)
Joint range of motion decreased	2 (1.1)	4 (2.7)
Skin and subcutaneous tissue disorders	27 (15.3)	18 (12.1)
Pruritus	22 (12.4)	14 (9.4)
Rash	2 (1.1)	0
Decubitus ulcer	2 (1.1)	0

*Source: ISS Table 14.3.3.2.2.1

Laboratory Findings

The Applicant reported that laboratory reference ranges differed in all 6 clinical studies, when those ranges were provided (they were not specified for studies 2001-10-03 and 2008-09-03). Additionally, in studies 2010, 2004 and 2005-10-05 (a Phase 2 study), labs were checked at a single postbaseline time point:

- study 2010: 4 hours after the end of the procedure for SOC, and 4 hours after removal of the topical agent (for NexoBrid and Gel Vehicle); this generally referred to the first and second application.
  - PTT and INR were measured only after the first application (NexoBrid and Gel Vehicle) or first treatment (SOC) in study 2010.
- in study 2004 (and 2005-10-05): 24 hours after start of debridement.

Therefore, the Applicant presented labs at an "integrated time point," defined as: Up to 24 hours after start of treatment. This refers to post surgery for SOC. However, for the NexoBrid and Gel Vehicle arms, it is unclear whether this refers to first application only or for first and second applications. Table 3 of the protocol for study 2010 seems to indicate that it is the first application only; however, Sec. 8.2.3.2.2 of the protocol ("Post second application assessments") seems to indicate that labs would also be obtained after a second application

(notably, excludes mention of PTT and INR after second application). This limited post-treatment testing could potentially have missed treatment-emergent changes in laboratory values.

Interpretability of labs at the integrated time point for the Phase 3 studies (Cohort 2) may be limited as post baseline results reflect integrated data from different time points. Additionally, this integrated approach does not permit assessment of the potential impact of 2 applications of NexoBrid. Urinalyses were only performed in study 2010.

For the shift tables, laboratory values were characterized as Low, Normal, or High based on lab values for each study, based on the reference ranges (when provided) used for each individual study. Each subject's worst outcome in either direction was considered; subjects could be counted as a shift to Low and to High if the subject experienced both shifts during the study.

White Blood Cells (total leukocytes, neutrophils, lymphocytes, monocytes)

In the Phase 3 studies, 29.4% of subjects in the NexoBrid group who had normal baseline total leukocytes had normal total counts at a post-treatment assessment, and 18.4% experienced a shift to high. In the SOC group, a higher proportion of subjects with baseline normal total leukocyte counts (38.5%) remained normal compared to the NexoBrid group, and a lower proportion shifted to high (9.9%). No subjects had a normal-to-low shift in total leukocyte counts in the NexoBrid group, and 1 subject (1.1%) experienced this shift in the SOC group. The same patterns were seen with neutrophil counts: a higher proportion of SOC subjects had baseline normal neutrophil counts (34.4%) and were normal at a post-treatment assessment compared to the NexoBrid group (25.9%), and a lower proportion of SOC subjects (12.2%) shifted to high compared to the NexoBrid group (19.3%). The proportions of subjects with normal lymphocyte counts at baseline who had normal values post-treatment was similar between treatment groups (NexoBrid- 80.0%; SOC- 78.9%). Additionally, the numbers of subjects who shifted from normal to low was similar between groups (NexoBrid- 13.3%; SOC- 14.4%). No subjects with normal baseline counts of lymphocytes shifted to high. A similar proportion of NexoBrid subjects had shifts from normal to low monocyte counts (4.4%), as SOC subjects who shifted from normal to high (4.4%).

In the SCS, the discussion hematology results did not include eosinophils. However, in the study report for study 2010, the most common shift for leukocytes was the shift from baseline normal to abnormal low eosinophils: 17 subjects (22.0%) in the NexoBrid group and 13 subjects (19.1%) in the SOC group.

Red Blood Cells

A higher proportion of subjects in the SOC group experienced a shift from normal to low in hemoglobin and hematocrit at a post-treatment assessment (31.2% and 31.2%, respectively) compared to the NexoBrid group (11.4% and 13.6%, respectively).

Coagulation Parameters

The Applicant considers "abnormalities of coagulation parameters" to be a potential risk of NexoBrid treatment based on nonclinical findings.

Per Section 4.2 of the Nonclinical Overview:

> In a repeat dose (intravenous) study in minipigs and farm pigs, treatment-related histological changes included hemorrhage in multiple tissues. Prolongation in the activated partial thromboplastin time (APTT) and prothrombin time (PT) was observed at all dose levels in both sexes relative to controls. The hemorrhagic events may be correlated to the changes in the coagulation parameters observed (prolongation of PT and APTT and decrease in fibrinogen).

Jerry Wang, Ph.D. discussed that in the single dose intravenous (IV) toxicity studies conducted in minipigs, a NOEL of 12 mg/kg was identified; however, higher doses resulted in "severe toxicities (mortality and generalized hemorrhage)." Dr. Wang also described "severe toxicities (hemorrhages in multiple tissues)" in the repeat-dose IV toxicity studies conducted in minipigs and juvenile pigs, and a NOAEL was not identified in these studies. However, Dr. Wang stated that "IV toxicity studies have limited value in assessing human risk and dermal toxicity studies are considered more relevant to human risk assessment."

See Section 5 of this document for Dr. Wang's review of the pharmacology/toxicology information.

The Applicant evaluated 3 coagulation parameters:

- activated partial thromboplastin time (aPTT): study 2010 and Phase 2 studies 2001-10-03 and 2002-04-01. However, as normal ranges for aPTT were not specified in study 2001-10-03, the Applicant presented aPTT analysis only for studies 2010 and 2002-04-01. Study 2002-04-01 was a prospective, three-arm study into which 148 subjects were randomized: 140 Debrase (now NexoBrid), 35 SOC, and 35 Vehicle. PTTs were assessed pre-treatment and at 24 and 48 hours post-treatment and at hospital discharge.
- International normalized ratio (INR)- study 2010 only
- platelets

There were no SAEs relating to coagulation abnormalities in the Phase 3 studies. There was 1 TEAE report of "coagulopathy" and 2 reports of "hemorrhagic anemia," and all 3 reports were in the SOC arm. "Anemia postoperative" was reported, as follows: 2 subjects in the NexoBrid group and one subject in the SOC group. "Post procedural hemorrhage" was reported in one subject in the NexoBrid group.

aPTT (study 2010)

The protocol specified that the PTT was to be obtained within 1 hour pre first treatment, then 4 hours post removal of first application only for NexoBrid and Vehicle arms and 4 hours post first treatment only in SOC arm.

In the NexoBrid group, 7 subjects (9.1%) had a shift to "abnormal high" aPTT at a post-treatment time point compared to 5 subjects (7.4%) in the SOC group. There were no PCS shifts in PTT (defined as >2 x upper limit of normal if Baseline is normal and >2 x Baseline if Baseline is > ULN). The proportions of subjects with shifts in PTT in either direction were generally similar between the NexoBrid and SOC groups.

Table 12: PTT Shifts from Baseline to Any Post Treatment Abnormal Result – Study 2010

Lab Value	Treatment	Baseline	Any Low n (%)	Any High n (%)
Activated Partial Thromboplastin Time (sec)	NexoBrid (N=77)	Normal	3 (3.9)	7 (9.1)
	SOC (N=68)	Normal	2 (2.9)	5 (7.4)
	Gel Vehicle (N=24)	Normal	1 (4.2)	3 (12.5)

*Source: Table 55 study report for study 2010
% = n/N*100, N = number of patients in the SAS, n = number of patients with respective category

INR (study 2010)

The protocol specified that the INR was to be obtained within 1 hour pre first treatment, then 4 hours post removal of first application only for NexoBrid and Vehicle arms and 4 hours post first treatment only in SOC arm

Shifts from normal to "any high" INR were similar between the NexoBrid and SOC groups, 10.4% and 8.8%, respectively. There were 2 reports of PCS changes (>1.5 if Baseline is <= 1.2; 1.5 x Baseline if Baseline is > 1.2) from normal to high, 1 in the NexoBrid group and 1 in the SOC group.

Table 13: INR Shifts from Baseline to Any Post Treatment Abnormal Result - Study 2010

Lab Value	Treatment	Baseline	Any High n (%)
International Normalized Ratio	NexoBrid (N=77)	Normal	8 (10.4)
	SOC (N=68)	Normal	6 (8.8)
	Gel Vehicle (N=24)	Normal	1 (4.2)

*Source: Table 56 study report for study 2010
Common normal range for INR (0.8-1.2) was used.
% = n/N*100, N = number of patients, n = number of patients with respective category

Platelets

In the Phase 3 studies, 29.4% of subjects in the NexoBrid group who had normal baseline total leukocytes had normal total counts at a post-treatment assessment, and 18.4% experienced a shift to high.

PCS low shifts in platelets were observed in 2 subjects (1.4%) in the NexoBrid group in the Phase 3 studies. However, there were no reports of thrombocytopenia as AEs in the NexoBrid group in Cohort 2 (there was 1 report in the SOC group). A total of 4 subjects (4.4%) in the SOC experienced shifts from normal to low at a post-treatment assessment. None of these events in the SOC group were classified as PCS.

Table 14: Shifts in Platelets – Pooled Phase 3 Studies (Cohort 2)

Parameter Baseline Value	NexoBrid			Standard of Care			Placebo Control (Gel Vehicle)		
	Value at any Post-treatment Time Point								
	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Platelets	(N*=138)			(N*=91)			(N*=20)		
Low	10 (7.2)	2 (1.4)	0	1 (1.1)	1 (1.1)	0	0	0	0
Normal	2 (1.4)	122 (88.4)	2 (1.4)	4 (4.4)	81 (89.0)	3 (3.3)	1 (5.0)	14 (70.0)	4 (20.0)
High	0	0	0	0	1 (1.1)	0	0	0	1 (5.0)

*Source: Table 95 Summary of Clinical Safety
N* = number of patients with baseline and at least 1 measurement after start of treatment.
Percentages are calculated based on N*.

Serum Chemistries
Serum chemistry testing results are discussed below.

Serum Proteins (protein, albumin, globulin)

For all parameters in both treatment groups in the Phase 3 studies, a higher proportion of subjects with low values pretreatment remained in the low category at the post-treatment assessment compared to the proportions who shifted from low to normal. A higher proportion of subjects with normal baseline values remained in the normal category at the post-treatment assessment compared to the proportions who shifted from normal to low. The proportions of subjects who shifted from normal to low was generally similar for each protein parameter between the NexoBrid and SOC treatment groups. No shifts to High were reported for any

serum protein parameter, which may be generally reflective or consistent with the study population. See Table 15.

Table 15: Shifts in Serum Proteins – Pooled Phase 3 Studies (Cohort 2)

Parameter Baseline Value	NexoBrid			Standard of Care			Placebo Control (Gel Vehicle)		
	Value at any Post-treatment Time Point								
	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)	Low n (%)	Normal n (%)	High n (%)
Protein	(N*=148)			(N*=111)			(N*=19)		
Low	62 (41.9)	4 (2.7)	0	41 (36.9)	5 (4.5)	0	4 (21.1)	0	0
Normal	39 (26.4)	43 (29.1)	0	23 (20.7)	40 (36.0)	0	6 (31.6)	9 (47.4)	0
High	0	0	0	0	2 (1.8)	0	0	0	0
Albumin	(N*=148)			(N*=111)			(N*=19)		
Low	41 (27.7)	2 (1.4)	0	27 (24.3)	4 (3.6)	0	3 (15.8)	0	0
Normal	41 (27.7)	64 (43.2)	0	29 (26.1)	50 (45.0)	0	2 (10.5)	14 (73.7)	0
High	0	0	0	0	1 (0.9)	0	0	0	0
Globulin	(N*=148)			(N*=111)			(N*=19)		
Low	10 (6.8)	6 (4.1)	0	8 (7.2)	7 (6.3)	0	3 (15.8)	0	0
Normal	8 (5.4)	124 (83.8)	0	5 (4.5)	91 (82.0)	0	1 (5.3)	15 (78.9)	0
High	0	0	0	0	0	0	0	0	0

*Source: Table 74 Summary of Clinical Safety
N* = number of patients with baseline and at least 1 measurement after start of treatment. Percentages are calculated based on N*.

Liver Function Tests (ALT, AST, alkaline phosphatase, total bilirubin, LDH)

In both treatment groups, most subjects with normal values for liver function tests (LFTs) at baseline, remained in the normal category at a post-treatment assessment: 75.7% to 94.6% across all parameters. Shifts from normal to high occurred for every parameter in both treatment groups, and the proportions of subjects who shifted from normal to high ranged from 0.7% to 5.4% in the NexoBrid group (highest percentage was for AST) and from 3.6% to 10.8% in the SOC group (also highest for AST).

Kidney Function Tests (BUN, creatinine)

The majority of subjects in both treatment groups in the Phase 3 trials with normal kidney function tests at baseline remained normal at post-treatment assessment. Specifically, in the NexoBrid group: for BUN- 115 subjects (92.7%) and for creatinine 118 subjects (79.7%); for SOC: for BUN- 82 subjects (94.3%) and for creatinine 79 subjects (71.2%) . No shifts from normal to high occurred for BUN or creatinine in the SOC group. In the NexoBrid group, 2 subjects (1.6%) experienced a normal to high shift, and 1 subject (0.7%) experienced a normal to high shift for creatinine.

Electrolytes (sodium, potassium, chloride, calcium, corrected calcium, phosphate)

A similar proportion of subjects in both treatment groups had normal baseline sodium levels and remained normal, with the proportions at post-treatment assessment being 76.4% in the NexoBrid group and 78.4% in the SOC group. Shifts from normal to low sodium occurred in 14.9% of NexoBrid subjects and 4.5% of SOC subjects. Even higher proportions of subjects in both treatment groups had baseline normal potassium values that remained normal posttreatment, ~90% in both groups. Shifts from normal potassium to low and to high occurred in both treatment groups, and the shifts in either direction occurred in ≤ 2% of subjects. Similarly, most subjects had normal chloride levels that remained normal (83.8% NexoBrid; 87.4% SOC), and the shifts from normal in either direction occurred in ≤ ~5% of subjects across treatment groups. Calcium levels either remained normal or shifted to low in both treatment groups: NexoBrid: 39.7% and 25.3%, respectively; SOC: 42.3% and 22.5%, respectively). For phosphate, 60.8% in the NexoBrid group and 72.1% in the SOC group remained normal. Shifts occurred in both directions for phosphate in both groups, with more subjects shifting to low (~13% in each group).

Blood Glucose

In both treatment groups in the Phase 3 studies, similar proportions of subjects had normal glucose levels that remained normal post-baseline: NexoBrid- 27%; SOC- 27.9%. Shifts from normal to high occurred in both groups: NexoBrid- 29.1%; SOC- 25.2%.

Blood Lipids (cholesterol, triglycerides)

Most subjects in both treatment groups had normal values for both parameters at baseline and remained normal post-treatment (74.8% to 79.7%). Shifts occurred in both directions for cholesterol in both treatment groups, and the greatest shift was from normal to low and occurred in 7.4% of NexoBrid subjects (2.7% in the SOC group). For triglycerides, for subjects with normal baseline values, shifts occurred only to high in both groups: NexoBrid- 9.5%; SOC- 8.1%.

Vital Signs

Temperature is not included in this discussion. Pyrexia is discussed in Section 8.2.5.2.

Vital signs were measured at baseline and at integrated time points of 1 hour from application or during treatment, 1 to 2 hours post-dressing (NexoBrid and vehicle groups only), and 24 hours after the start of treatment. The Applicant reported that means and medians were within normal ranges for all vital signs at all specified time points. The Applicant presented the PCS changes for each Phase 3 study separately. Potentially clinically significant changes occurred in both directions for most vital signs in both treatment groups in study 2010. The highest rate for PCS shifts in both treatment groups was a shift from normal to high for heart rate: 9 subjects (11.7%) in the NexoBrid group and 8 subjects (11.8%) in the SOC group. Although the protocol specified time points for vital sign assessment, these isolated measures may be of limited interpretability in this population with significant potential for unstable clinical courses.

A total of 5 AEs of tachycardia occurred in the NexoBrid group, and one AE of sinus tachycardia was reported in the SOC group.

Electrocardiograms (ECGs)

The Applicant evaluated the QT effects of NexoBrid in a cardiac substudy of study 2010 by using Concentration-QT analysis. The Applicant found that this substudy (p. 183 of the study report for study 2010):

> …showed no clear signal of any effect of NexoBrid on heart rate, AV conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were no new clinically relevant morphological changes demonstrating a signal of concern.
>
> There also was no signal of any clinically significant effect of NexoBrid on cardiac repolarization as evidenced by the results of the by time point analysis.

The Interdisciplinary Review Team (IRT) for Cardiac Safety Studies reviewed the report for the cardiac substudy and concluded:

> No large (>20 msec) mean increases in the QTc interval was detected when NexoBrid was applied to a mean of 6% total body surface in this QT assessment. We are reluctant to draw conclusions of lack of an effect in an absence of a positive control or large exposure margin, or an integrated nonclinical safety assessment conduct according to best practices (ICH S7b Q&A 1.1 and 1.2).

QT

The Applicant did not conduct a thorough QT (TQT) study. The IRT for Cardiac Safety Studies determined under the IND (65448) that a TQT study was not required.

Immunogenicity

The submission included an "Integrated Summary of Immunogenicity." The Applicant stated that 68 subjects in the NexoBrid arm in study 2010 had baseline testing for anti-drug antibodies (ADA), and 62 subjects were evaluable. The Applicant reported that 25 of the evaluable subjects (40.3%) tested positive for ADA at baseline. Of these 25 subjects, 3 did not meet the complete eschar removal endpoint; however, the Appplicant concluded that this was due to technical issues relating to study procedures.

They reported that 58 subjects (93.5%) had either treatment-emergent ADA (36 subjects; 58.1% of ADA evaluable subjects) or treatment-boosted (22 subjects; 35.5%). In the evaluation of allergenicity, the Applicant identified 2 cases of "allergic reactions" (one subject ADA positive at baseline; one not) and 2 cases of "rash" (one subject ADA positive at baseline; the other subject did not have a baseline sample). These cases are discussed in Section 8.2.5.5.

Under the conditions of intended use, no impact of ADA positivity on efficacy or safety was established.

Also See Section 6.

8.1.11. Analysis of Submission-Specific Safety Issues

Based on safety data from early Phase 2 studies (studies 2001-10-03 and 2002-04-01, both completed in 2005), the Applicant identified pain, pyrexia, and wound infection as key risks of NexoBrid.

To mitigate the risks of pain, pyrexia, and wound infection, the Applicant implemented the following measures in all clinical studies subsequent to those Phase 2 studies:

- For pain: Analgesia appropriate for an extensive dressing change was to be administered prior to any wound treatment procedures.

- For pyrexia and wound infection: Wounds were to be soaked with antimicrobial solution for at least 2 hours before and after NexoBrid is applied.

The Applicant also identified immediate hypersensitivity reactions (which they reported as being a known risk of bromelain) and "coagulation parameter abnormalities" (based on findings in the nonclinical program) as additional potential risks of treatment. See Section 8.2.4 for discussion of coagulation parameters ("Laboratory Findings" section).

Discussion of events in this section will continue to focus on Cohort 2.

8.1.11.1. Pain

To mitigate the risk of pain identified in early Phase 2 studies, the Applicant implemented pain control measures for NexoBrid-related treatment procedures in all clinical studies subsequent to those Phase 2 studies: Analgesia appropriate for an extensive dressing change was to be administered prior to any wound treatment procedures. Examples of possible pain management regimens described in the protocol for study 2010 were all intravenously administered and included combinations of fentanyl, midazolam, and ketamine, and propofol with or without alfentanil or remifentanil.

The Applicant grouped the following pain-related PTs for evaluation of the pain adverse reaction: pain, pain in extremity, wound complication (referring to TW-related pain), and post-traumatic pain. The rates of pain TEAEs were generally similar between the NexoBrid and SOC groups. Pain-related events were reported at similar incidences in the NexoBrid and SOC arms.

Table 16: Summary of Pain-related TEAEs by Preferred Term - Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid (N=177)	Standard of Care (N=149)	Placebo Control (Gel Vehicle) (N=24)
Preferred Term	Patients n (%)	Patients n (%)	Patients n (%)
Any Pain TEAEs	8 (4.5)	6 (4.0)	2 (8.3)
Pain	7 (4.0)	6 (4.0)	0
Pain in extremity	1 (0.6)	0	1 (4.2)
Wound complication[a]	1 (0.6)	0	0
Post-traumatic pain	0	0	1 (4.2)

*Source: Table 35 of Summary of Clinical Safety
TEAE = treatment-emergent adverse event
[a] Verbatim term: uncontrolled Target wound-related pain.

In study 2010, 5% of NexoBrid subjects (n= 4) received general anesthesia, and 88% (42 subjects) received general anesthesia in the SOC group. This suggests that the approach to pain management is based on the judgement of the provider. Therefore, treatment with NexoBrid may not intrinsically translate to avoidance of general anesthesia.

8.1.11.2. Pyrexia

For this analysis, the Applicant pooled the following fever-related PTs: pyrexia, hyperthermia, and body temperature increased. In the Phase 3 studies (and some Phase 2 studies), occurrences of temperatures >39°C (102°F) were to have been recorded as “pyrexia” AEs. However, investigators could exercise judgement in recording a lower temperature as a pyrexia

AE. The Applicant did not discuss a possible mechanism for the pyrexia (e.g.., independent of infection). Fever can be a manifestation of the pro-inflammatory state and metabolic and physiologic disruptions associated with severe burn injuries.[26]

Overall, "fever-related" TEAEs were higher in the NexoBrid group. "Hyperthermia" may represent a potentially fatal, medical state, distinct from "fever."[27] However, there were no serious adverse events of hyperthermia (nor any severe fever-related events). This suggests that these events may not have represented true hyperthermia. If hyperthermia events are removed from the analyses, the overall rates become 12.4% for NexoBrid and 9.4% in the SOC i.e., the incidence remains higher in the NexoBrid group, and the difference between treatment groups remains 3%.

The measures that the Applicant implemented to mitigate pyrexia were the same as those for mitigating wound infection, which suggests that the Applicant considered pyrexia to be secondary to treatment-related wound infection.

Table 17: Summary of Fever-related TEAEs by Preferred Term - Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid (N=177)	Standard of Care (N=149)	Placebo Control (Gel Vehicle) (N=24)
Preferred Term	Patients n (%)	Patients n (%)	Patients n (%)
Any Fever TEAEs	27 (15.3)	18 (12.1)	2 (8.3)
Pyrexia	21 (11.9)	13 (8.7)	2 (8.3)
Hyperthermia	5 (2.8)	4 (2.7)	0
Body temperature increased	1 (0.6)	1 (0.7)	0

*Source: Table 38 of Summary of Clinical Safety

8.1.11.3. Wound Infection

Wounds were cultured within 24 hours pre-treatment. Post-treatment wound cultures were obtained as follows:

- NexoBrid subjects: at the end of the 2-hour antibacterial soaking period.

[26] D'Avignon LC and Murray CK. Fever in the burn patient. http://www.antimicrobe.org (accessed June 1, 2020)
[27] Dinarello CA and Port R. Pathophysiology and treatment of fever in adults. In: UpToDate, Weller PF (Ed), UpToDate, Waltham, MA. (Accessed on May 7, 2021.)

- SOC: post-debridement, prior to dressing of wound.

Invasive infection, as determined by wound biopsy, was to have been recorded as an AE. Investigators applied their clinical judgment to determine when other wound infection events would be recorded as an AE.

The Applicant analyzed groupings of PT's by the following 3 categories:

- PT "wound infection" in the Infections and infestations MedDRA system organ class

- TW infections excluding fungal: wound infection, infection, wound infection bacterial, staphylococcal infection, burn infection, proteus infection, bacterial infection, staphylococcal skin infection, staphylococcal infection, wound infection staphylococcal, and localized infection.

- TW infections fungal: candida infection, fungal infection, fungal skin infection, wound infection fungal.

The category of "Wound infection" in the Infections and infestation system organ class may be the least interpretable, as the recorded events may not have reflected a process at a TW. The incidences of events were similar between the NexoBrid and SOC groups for this category (~5.0% in each group). The other 2 categories specifically relate to the TW.

The incidence of infections excluding fungal was higher in the SOC group (9%) compared to the NexoBrid group (6%). "Staphylococcal" was the only reference to a specific microbial category of infection: There was one report each of "Staphylococcal infection," "Staphylococcal skin infection," and "Wound infection Staphylococcal"; all in the SOC group. All of the fungal events occurred in the NexoBrid group ("fungal infection," "fungal skin infection," and "wound infection fungal"). The only reference to a fungus genus in the summary table of all AEs in Cohort 2 (Table 14.3.1.2.2) was "Candida infection." However, it does not appear that this AE referred to a target wound, since it is not included in the findings for the analysis of fungal infections at TW sites.

Table 18: Summary of Wound Infection TEAEs - Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid N=177	Standard of Care N=149	Placebo Control (Gel Vehicle) N=24
Preferred Term	Patients n (%)	Patients n (%)	Patients n (%)
Preferred term of Wound Infection within Infection Overall system organ class	9 (5.1)	7 (4.7)	0

Target Wound-Related Infections excluding fungal by grouped preferred	11 (6.2)	13 (8.7)	0
Target Wound Fungal Infection by grouped preferred term	3 (1.7)	0	0

*Source: Table 41 Summary of Clinical Safety

Three wound infections were reported as SAEs in Cohort 2: 2 "wound infection bacterial" in the NexoBrid group, and 1 "wound infection" in the SOC group. From review of the narratives, all of these appear to have been TW infections:

- (b) (6) A 5 y/o female in the SOC group experienced a methicillin-resistant *Staphylococcus aureus* "wound infection" 46 days after completion of study treatment at the TWs which were 8% TBSA and involved the anterior and posterior trunk. The event resolved ~ 6 weeks later.

- (b) (6) A 33 y/o female experienced sepsis and "wound infection" 22 days after NexoBrid application. Burn wounds included areas on both legs; the TW was 5% TBSA on the right leg. Cultures of leg wounds, obtained 22 days after study treatment was applied, grew *Pseudomonas aeruginosa*. Growth was still "abundant" 11 days later at the NexoBrid treated site (right leg) and scant on the left. She was ultimately lost to follow-up.

- (b) (6) A 24 y/o male in the NexoBrid group experienced "wound infection bacterial" (*Hafnia alvei*) 4 days after application of study treatment. His TW was 5% TBSA and was located on the posterior trunk and upper right arm. The event was reported as resolved 9 days later.

A summary of wound infection TEAEs in the Phase 3 studies by preferred term is presented in Table 19 below.

Table 19: Summary of Wound Infection TEAEs by Preferred Term - Pooled Phase 3 Studies (Cohort 2)*

	NexoBrid N=177	Standard of Care N=149	Placebo Control (Gel Vehicle) N=24
Special Interest Event Group Preferred Term	Patients n (%)	Patients n (%)	Patients n (%)
Wound Infection TEAEs	11 (6.2)	13 (8.7)	0
Wound infection	8 (4.5)	6 (4.0)	0

Wound infection bacterial	3 (1.7)	4 (2.7)	0
Staphylococcal infection	0	1 (0.7)	0
Staphylococcal skin infection	0	1 (0.7)	0
Wound infection staphylococcal	0	1 (0.7)	0

*Source: Table 14.3.1.12.2 Integrated Summary of Safety

Table 20: Summary of Wound Fungal Infection TEAEs by Preferred Term - Pooled Phase Studies (Cohort 2)*

	NexoBrid N=177	Standard of Care N=149	Placebo Control (Gel Vehicle) N=24
Preferred Term	Patients n (%)	Patients n (%)	Patients n (%)
Special Interest Event Group Preferred Term	3 (1.7)	0	0
Fungal infection	1 (0.6)	0	0
Fungal skin infection	1 (0.6)	0	0
Wound infection fungal	1 (0.6)	0	0

*Source: Table 14.3.1.13.2 Integrated Summary of Safety

8.1.11.4. Sepsis

The overall incidences of sepsis-related TEAEs were similar in the NexoBrid group (2.8%) and the SOC group (2.0%).

Table 21. Summary of Sepsis-related Treatment-emergent Adverse Events by Preferred Term in Pooled Phase 3 Studies (Cohort 2)*

Preferred Term	NexoBrid (N=177)	Standard of Care (N=149)	Placebo Control (Gel Vehicle) (N=24)
	Patients n (%)	Patients n (%)	Patients n (%)
Any Sepsis TEAEs (Sepsis SMQ)	5 (2.8)	3 (2.0)	0
Sepsis	4 (2.3)	1 (0.7)	0
Bacteremia	2 (1.1)	0	0
Urosepsis	1 (0.6)	0	0
Septic shock	0	1 (0.7)	0
Staphylococcal bacteremia	0	1 (0.7)	0

*Source: Table 44 Summary of Clinical Safety

Of the sepsis-related AEs reported in the NexoBrid group, 5 were reported as SAEs (urosepsis and the 4 events of sepsis):

- (b) (6) ((b) (6) A 52 y/o male sustained burns to ~ 23.5 % TBSA. He received 2 applications of Debrase (now NexoBrid) to 19.5% TBSA (anterior trunk, arms, hands, and right leg). The onset appears to be 2 to 3 days post treatment, with fever, acidosis, and leukocytosis. Blood cultures were reported as "positive for *Acinetobacter* and *Staphylococcus aureus*" (time point is unclear). The SAE (reported as "sepsis/severe inflammatory response" in the narrative) was considered life-threatening. The subject was treated; however, the narrative does not include any information regarding the hospital course (other than a listing of medications and some lab values form the day of onset of symptoms/signs). The event(s) was considered resolved ~ 15 days later. The narrative does not include any discussion of the status of the wounds e.g., signs of infection.

  Comment: The provided information does not permit an assessment of relatedness to study treatment. However, it is noted that ~ 83% of the burn wound area was treated with Debrase.

- (b) (6) ((b) (6) A 33 y/o female sustained burns to 19.75% TBSA. NexoBrid was applied to 5% TBSA (right leg), apparently only a single application. The wound was autografted (time point not specified). Approximately 21 days following study treatment, "systemic sepsis associated with wound infection related to extension of the wounds on both legs." Reports of cultures from wounds on both legs were "abundant" *Pseudomonas aeruginosa*. Repeat wound cultures ~11 days later (~32 days post study treatment) indicated continued abundant growth of the organism from the wound on the right leg (TW), with scant growth reported from the left. She was discharged ~56 days after application of study treatment, with the sepsis and wound infection considered "controlled but unresolved." She was lost to follow-up.

Comment: The sepsis was attributed to the wounds on both legs, which would include a wound that did not receive NexoBrid treatment.

- (b) (6) ((b) (6) A 56 y/o male experienced burns to 14.5% TBSA. NexoBrid was applied to 4.5% TBSA (left lower arm); he received one application. He was hospitalized for cellulitis of the left leg 753 days following the NexoBrid application. On the same day, he was diagnosed with "sepsis secondary to extremity cellulitis." The area of cellulitis was not part of the burn injury area or at a site where NexoBrid had been applied. The cellulitis and sepsis were reported as resolved 756 days after study treatment.

  Comment: The cellulitis (sepsis source) did not relate to the NexoBrid-treated wound. The status of that burn injury at the time of cellulitis and sepsis was not reported.

- (b) (6) ((b) (6) This subject died and has been previously discussed. He experienced "urosepsis" and "sepsis." See Section 8.2.4.

8.1.11.5. Hypersensitivity

The Applicant has identified "immediate hypersensitivity" as a potential risk of NexoBrid treatment. The marketing application included an "Integrated Summary of Immunogenicity," in which the Applicant stated (p. 8),

> The plant-derived glycoprotein (Stem Bromelain) is anticipated to be immunogenic in humans by virtue of its xenogeneic nature. Accordingly, it is possible that treatment-emergent antibodies could be detected following topical administration of NexoBrid to damaged cutaneous tissue…

Factors which the Applicant believes to lessen the risks of immune complex-related loss of efficacy and hypersensitivity include the following:

> NexoBrid is indicated for 1 or 2 topical applications of 4 hours each, administered up to 24 hours apart, to debride deep partial and full thickness burn wounds. Thus, although NexoBrid treatment may induce formation of anti-drug antibodies (ADA), these will be detected at time point after eschar debridement when the drug proteins have already been eliminated from the circulation.

The Applicant acknowledges the potential for a treatment-related allergic reaction in patients due to cross-reactivity in individuals who are pre-sensitized to determinants on bromelain:

> Apart from pre-existing antibodies that cross-react with carbohydrate determinants present in many plant-derived proteins, it is possible that patients could have been pre-sensitized to the protein constituents of the NexoBrid active substance via dietary

exposure.

The Applicant searched the study 2010 database for PTs coded under the Immune system disorders system organ class and AEs referring to the following Standardized MedDRA Queries (SMQs) :

- Anaphylactic reaction
- Hypersensitivity
- Angioedema
- Eosinophilic pneumonia
- Periorbital and eyelid disorders

The Applicant also searched AEs in the Immune system disorders system organ class. The Applicant identified the following 4 events in study 2010:

- Subject (b) (6) experienced a hypersensitivity reaction one hour after NexoBrid application. The subject was ADA positive at baseline (titer: 6250). Presentation included urticaria and itching. Intravenous hydromorphone had begun 30 minutes prior to reaction and was continued for an unclear duration.

  Comment: The nature of the reaction and the time of onset in this ADA-positive subject, may implicate NexoBrid in the reaction. Hydromorphone cannot be excluded, given the temporal relationship of the reaction to exposure to the medication, and the Applicant related this reaction to the hydromorphone.

- Subject (b) (6) developed a "local rash" after the second application of NexoBrid. The subject was ADA positive at baseline (titer: 250). The eruption was "not urticarial," but was otherwise not characterized. The location of the eruption relative to the treatment site(s) was not specified.

  Comment: The narrative information is too vague and limited to permit a determination of the possible nature of the rash.

- Subject (b) (6) experienced a "torso rash" during study treatment. Treatment was not interrupted, and the rash resolved 40 minutes after its appearance. This subject did not have a sample for testing of ADA status at baseline.

  Comment: The narrative included no clinical descriptors of the rash. However, the transient nature raises a possibility of urticaria. It is noted that treatment was not interrupted. The limited narrative information allows only limited comment.

- Subject (b) (6) experienced "a mild event of hypersensitivity after receiving hydromorphone."

Comment: Above is the only information describing the event in the narrative. Thus, the information is vague and limited. However, the temporal relationship with hydromorphone could suggest a possible relatedness to that medication.

A 5th event was identified in study 2004: subject with a history of latex allergy experienced anaphylactic shock 22 days after treatment. The reaction was attributed to latex exposure.

Comment: This is the only SAE in the hypersensitivity analysis.

8.1.12. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Clinician-reported outcomes are discussed in section 8.1.

8.1.13. Safety Analyses by Demographic Subgroups

The Applicant presented safety analyses for demographic subgroups for Cohort 1, the pooled Phase 2 and 3 studies. This pool includes pediatric subjects from studies 2004 and 2008-09-03, the only studies that included pediatric subjects. There were no vehicle-treated subjects <18 years of age.

Age (<18 vs ≥18 years of age) - Pooled Cohort 1

In both the NexoBrid and SOC groups, mean % TBSA of TWs was higher in subjects < 18 years compared to those > 18 years of age. The number of subjects < 18 years relative to the number ≥ 18 years is too small to permit meaningful comparison(s) between the age groups.

Table 22: Overview of the Incidence of TEAEs by Age (<18 vs ≥18 years of age) – Pooled Phase 2 and Phase 3 Studies (Cohort 1)*

	<18 Years of Age			≥18 Years of Age		
	NXB N=20	SOC N=16	PBO N=0	NXB N=280	SOC N=179	PBO N=68
Baseline Characteristics						
Mean (SD) %TBSA All Wounds	13.0 (4.75)	14.7 (6.80)	-	12.8 (7.22)	11.2 (6.38)	11.6 (7.37)
Mean (SD) %TBSA of TWs	11.4 (3.55)	12.7 (5.80)	-	8.4 (5.55)	7.6 (4.60)	5.9 (3.45)
Mean (SD) number of TWs	2.1 (0.79)	2.6 (0.96)	-	1.8 (1.12)	1.6 (0.90)	1.3 (0.61)
Any TEAE	13 (65.0)	9 (56.3)	-	180 (64.3)	98 (54.7)	50 (73.5)

Any Serious TEAE	1 (5.0)	2 (12.5)	-	24 (8.6)	10 (5.6)	7 (10.3)

*Source: Table 53 Summary of Clinical Safety
NXB = NexoBrid; PBO = placebo control (Gel Vehicle); SD = standard deviation; SOC = standard of care; TBSA = Total Burn Surface Area; TEAE = treatment-emergent adverse event; TW = target wound

Gender – Pooled Cohort 1

Males constituted 73.3% of the NexoBrid group (n=300) and 76.4% of the SOC group (n=195). Males and females generally had similar baseline burn characteristics (%TBSAs and number of TWs) across treatment groups. "Any TEAE" was most commonly reported in the vehicle group for males and females. "Any Serious TEAE" was reported at the highest frequency in the Vehicle group for males (12.8%) and in the NexoBrid group for females (11.3%). "Any Serious TEAE" was reported in a similar proportion of males in the NexoBrid (7.3%) and SOC (6.0%) groups and in a larger proportion of females in the NexoBrid group (11.3%) compared to the SOC group (6.5%).

Table 23: Overview of the Incidence of TEAEs by Gender (Male and Female) – Pooled Phase 2 and Phase 3 Studies (Cohort 1)*

	Male			Female		
	NXB N=220	SOC N=149	PBO N=47	NXB N=80	SOC N=46	PBO N=21
Baseline Characteristics						
Mean (SD) %TBSA all Wounds	12.8 (7.11)	11.3 (6.51)	11.6 (7.41)	12.8 (7.05)	11.9 (6.41)	11.7 (7.46)
Mean (SD) %TBSA TWs	8.6 (5.52)	8.0 (5.01)	5.8 (3.28)	8.7 (5.40)	8.1 (4.56)	6.2 (3.88)
Mean (SD) number of TWs	1.8 (0.98)	1.7 (0.93)	1.1 (0.51)	2.1 (1.37)	1.7 (0.99)	1.5 (0.75)
Adverse Events						
Any TEAE	145 (65.9)	82 (55.0)	35 (74.5)	48 (60.0)	25 (54.3)	15 (71.4)
Any Serious TEAE	16 (7.3)	9 (6.0)	6 (12.8)	9 (11.3)	3 (6.5)	1 (4.8)

*Source: Table 54 Summary of Clinical Safety
NXB = NexoBrid; PBO = placebo control (Gel Vehicle); SD = standard deviation; SOC = standard of care; TBSA = Total Burn Surface Area; TEAE = treatment-emergent adverse event; TW = target wound

Race – Pooled Cohort 1

Caucasians constituted 69.0% of the NexoBrid group (n=300) and 70.8% of the SOC group (n=195). There were too few subjects of other races to permit meaningful comparisons Mean % TBSA of TWs was lowest in Black subjects (5.5%). The percentage of "Any TEAE" was highest in Black subjects (73.9%).

Table 24: Overview of the Incidence of TEAEs by Race – Pooled Phase 2 and Phase 3 Studies (Cohort 1)

	NXB N=300	SOC	PBO
Caucasian	n=207	n=138	n=42
Mean (SD) %TBSA of All Wounds	13.1 (7.14)	11.1 (6.15)	11.7 (6.76)
Mean (SD) %TBSA of TWs	8.9 (5.62)	8.0 (4.65)	6.3 (3.67)
Mean (SD) Number of TWs	1.9 (1.02)	1.7 (0.94)	1.3 (0.64)
Any TEAE	146 (70.5)	72 (52.2)	28 (66.7)
Any Serious TEAE	19 (9.2)	7 (5.1)	4 (9.5)
Middle Eastern	N=20	N=4	N=0
Mean (SD) %TBSA of All Wounds	12.6 (6.97)	12.7 (6.04)	-
Mean (SD) %TBSA of TWs	10.9 (6.08)	9.9 (4.52)	-
Mean (SD) Number of TWs	2.4 (1.27)	2.5 (0.58)	-
Any TEAE	10 (50.0)	2 (50.0)	-
Any Serious TEAE	1 (5.0)	1 (25.0)	-
Black	N=23	N=22	N=12
Mean (SD) %TBSA of All Wounds	9.7 (6.64)	9.2 (5.81)	5.8 (3.93)
Mean (SD) %TBSA of TWs	5.5 (3.73)	6.7 (5.29)	3.7 (1.33)
Mean (SD) Number of TWs	1.5 (0.79)	1.7 (0.70)	1.3 (0.62)
Any TEAE	17 (73.9)	15 (68.2)	12 (100)
Any Serious TEAE	2 (8.7)	3 (13.6)	2 (16.7)
Asian	N=38	N=20	N=12
Mean (SD) %TBSA of All Wounds	14.3 (7.23)	13.3 (7.18)	18.0 (7.27)
Mean (SD) %TBSA of TWs	8.5 (5.10)	6.7 (3.49)	7.0 (3.10)
Mean (SD) Number of TWs	1.9 (1.45)	1.3 (1.13)	1.0 (0)
Any TEAE	14 (36.8)	9 (45.0)	9 (75.0)
Any Serious TEAE	3 (7.9)	1 (5.0)	1 (8.3)
Other	N=12	N=11	N=2
Mean (SD) %TBSA of All Wounds	9.5 (4.37)	16.9 (7.86)	7.5 (9.19)
Mean (SD) %TBSA of TWs	7.2 (3.43)	12.8 (6.91)	5.5 (6.36)
Mean (SD) Number of TWs	1.5 (1.17)	2.3 (0.79)	2.0 (1.41)
Any TEAE	6 (50.0)	9 (81.8)	1 (50.0)
Any Serious TEAE	0	0	0

*Source: Table 55 Summary of Clinical Safety
NXB = NexoBrid; PBO = placebo control (Gel Vehicle); SD = standard deviation; SOC = standard of care; TBSA = Total Burn Surface Area; TEAE = treatment-emergent adverse event; TW = target wound

8.1.14. Specific Safety Studies/Clinical Trials

No specific safety studies were conducted for this program.

8.1.15. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were no events reported in the "Neoplasms benign, malignant and unspecified (incl cysts and polyps" system organ class in the Phase 2 and 3 studies.

Agency-recommended language for section 31.1 of the label (Carcinogenesis, Mutagenesis, Impairment of Fertility) follows:

> Carcinogenicity or fertility studies have not been conducted with (NexoBrid).
>
> (NexoBrid) was not genotoxic in a bacterial reverse mutation assay and an in vitro mammalian chromosome aberration assay.

Human Reproduction and Pregnancy

Two pregnancies were reported in study 2010, one in the NexoBrid group and one in the SOC group:

- A 24 y/o female who received NexoBrid treatment on (b) (6) and got pregnant during the follow-up period; however, the post-treatment timeframe was not provided in the narrative. She delivered on (b) (6) The outcome of the pregnancy was a live birth with congenital anomalies including Trisomy 21.

- A 39 y/o female was randomized to the SOC group. However, study eschar removal treatment was never undertaken for the subject.

Pediatrics and Assessment of Effects on Growth

The Applicant was not required to conduct a pediatric assessment, as NexoBrid received Orphan Drug designation. See Section 3.2.

However, 2 completed studies enrolled pediatric subjects:

- Study 2004 allowed enrollment of subjects 4 to 55 years of age and enrolled 182 subjects, ~20% of whom were < 18 years of age.
- Study 2008-09-03 allowed enrollment of subjects 4 to 70 years of age) and enrolled 36 subjects in total. From Listing 16.2.4-6 ("Demographics"), 2 pediatric subjects were enrolled: a 9 year-old male and a 10.2 year old female.

Additionally, at the time of submission of the BLA, a Phase 3 pediatric study (MW2012-01- 01 or CIDS) was ongoing in the United States, European Union, and Rest of World (ROW). This study is evaluating NexoBrid compared to SOC in the treatment of DPT and/or FT thermal burns, ultimately down to 0 years of age. (b) (4)

(b) (4) (b) (4)

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The product is not a controlled substance and does not have the potential for abuse or dependence. Withdrawal and rebound phenomena do not apply to this development program.

8.1.16. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Dr. Weintraub identified foreign postmarketing safety reports of anaphylaxis associated with use of NexoBrid. The Applicant listed immediate hypersensitivity reactions as an adverse reaction for NexoBrid and stated that hypersensitivity reactions have been reported with bromelain. However, the Applicant has not reported anaphylaxis with NexoBrid specifically.

Expectations on Safety in the Postmarket Setting

See "Safety Concerns Identified Through Postmarket Experience."

8.1.17. Integrated Assessment of Safety

The clinical development program consisted of 8 studies (6 Phase 2 studies and 2 Phase 3 studies) in which 467 subjects were treated with NexoBrid, 454 of whom were treated at the 2 grams (g) dose, the dose that the Applicant proposes in labeling. The discussion of safety generally focuses on the Phase 3 studies (Cohort 2), the primary safety data.

The 2 Phase 3 studies formed Cohort 2 and provided the primary safety data, with enrollment as follows:

- NexoBrid: n=177
- SOC: n=149
- Gel Vehicle: n= 24

The Applicant reported 8 deaths in the clinical development program: 7 in subjects who received NexoBrid and 1 in a subject who received SOC. A total of 7 deaths occurred during the Acute Period i.e., within 3 months post-wound closure. Despite the imbalance in reported deaths, generally there was no apparent relatedness to study treatment (e.g., death was

remote to study treatment, with reasonable attribution to another cause), or there were confounders to the assessment of relatedness (e.g., SOC treatment in same timeframe; underlying illness). For narratives that included information from autopsy reports, that information was in the form of excerpts and sometimes did not include a cause of death determination. See Appendix 19.6

The overall percentage of subjects who experienced SAEs in the Phase 3 studies was slightly higher in the NexoBrid arm compared to SOC. There were only single reports of most SAEs. Sepsis and "Wound infection bacterial" were the only 2 SAEs that were reported in more than one subject, and the multiple reports of both of these SAEs in a treatment group occurred in the NexoBrid arm.

The overall incidence of AEs that investigators graded as severe in Cohort 2, was slightly higher in the NexoBrid group (9.0%) compared to the SOC group (7.0%). The only severe events for which there were multiple reports were:

- Pain: 3 subjects (2%) NexoBrid; 2 subjects (1%) SOC
- Sepsis: 3 subjects (2%) NexoBrid; 2 subjects (1%) SOC (in the SOC group, represents one report of "sepsis", and one report of "septic shock")
- Scar: 2 subjects (1%) NexoBrid; none in the SOC group

TEAEs were most frequently reported in the Infections and Infestations system organ class for both the NexoBrid and SOC groups, 23.2% and 19.5%, respectively. For both treatment groups, Wound infection was the most frequently reported PT in this system organ class and was reported with similar frequency in both treatment groups: NexoBrid- 9 subjects (5.1%) and SOC- 7 subjects (4.7%). Events were next most frequently reported in the Skin and subcutaneous tissue disorders system organ class: NexoBrid- 20.9% and SOC- 16.8%. For both treatment groups, Pruritus was the most frequently reported PT in this system organ class and was reported with a higher frequency in the NexoBrid- 27 subjects (15.3%) compared to SOC- 19 subjects (12.8%). Also, Pruritus was the overall most frequently reported PT in both treatment groups.

Overall, 63 subjects (36%) in the NexoBrid group and 45 subjects (30%) experienced local TEAEs that were related to the TW. Generally, there were single reports of most events. Events were most commonly reported in the Skin and subcutaneous tissue disorders system organ class: 27 subjects (15%) in the NexoBrid group and 18 subjects (12%) in the SOC group. The most common TEAE in this SOC in both treatment groups was Pruritus: 22 subjects (12%) in the NexoBrid group and 14 subjects (9%) in the SOC group. Events for which there were multiple reports in either treatment group are discussed in Section 8.2.3.

Submission-Specific Safety Issues

The Applicant identified pain, pyrexia, wound infection, immediate hypersensitivity reactions, and coagulation parameter abnormalities as key risks of NexoBrid treatment. The reviewer

included in the following discussion, as it was considered to relate to pyrexia and wound infection.

1. Pain (see Section 8.2.5.1)

In the absence of adequate control measures, it is readily apparent why NexoBrid-related procedures would be painful (likely, even, intensely so): wound preparation requires removal of gross contaminants and blisters, then a mixture of proteolytic enzymes (NexoBrid), intended to dissolve leathery eschar, is applied to an open wound, and, finally, the dissolved eschar is rubbed off, with rubbing to be continued "until the appearance of a pinkish surface with bleeding points or a whitish tissue."[28] With pain management control for NexoBrid treatment, pain-related TEAEs were reported at similar rates in the NexoBrid and SOC groups. However, the pain control measures for NexoBrid are not trivial and may include general anesthesia i.e., the same method of pain control as for surgical SOC. Therefore, treatment with NexoBrid may not intrinsically translate to avoidance of general anesthesia.

2. Pyrexia (see Section 8.2.5.2)

Overall, "fever-related" TEAEs were higher in the NexoBrid group (15.3%) compared to the SOC group (12%). Temperatures >39°C (102°F) were to have been recorded as "pyrexia" AEs. Although the cut-point for defining fever (>39°C) may appear somewhat high, potentially missing some events that might generally be considered fever e.g., 101°F, this cut-point is among the criteria for defining sepsis in burn patients.[11] Additionally, investigators could exercise judgement in recording a lower temperature as a pyrexia AE. The Applicant did not discuss a possible mechanism for the pyrexia (e.g.., independent of infection). Fever can be a manifestation of the pro-inflammatory state and metabolic and physiologic disruptions associated with severe burn injuries.[23] However, it appears that the Applicant considered it to be infection related, as the mitigation efforts for this adverse reaction were the same as those for wound infection.

3. Wound infection (see Section 8.2.5.3)

Although the overall incidences of wound infection were similar between the NexoBrid and SOC groups (~5.0% in each group), the events in this category may not have all reflected events at TWs. When TWs were specifically considered, non-fungal infections occurred at a

[28] Protocol for study MW 2010-03-02, Version 11; p. 58 of 173.

higher incidence in the SOC arm compared to the NexoBrid arm, 9% and 6%, respectively. All of the fungal TW infection events (n=3) were reported in the NexoBrid arm, ~2%. The 3 wound infections that were reported as SAEs appeared to have occurred at TWs and were reported in both treatment arms: 2 in the NexoBrid arm and 1 in the SOC arm. A total of 3 wound infections were reports as SAEs, and, from the narratives, all appeared to be infections involving TWs. A total of 2 of these SAEs occurred in the NexoBrid group, and 1 was in the SOC group. Therefore, the occurrence of TW infections was generally similar between treatment groups.

4. Sepsis (see Section 8.2.5.4)

The overall incidences of sepsis-related TEAEs were similar in the NexoBrid group (2.8%) and the SOC group (2.0%). Of the 5 events that occurred in the NexoBrid arm, 4 were SAEs, and a relatedness of the SAEs to NexoBrid could either not be determined from the narrative information (n=2) or seemed unrelated (n=2).

5. Immediate hypersensitivity reactions (see Section 8.2.5.5)

This reaction likely relates to cross reaction to determinants on bromelain in individuals who are already sensitized. A NexoBrid-induced hypersensitivity reaction to NexoBrid seems an unlikely scenario, as the product is intended for treatment for one burn episode (which the Applicant proposes may consist of 2 applications of 4 hours each). Also, the likelihood of an individual sustaining more than one serious burn injury over a lifetime would seem low. Only one hypersensitivity event was considered an SAE in the Phase 3 studies: a subject with a history of latex allergy experienced anaphylactic shock that was attributed to latex exposure. However, anaphylaxis following exposure to NexoBrid has been reported postmarketing.

6. Coagulation Parameters (See Section 8.2.3)

There were no SAEs relating to coagulation abnormalities in the Phase 3 studies. There was 1 TEAE report of “coagulopathy” and 2 of “hemorrhagic anemia”; all 3 reports were in the SOC arm. “Anemia postoperative” was reported, as follows: 2 subjects in the NexoBrid arm and one subject in the SOC arm. “Post procedural hemorrhage” was reported in one subject in the NexoBrid group. From the available information, clinical manifestations of abnormalities of coagulation parameters were not apparent.

Dosing

The Applicant intends that NexoBrid may be applied 1 or 2 times, to ≤15% TBSA, with the

duration of each application being 4 hours and that it may be applied to up to (b) (4)% TBSA (in 2 separate sessions treating up to (b) (4) The Applicant intends that NexoBrid be applied at a dose of 2 g NexoBrid per 1% of TBSA.

In the Phase 3 studies, only 18 subjects (10%) received 2 applications of NexoBrid, and only 19 subjects (11%) had TBSA > 15%. Maximal use data are limited for use on mean TBSA > 10%. Of 19 subjects who applied 2 doses and had maximal use data (studies 2010 and MW2008-09-03), only 2 subjects received the (b) (4) dosage of 60 g, and the data are limited for doses greater than 20 g per application.

Thus, the data are too limited to adequately assess the safety of 2 applications, use in subjects with > 15% TBSA or the (b) (4) dosage of 60 g. Additionally, the Applicant did not define the interval between the 2 applications. The estimated systemic half-live is ~ 12 hours. Therefore, applications should be spaced at appropriate intervals to avoid systemic accumulation. The PK data revealed quantifiable serum concentrations through 48 hours following topical application. See the clinical pharmacology review in Section 6 for the detailed discussion.

In short, the provided data are inadequate to support the dosing regimen proposed by the Applicant in draft labeling. To support this regimen, the Applicant will need to conduct an adequate maximal use study, consisting of an appropriate number of subjects, with %TBSA in the upper range, who receive 2 applications of NexoBrid, at doses at the upper end of what is proposed in draft labeling. Based on the available data, the labeled dosing regimen would need to be very restrictive and redefine the target population according to %TBSA, number of applications and maximum dosage.

Summary

The 2 Phase 3 studies provided the primary safety data, with enrollment as follows: NexoBrid- n=177, SOC- n=149, and Gel Vehicle- n= 24. The Applicant reported 8 deaths in the clinical development program, 7 in subjects who received NexoBrid and 1 in a subject who received SOC. Despite the imbalance in reported deaths, generally there was no apparent relatedness to study treatment (e.g., death was remote to study treatment, with reasonable attribution to another cause), or there were confounders to the assessment of relatedness (e.g., SOC treatment in same timeframe; underlying illness).

The overall percentage of subjects who experienced serious adverse events in the Phase 3 studies was slightly higher in the NexoBrid arm [15 (8.5%)] compared to SOC [10 (6.7%)]. There were only single reports of most SAEs. Sepsis and “Wound infection bacterial” were the only 2 SAEs that were reported in more than one NexoBrid-treated subject, with more reports in the NexoBrid arm[3 (1.7%) and 2 (1.1%), respectively], as compared to SOC [1 (0.7%) report of sepsis].

Treatment-emergent adverse events (TEAEs) were most frequently reported in the Infections and Infestations system organ class for both the NexoBrid and SOC groups, 23.2% and 19.5%, respectively. For both treatment groups, Wound infection was the most frequently reported PT in this system organ class and was reported with similar frequency in both treatment groups: NexoBrid- 9 subjects (5.1%) and SOC- 7 subjects (4.7%). Events were next most frequently reported in the Skin and subcutaneous tissue disorders system organ class: NexoBrid- 20.9% and SOC- 16.8%. For both treatment groups, Pruritus was the most frequently reported preferred term (PT) in this system organ class and was reported with a higher frequency in the NexoBrid- 27 subjects (15.3%) compared to SOC- 19 subjects (12.8%). Also, Pruritus was the overall most frequently reported PT in both treatment groups.

The Applicant identified pain, pyrexia, wound infection, immediate hypersensitivity reactions, and coagulation parameter abnormalities as key risks of NexoBrid treatment. With pain management control for NexoBrid treatment, pain-related TEAEs were reported at similar rates in the NexoBrid and SOC groups: 8 (4.5%) and 6 (4.0), respectively. Overall, "fever-related" TEAEs were reported in a higher proportion of subjects in the NexoBrid group, 27 (15.3%), compared to the SOC group, 18 (12%). Non-fungal TW infections occurred at a higher incidence in the SOC arm compared to the NexoBrid arm, 9% and 6%, respectively. All of the fungal TW infection events (n=3) were reported in the NexoBrid arm, ~2%. A total of 4 events were reported in the Immune system disorders system organ class in NexoBrid subjects in study 2010: 2 events were apparent reactions to hydromorphone, and 2 were vague reports of "rash." The single report of anaphylactic shock in the Phase 3 studies (study 2004) was due to a latex allergy. There was 1 TEAE report of "coagulopathy" and 2 of "hemorrhagic anemia"; all 3 reports were in the SOC arm. The overall incidences of sepsis-related TEAEs were similar in the NexoBrid group 5 (2.8%) and the SOC group 3 (2.0%). Of the 5 events that occurred in the NexoBrid arm, 4 were SAEs, and a relatedness of the SAEs to NexoBrid could either not be determined from the narrative information (n=2) or seemed unrelated (n=2).

The available safety information suggests that the safety profile of NexoBrid in the target population could be similar to SOC. However, ultimately, safety of NexoBrid cannot be established given that the microbial control strategy does not mitigate the risk of potential adventitious agents that may be introduced during the manufacturing process. See Sections 4.2 and 4.3.

8.2. Statistical Issues

Study 2010 is the key study supporting the efficacy of NexoBrid. Study 2010 demonstrated that NexoBrid is superior to vehicle gel in the incidence of eschar removal. Other endpoints compared NexoBrid to SOC. NexoBrid was superior to SOC for the incidence of surgical excision for eschar removal. However, the planned secondary endpoint of blood loss due to eschar removal was not interpretable due to the large amount of missing data and concerns with

interpreting the blood loss calculations over potentially lengthy eschar removal treatment periods make it difficult to interpret the results of this endpoint and translate it to clinical benefit for the subjects. In addition, although Study 2010 utilized blinded assessors for eschar removal, wound closure, and scar assessments, clinical site inspections indicated that at least at some centers, procedures to maintain the blind were not consistently followed, which increases the challenges of interpreting the supportive efficacy endpoints.

8.3. Conclusions and Recommendations

The Applicant provided substantial evidence of effectiveness from a randomized, vehicle-controlled, Phase 3 study, MW2010-03-02 (2010), which evaluated NexoBrid for eschar removal in the target population of adult subjects with DPT and/or FT thermal burns. The available safety information suggests that the safety profile of NexoBrid in the target population could be similar to SOC. However, the safety of NexoBrid cannot be established given that the microbial control strategy does not mitigate the risk of potential adventitious agents that may be introduced during the manufacturing process. The OPQ could not conclude that manufacture of NexoBrid is well-controlled, such that production of a pure product that is potent for the duration of shelf-life would result. Further, the requisite manufacturing facility inspections could not be performed due to travel restrictions related to the global pandemic. Before this application can be approved, these inspections will need to be completed and any findings assessed. Therefore, the Division of Dermatology and Dentistry recommends a Complete Response action at this time. Additionally, to support the proposed dosing regimen, the Applicant will need to conduct an adequate maximal use study, consisting of an appropriate number of subjects, with %TBSA in the upper range, who receive 2 applications of NexoBrid, at doses at the upper end of what is proposed in draft labeling.

9 Advisory Committee Meeting and Other External Consultations

Advisory committee meeting was not convened for discussion of this application.

10 Pediatrics

See Section 10.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling is being held until the next review cycle.

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS review has been deferred.

13 Postmarketing Requirements and Commitment

No PMCs or PMRs for this review cycle.

14 Division Director (DPT-II) Comments

Not applicable.

15 Division Director (OCP) Comments

Not applicable.

16 Division Director (OB) Comments

Not applicable.

17 Division Director (Clinical) Comments

Not applicable.

18 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to issue a Complete Response action for BLA 761192 submitted in support of the marketing approval for NexoBrid. NexoBrid, a new botanical and biologic product, contains proteolytic enzymes enriched in bromelain. The Applicant proposes the product be indicated for eschar removal (or debridement) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

Evidence of effectiveness is derived primarily from a single randomized, controlled, phase 3 study which compared NexoBrid for eschar removal in adult subjects with DPT and/or FT thermal burns to gel vehicle or standard of care (SOC) controls. NexoBrid was superior to gel vehicle for the primary endpoint, incidence of ≥95% eschar removal, and superior to SOC for the secondary endpoint of incidence of excision for eschar removal. Supportive evidence of effectiveness in eschar removal was provided from an open-label phase 3 study in which Debrase (now called NexoBrid) was superior to SOC with a smaller proportion of Debrase-treated subjects with DPT wounds undergoing excision compared to subjects receiving SOC.

In clinical trials, serious adverse events were slightly higher in the NexoBrid arm as compared to SOC (8.5% vs. 6.7%). The most common serious adverse events involved sepsis or bacterial wound infection (5 total reports on NexoBrid vs. 1 report on SOC).

Approval of NexoBrid is not recommended at this time due to numerous deficiencies which preclude a full evaluation of product quality. Identified deficiencies pertain to botanical raw material authentication, and the microbial control strategy for the manufacture of the bromelain special production and drug substance, and for the drug product. Additionally, the requisite manufacturing facility inspections could not be conducted due to travel restrictions during the global pandemic. Before this application can be approved, these inspections will need to be completed and any findings assessed. Further, there are insufficient data submitted to support the applicant's proposed dosing recommendations; labeling discussions remain unresolved at this time.

19 Appendices

19.1. References

See footnotes

19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): *MW2002-04-01, MW2004-11-02, MW2010-02-03*

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 88		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Recommended revisions to the nonclinical portions of labelling

Revisions to the applicant's proposed wording for the nonclinical and related sections of the labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~strikethrough~~ wording be deleted from the NEXOBRID label proposed by the applicant. The subheadings in Section 8.1 should be in underlined format. Refer to the clinical review for recommended revisions to the clinical portions of labeling in Section 8.

(b) (4)

(b) (4)

Clean version of the recommended nonclinical portions of labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

NEXOBRID contains proteolytic enzymes indicated for eschar removal (b) (4) in adults with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

8.1 Pregnancy

Risk Summary

There are no available data on NEXOBRID use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In embryofetal developmental studies in rats and rabbits, intravenous doses up to 4 and 0.1 mg/kg/day NEXOBRID were administered to pregnant rats and rabbits, respectively, during organogenesis. No significant developmental toxicities were observed in these studies. However, severe maternal toxicities were noted and the tolerable maternal exposure levels were much lower compared with the maximum human exposure in clinical setting.

12.1 Mechanism of Action

The mixture of enzymes in NEXOBRID dissolves burn wound eschar. The specific components responsible for this effect have not been identified.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity or fertility studies have not been conducted with NEXOBRID.

NEXOBRID was not genotoxic in a bacterial reverse mutation assay and an in vitro mammalian chromosome aberration assay.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance of the Assays for Measuring NexoBrid in Human Serum

To detect and quantify NexoBrid in human serum, the Applicant developed and validated a modified sandwich ECL immunoassay based on immunorecognition of NexoBrid active

ingredient proteins by affinity-purified rabbit polyclonal anti-NexoBrid antibodies. The anti-NexoBrid antibodies are labeled with SulfoTag® (a Ruthenium ester) and biotin. The Applicant assessed the systemic exposure of NexoBrid in studies MW2008-09-03 and MW2010-03-02 using this method. The ECL-based assay was originally developed and validated in 2009 by (b) (4) However, during the clinical development cycle the Applicant switched to a different bioanalysis site (b) (4) (b) (4) While both sites used the same assay principle, two different lots of anti-NexoBrid polyclonal antibodies were used by the Applicant at each site. Table A1 and Table A2 provide a summary of the validation parameters and method performance for the ECL-assay to detect NexoBrid in human serum at the (b) (4) site and (b) (4) site respectively. Note that while the assay to measure NexoBrid in human serum was validated at both sites, the Applicant was unable to conduct a cross-validation study across the two sites due to loss of samples from the (b) (4) site. As a result it is difficult to bridge the PK data generated at the (b) (4) site and the (b) (4) site. This issue primarily affected the analysis of samples for PK assessment from study MW2008-09-03. Samples for the first 23 patients from study MW2008-09-03 were analyzed at the (b) (4) site and for the remaining 13 patients at the (b) (4) site. Samples from the study MW 2010-03-02 were analyzed exclusively at the (b) (4) site.

Table A29: Summary method performance of a bioanalytical method to measure NexoBrid in human serum ((b) (4) site)

Bioanalytical method validation report name, amendments, and hyperlinks	Immunoassay Method Validation Report: Validation of an Electrochemiluminescence (ECL) method for the quantitation of Debrase in Human Serum. (b) (4); 2009 (090656VBWS_MYI) Two bridging validation reports for update of LTS data, qualification of a new Reference Standard lot and qualification of new lots of labeled reagents: Immunoassay Method Partial Validation Report: Partial Validation of an Electrochemiluminescence (ECL) method for the quantitation of Debrase in Human Serum. (b) (4); 2010 (100051PVEKF_MYI) Revised Immunoassay Method Partial Validation Report: Partial Validation of an Electrochemiluminescence (ECL) method for the quantitation of Debrase in Human Serum. (b) (4); 2011 (100051PVEKF_MYI R1)	
Method description	A modified sandwich ECL immunoassay is based on immunorecognition of NexoBrid active ingredient proteins by affinity-purified rabbit polyclonal anti-NexoBrid antibodies. The anti-NexoBrid antibodies are labeled with SulfoTag® (a Ruthenium ester) and biotin. The standard calibrators, quality control (QC) controls, and samples are incubated with both the biotinylated and the ruthenylated antibodies for 2 hours and immobilized on a streptavidin-coated microplate by binding of the capture antibody, which would pull the analyte in matrix down onto the plate. All other reagents are washed off at this stage. In the presence of the proprietary (b) (4), the plates are then read on the ECL reader. A NexoBrid standard curve is created for each microplate, and the concentration of NexoBrid in the samples is interpolated.	
Materials used for calibration curve & concentrations	Debrase powder Lot F 05-52 090656VBWS_MYI, Lot 1-05-17 (100051PVEKF_MYI).	
Validated assay range	3.906 ng/mL (LLOQ) - 500.0 ng/mL (ULOQ)	
Material used for QCs & concentrations	Debrase powder Lot F 05-52 090656VBWS_MYI, Lot 1-05-17 (100051PVEKF_MYI). QCs concentrations: ULOQ – 500 ng/ml, HQC – 400 ng/ml, MQC – 50 ng/ml, LQC – 10 ng/ml, LLOQ – 3.906 ng/ml.	
Minimum required dilutions (MRDs)	1:5	
Source & lot of reagents (LBA)	Biotinylated rabbit anti-Debrase antibody, prepared by (b) (4) sulfoTAG labeled (b) (4) prepared by (b) (4) (b) (4) (b) (4); Blocker (b) (4) in PBS, (b) (4); (b) (4) protease inhibitor tablet, (b) (4) Dulbeccos PBS, 10X DPBS, (b) (4); Tween-20, (b) (4) HPLC grade water, (b) (4); pooled human serum, (b) (4).	
Regression model & weighting	5-parameter logistic curve-fit	
Validation parameters	Method validation summary	Source location

Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Table 3 of Report # 090656VBWS
	Cumulative accuracy (%bias) from LLOQ to ULOQ Debrase	-1.3 to 6.3% x to y%	Table 3 of Report # 090656VBWS
	Cumulative precision (%CV) from LLOQ to ULOQ Debrase	2.0 to 9.6% x to y%	Table 3 of Report # 090656VBWS
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs: Debrase LLOQ: -17.8% to 28.0% (mean -2.5%) LQC: -31.5% to 13.8% (mean -3.8%) MQC: -20.1% to 7.8% (mean -4.6%) HQC: -20.6% to 7.7% (mean -5.1%) ULOQ: -15.8% to 10.3% (mean -6.9%)		Table 4 of Report # 090656VBWS
	Inter-batch %CV QCs: Debrase	≤ 18.4% ≤ x%	Table 4 of Report # 090656VBWS
	Total Error (TE) QCs: Debrase	≤20.9 % ≤ x%	Table 4 of Report # 090656VBWS
Selectivity & matrix effect	Selectivity of the assay was determined by spiking five individual male and five individual female adult human serum samples with Debrase at the LQC (10.00 ng/mL). Recovery was acceptable for 90% of the samples. 100% un-spiked samples tested BQL.		Table 11 of Report # 090656VBWS
Interference & specificity	Specificity was not performed for this study.		-
Hemolysis effect	Hemolysis effect was not assessed.		-
Lipemic effect	Lipemic effect was not assessed.		-
Dilution linearity & hook effect	Dilutional linearity was demonstrated up to 1000-fold from as high as 5 x 10^5 ng/mL Observed bias ranged from 2.3% to 16.6%.		Table 10 of Report # 090656VBWS

Bench-top/process stability	Bench-top stability was established after 3 and 24 hours of storage of LQC and HQC stability samples in room temperature. Observed bias ranged from -14.2% to -9.8% after 3 hours, and from -27.0% to -19.1% after 24 hours. Debrase was not stable after storage for 24 hours at room temperature but was stable after 3 hours of room temperature storage. Refrigerated stability (4°C) of LQC and HQC stability samples was established up to 24 hours. Observed bias ranged from -12.4% to 4.1% after 3 hours, and from -16.6% to -6.4% after 24 hours. Debrase was stable after 24 hours of 4°C storage.	Table 6 of Report # 090656VBWS Table 7 of Report # 090656VBWS
Freeze-Thaw stability	Freeze-Thaw stability of LQC and HQC was established after 5 freeze/thaw cycles. Observed bias ranged from -12.6% to -2.1	Table 8 of Report # 090656VBWS
Long-term storage	Long-Term Stability (-80°C): Stability of Debrase using LQC and HQC samples was established up to 30 days. Long-term stability (LTS) of Debrase in human serum was performed after 364 days of storage at -20 °C and -80 °C. Debrase was stable for up to 364 days after being stored at -20 °C and -80 °C.	Table 9 of Report # 090656VBWS Table A-1 and A-2 of Report # 100051PVEKF_MYI_R1 Addendum A
Parallelism	Parallelism data for Debrase in human serum obtained during Study MW 2008-09-03 was demonstrated.	100040AEKF_MYI, Table C-1, Table B-A-7
Carry over	Not applicable for this assay method	-
Method performance in study Feasibility Study: Enzymatic Debridement in Patients with Partial Thickness Burns" MW2008-09-03 PK Report. This report includes both (b) (4) site and (b) (4) site PK data.		
Assay passing rate	Analytical passing rate: 100% (7/7) 100% (6/6) 100%, 100% (6/6, 2/2)	Table 2 MW 2008-09-03 Bioanalytical report 100040AEKF_MYI, Table 1 100040AEKF_MYI_R1, Table A-1 100040AEKF_MYI_R2, Tables A-1 and B-A-1

Standard curve performance	Cumulative bias range: -2.9% to 9.1% Cumulative precision: ≤5.5% CV Cumulative bias range: -2.8% to 9.6% Cumulative precision: ≤9.7% CV Cumulative bias range: -1.0% to 3.6% Cumulative precision: NA Cumulative bias range: -0.8% to 2.6% Cumulative precision: NA	Table 3 MW 2008-09-03 Bioanalytical report 100040AEKF_MYI_R2, Table 3 Table A-3 Table B-A-3 Table B-B-3
QC performance	Cumulative bias range: -1.2% to 8.1% Cumulative precision: ≤9.9% CV TE: ≤15.3% Cumulative bias range: -4.3% to 1.0% Cumulative precision: ≤6.5% CV TE: ≤8.1% Cumulative bias range: -3.8% to -3.1% Cumulative precision: ≤7.6% CV TE: ≤10.7% Cumulative bias range: -6.9% to -1.1% Cumulative precision: ≤11.5% CV TE: ≤17.2%	Table 4 MW 2008-09-03 Bioanalytical report 100040AEKF_MYI_R2, Table 4 Table A-4 Table B-A-4 Table B-B-4
Method reproducibility	Incurred sample reanalysis was performed in 20/48 (42%) of study samples. Repeat analysis of incurred samples demonstrated that 100% of samples were within ±30% per specification.	Table D-1 Appendix D MW 2008-09-03 Bioanalytical report 100040AEKF_MYI_R2, Table D-1
Study sample analysis/ stability	Samples were analyzed as received. Of the 139 samples that were analyzed, 6 samples were analyzed outside of the established stability limit of 364 days at -80 °C.	

Table A2: Summary method performance of a bioanalytical method to measure NexoBrid in human serum ((b) (4) site)

Bioanalytical method validation report name, amendments, and hyperlinks	Immunoassay Partial Method Validation Report: Validation of an Electrochemiluminescence (ECL) method for the quantitation of Debrase in Human Serum. (b) (4) 2015 (141049PVRDW_MYI) An updated validation report including full long-term stability (LTS) data was issued in 2018 (141049PVRDW_MYI_R1). Editorial updates were included in November 2019 (141049PVRDW_MYI_R2), and critical reagent information was added in Jan 2020 (141049PVRDW_MYI_R3).		
Method description	A modified sandwich ECL immunoassay is based on immunorecognition of NexoBrid active ingredient proteins by affinity-purified rabbit polyclonal anti-NexoBrid antibodies. The anti-NexoBrid antibodies are labeled with SulfoTag® (a Ruthenium ester) and biotin. The standard calibrators, quality control (QC) controls, and samples are incubated with both the biotinylated and the ruthenylated antibodies for 2 hours and immobilized on a streptavidin-coated microplate by binding of the capture antibody, which would pull the analyte in matrix down onto the plate. All other reagents are washed off at this stage. In the presence of the proprietary (b) (4) (b) (4) the plates are then read on the ECL reader. A NexoBrid standard curve is created for each microplate, and the concentration of NexoBrid in the samples is interpolated.		
Materials used for calibration curve & concentrations	NexoBrid powder Lot MD2/L-02-42 (141049PVRDW_MYI, 141049PVRDW_MYI_R1), Debrase, lot MD2/01850 (141049PVRDW_MYI_R2, 141049PVRDW_MYI_R3).		
Validated assay range	10.0 ng/mL (LLOQ) - 500.0 ng/mL (ULOQ)		
Material used for QCs & concentrations	NexoBrid powder Lot MD2/L-02-42 (141049PVRDW_MYI, 141049PVRDW_MYI_R1), Debrase, lot MD2/01850 (141049PVRDW_MYI_R2, 141049PVRDW_MYI_R3). QCs concentrations: ULOQ – 500 ng/ml, HQC – 400 ng/ml, MQC – 200 ng/ml, LQC – 25.0 ng/ml, LLOQ – 10.0 ng/ml.		
Minimum required dilutions (MRDs)	1:5		
Source & lot of reagents (LBA)	anti-Debrase antibody, prepared by (b) (4); sulfoTAG labeled (b) (4) ID No. NB2156p48 prepared by (b) (4) Biotinylated (b) (4) ID No. NB2156p47 prepared by (b) (4) (b) (4) (b) (4) in PBS, (b) (4); (b) (4) protease inhibitor tablet, (b) (4) Dulbeccos PBS, 10X DPBS, (b) (4); Tween-20, (b) (4) (b) (4); water, (b) (4) pooled human serum, (b) (4)		
Regression model & weighting	5-parameter logistic curve-fit		
Validation parameters	Method validation summary		Source location
Standard calibration curve performance	Number of standard calibrators from LLOQ to ULOQ	8	Table 3 of Report # 141049PVRDW_MYI

during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ Debrase	-1.3 to 2.3%	Table 3 of Report # 141049PVRDW_MYI
	Cumulative precision (%CV) from LLOQ to ULOQ Debrase	1.0 to 2.6%	Table 3 of Report # 141049PVRDW_MYI
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs QCs: Debrase LLOQ: -18.1% to 10.2% (mean -3.4%) LQC: -14.4% to 10.1% (mean 0.1%) MQC: -17.2% to 15.4% (mean -1.7%) HQC: -17.2% to 19.9% (mean 0.1%) ULOQ: -17.1% to 19.6% (mean -0.9%)		Table 4 of Report # 141049PVRDW_MYI
	Inter-batch %CV QCs: Debrase	≤ 12.4%	Table 4 of Report # 141049PVRDW_MYI
	Total Error (TE) QCs: Debrase	≤ 13.3%	-
Selectivity & matrix effect	Selectivity of the assay was determined by spiking five individual male and five individual female adult human serum samples with NexoBrid at the LLOQ (10.00 ng/mL) and LQC (25 ng/ml). Recovery was acceptable for 100% of the samples at both levels. 100% un-spiked samples tested BQL.		Table 6 of Report # 141049PVRDW_MYI
Interference & specificity	Specificity was not performed for this study.		-
Hemolysis effect	Three replicates each from samples were spiked with NexoBrid at LQC (25.0 ng/mL) and HQC (400 ng/mL) levels in human serum containing 5% (v/v) lysed whole blood. All hemolyzed samples met acceptance criteria at both the HQC and LQC concentration levels.		Table 7 of Report # 141049PVRDW_MYI
Lipemic effect	Assessed by analyzing samples spiked with NexoBrid at LQC (25.0 ng/mL) and HQC (400 ng/mL) levels prepared with lipemic serum. Lipemic QC samples were tested twice and did not meet the acceptance criteria at either the HQC or LQC levels. Study samples will be visually inspected for lipemia prior to analysis.		Table 8 of Report # 141049PVRDW_MYI
Dilution linearity & hook effect	Dilutional linearity was determined from up to 100,000-fold of the ULOQ. The results indicate that it is possible to dilute samples down onto the quantitative part of the curve with a dilution factor up to 1:5000.		Table 5 of Report # 141049PVRDW_MYI

Bench-top/process stability	Bench-top stability was established after 1, 2, 4, and 8 hours of storage in room temperature. Observed bias ranged from -14.0% to 3.5%. Refrigerated stability (4°C) was established up to 24 hours. Observed bias ranged from -12.8% to -1.2%.	141049PVRDW_MYI_R1, Table A-5.2 Table A-7
Freeze-Thaw stability	Freeze-Thaw stability was established after 4 freeze/thaw cycles. Observed bias ranged from 0.4% to 7.2%.	141049PVRDW_MYI_R1, Table A-6
Long-term storage	Long-Term Stability (-20°C): Stability of NexoBrid using LQC and HQC samples was established up to 93 days. Long-Term Stability (-80°C): Stability of NexoBrid using LQC and HQC samples was established up to 561 days.	141049PVRDW_MYI_R1, Table A-9.2 Table A-10
Parallelism	A sample dilution response curve was not evaluated for parallelism to the standard concentration response curve.	-
Carry over	Not applicable for this assay method	-
Method performance in study A multicenter, multinational, randomized, controlled, assessor blinded study, performed in subjects with thermal bums, to evaluate the efficacy and safety of NexoBrid compared to Gel Vehicle and compared to Standard of Care" MW 2010-03-02 PK Report		
Assay passing rate	Analytical passing rate: 70% (16/23)	151726ARDW_MYI, Table 1
Standard curve performance	• Cumulative bias range: -0.9 to 2.5% • Cumulative precision: ≤5.9% CV	Table 3 Immunoassay bioanalytical report 151726ARDW_MYI (appendix of PK report)
QC performance	• Cumulative bias range: -9.5 to -7.5% • Cumulative precision: ≤ 12% CV • TE: ≤ 19.7%	Table 2 Immunoassay bioanalytical report 151726ARDW_MYI (appendix of PK report)
Method reproducibility	Incurred sample reanalysis was performed in 35/246 (14.2%) of study samples. 71.4 % of samples were within ±30% per specification.	Table 7 Immunoassay bioanalytical report 151726ARDW_MYI (appendix of PK report)
Study sample analysis/ stability	Samples were analyzed as received. Of the 246 samples that were analyzed, 88 samples were analyzed outside of the established stability limit of 561 days at -80 °C or 93 days at -20 °C. The Applicant was asked to reanalyze PK parameters by excluding samples that were stored beyond the established long term stability period.	

19.4.2. Individual Study Review(s)

Study MW2008-09-03

Study MW2008-09-03 was a Phase 2, open-label, single-arm, multi-center study. Thirty Six (36) patients were enrolled in this study which included children (4 to 17 years of age) and adults (18 to 70 years of age) with thermal burn wounds, defined as 'partial thickness' (mid and deep dermal) and/or full thickness (FT), with a range of 4% to 30% TBSA, with total of ≤30% TBSA burns requiring hospitalization. Of the 36 patients enrolled, 22 patients treated with single application and 14 patients treated with two consecutive applications of NexoBrid. Each subject received NexoBrid at a dose of 2 grams or 5 grams of NexoBrid sterile powder that were mixed in 20 grams or 50 grams of sterile Gel Vehicle respectively (ratio of 1:10) to obtain NexoBrid Gel. Twenty (20) grams of NexoBrid gel was applied on 1% of TBSA for four hours. NexoBrid was not applied to more than 15% TBSA in any one session. Subjects received NexoBrid in two separate sessions if the burned wound area was more than 15% TBSA or if the debridement of the first application was not complete and another treatment session was required.

PK Sampling: Blood samples were taken from each subject to measure NexoBrid absorption. For subjects with one single application (for patients with ≤15% TBSA), blood samples were taken prior to NexoBrid treatment, then 2, 4, 12, 24, and 48 hours post start of application. For patients with two planned applications (for patients up to 30% TBSA) blood samples were taken before the first treatment (time 0), 0.5 hour and 4 hours (time 0 of second application). Following the second application, blood samples were taken at 0.5, 4, 24, and 48 hours after start of debridement.

Summary of pharmacokinetics:
Quantifiable concentrations were observed in all 36 patients evaluated up to 48 hours post dose administration. It was noted that 7 patients had measurable concentrations of NexoBrid in the pre-dose samples. The reason for this is not understood and for the purpose of PK calculations, these concentrations were set equal to zero.

PK analysis was conducted at 2 bioanalytical sites – (b) (4) for the first 23 patients, and (b) (4) for the remaining 13 patients. Evaluation of the data demonstrated a difference in exposure between the 2 analysis sites utilized for this study with values for patients from the (b) (4) analysis site revealing much higher exposures than from the patients from the (b) (4) analysis site (See section 6.3.2 for additional discussion). Therefore, the PK parameters are separated based on analysis site (either (b) (4) or (b) (4). Table A3 summarizes the individual and mean NexoBrid PK parameters from study MW2008-09-03 for samples analyzed at the (b) (4) site. Table A4 summarizes the individual and mean NexoBrid PK parameters from study MW2008-09-03 for samples analyzed at the (b) (4) site.

Table A3. Individual and mean NexoBrid PK parameters from study MW2008-09-03 for samples analyzed at the (b) (4) site

Analysis Site	Treatment	Subject ID	Total %TBSA Treated	Dose / Treatment	Gender	T_{max} (hr)	C_{max} (ng/mL)	C_{max} / Dose	AUC_{0-4} (hr*ng/mL)	AUC_{0-4} / Dose	AUC_{last} (hr*ng/mL)	AUC_{last}/ Dose	$t_{1/2}$ (hr)
(b) (4)	1	(b) (6)	5.0	10	(b) (6)	3.9	222	22.2			455	45.5	
			18	18		3.8	319	17.7			648	36.0	
			10	16		4.0	259	16.2	630	39.4	630	39.4	
			11	10		4.0	597	59.7	1810	181	1810	181	
			36	25		4.0	1770	70.8			4540	181	
			15	10		4.0	412	41.2			810	81.0	
			24	24		4.1	469	19.5	1540	64.0	1580	65.7	
			24	20		4.0	818	40.9	2300	115	2300	115	
			25	24		0.75	627	26.1	2020	84.3	2090	87.0	
			10	20		2.5	1010	50.5	2830	141	10800	541	14
			19	15		0.50	600	40.0	2110	141	2200	146	
			29	36		4.0	862	23.9	2240	62.1	2240	62.1	
			17	16		4.0	2440	153			5740	359	
					N	**13**	**13**	**13**	**8**	**8**	**13**	**13**	**1**
					Mean	**3.34**	**800**	**44.7**	**1930**	**103**	**2760**	**149**	**14.0**
					SD	**1.27**	**640**	**36.6**	**648**	**48.8**	**2870**	**147**	
					CV%	**38.2**	**79.9**	**81.8**	**33.5**	**47.1**	**104**	**98.5**	
					Geometric Mean	**2.87**	**630**	**36.0**	**1800**	**92.7**	**1840**	**105**	**14.0**
					Geometric CV%	**79.9**	**79.7**	**71.7**	**48.5**	**55.6**	**116**	**100**	
					Min	**0.500**	**222**	**16.2**	**630**	**39.4**	**455**	**36.0**	**14.0**
					Median	**4.00**	**600**	**40.0**	**2070**	**99.8**	**2090**	**87.0**	**14.0**
					Max	**4.08**	**2440**	**153**	**2830**	**181**	**10800**	**541**	**14.0**
					CI 90% Lower Mean	**2.71**	**484**	**26.6**	**1500**	**70.8**	**1340**	**76.6**	
					CI 90% Upper Mean	**3.97**	**1120**	**62.8**	**2370**	**136**	**4170**	**222**	
(b) (4)	2	(b) (6)	5.0	10	(b) (6)	0.50	190	19.0	669	66.9	2840	284	13
			18	26		4.0	860	33.1	2200	84.7	10300	395	
			10	14		4.2	459	32.8	755	53.9	4170	298	
			11	12		4.0	483	40.3	879	73.3	4700	392	
			36	35		4.0	2930	83.7	6370	182	49100	1400	
			15	14		4.0	289	20.6	770	55.0	3360	240	
			24	20		4.0	645	32.3	2280	114	7490	374	
			24	26		4.0	467	18.0	1580	60.8	5870	226	
			25	26		0.50	865	33.3	2920	112	8210	316	9.0
			19	25		4.0	605	24.2	1880	75.3	7920	317	
			29	24		4.0	806	33.6	2390	99.6	10600	441	
			17	6		0.67	786	131	2800	467	13300	2220	15
					N	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**3**
					Mean	**3.16**	**782**	**41.8**	**2130**	**120**	**10600**	**575**	**12.4**
					SD	**1.57**	**711**	**33.0**	**1570**	**115**	**12500**	**605**	**3.22**
					CV%	**49.7**	**90.9**	**78.8**	**73.6**	**95.4**	**118**	**105**	**26.0**
					Geometric Mean	**2.45**	**617**	**34.6**	**1710**	**96.0**	**7610**	**427**	**12.1**
					Geometric CV%	**112**	**75.6**	**64.0**	**77.4**	**67.2**	**87.9**	**79.4**	**27.9**
					Min	**0.500**	**190**	**18.0**	**669**	**53.9**	**2840**	**226**	**8.96**
					Median	**4.00**	**625**	**32.9**	**2040**	**80.0**	**7700**	**346**	**12.9**
					Max	**4.17**	**2930**	**131**	**6370**	**467**	**49100**	**2220**	**15.3**
					CI 90% Lower Mean	**2.34**	**413**	**24.7**	**1310**	**60.9**	**4160**	**261**	**6.96**
					CI 90% Upper Mean	**3.97**	**1150**	**58.9**	**2940**	**180**	**17100**	**889**	**17.8**

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Table A4. Individual and mean NexoBrid PK parameters from study MW2008-09-03 for samples analyzed at the (b) (4) site

Analysis Site	Treatment	Subject ID	Total %TBSA Treated	Dose / Treatment	Gender	T_{max} (hr)	C_{max} (ng/mL)	C_{max} / Dose	AUC_{0-4} (hr*ng/mL)	AUC_{0-4} / Dose	AUC_{last} (hr*ng/mL)	AUC_{last}/ Dose	$t_{1/2}$ (hr)
(b) (4)	1	(b) (6)	6.0	15	(b) (6)	3.8	2120	141	5880	392	13400	891	11
			5.5	10		4.0	4970	497	14900	1490	30700	3070	9.2
			4.0	5		4.0	888	178	2150	430	4570	914	15
			10	7		2.0	2530	361	6400	914	22600	3230	
			10	5		2.0	4500	900	11000	2210	23100	4610	24
			8.0	10		2.0	2640	264	7740	774	18500	1850	12
			7.0	10		4.0	13200	1320	23200	2320	72200	7220	25
			7.5	15		1.9	2410	161	6960	464	12200	812	12
			7.5	35		1.8	5530	158	16500	472	30100	859	10
			13	29		2.0	4880	168	13300	458	26800	925	9.3
			15	30		1.9	11100	370	32000	1070	75900	2530	8.8
			6.0	12		1.9	10600	883	30200	2520	53800	4490	11
			6.0	12		1.9	1900	158	5680	474	16900	1410	10
			2.0	6		1.9	951	159	2770	462	5650	942	14
			7.5	17		3.9	13500	794	38700	2280	167000	9810	9.8
			4.0	8		26	1690	211	516	64.5	29900	3740	14
			3.0	10		1.7	2110	211	6330	633	12200	1220	20
			14	30		4.0	15700	523	44100	1470	117000	3920	9.4
			6.0	6		1.9	7090	1180	20500	3420	43500	7260	8.5
			23	30		0.90	10700	357	29100	971	52000	1730	9.3
			14	15		4.2	6860	457	15600	1040	16700	1110	
					N	**21**	**21**	**21**	**21**	**21**	**21**	**21**	**19**
					Mean	**3.72**	**5990**	**450**	**15900**	**1160**	**40200**	**2980**	**12.8**
					SD	**5.26**	**4650**	**358**	**12600**	**897**	**40000**	**2530**	**5.04**
					CV%	**141**	**77.5**	**79.6**	**79.5**	**77.5**	**99.5**	**84.8**	**39.4**
					Geometric Mean	**2.68**	**4300**	**343**	**10500**	**839**	**27200**	**2170**	**12.1**
					Geometric CV%	**74.6**	**108**	**85.2**	**150**	**112**	**114**	**95.9**	**34.2**
					Min	**0.900**	**888**	**141**	**516**	**64.5**	**4570**	**812**	**8.52**
					Median	**2.00**	**4880**	**357**	**13300**	**914**	**26800**	**1850**	**10.9**
					Max	**26.2**	**15700**	**1320**	**44100**	**3420**	**167000**	**9810**	**25.3**
					CI 90% Lower Mean	**1.74**	**4250**	**315**	**11100**	**820**	**25200**	**2030**	**10.8**
					CI 90% Upper Mean	**5.70**	**7740**	**585**	**20600**	**1500**	**55300**	**3930**	**14.8**
(b) (4)	2	(b) (6)	14	15	(b) (6)	4.0	5280	352	14000	935	44600	2970	
					N	**1**	1	**1**	**1**	**1**	**1**	1	0
					Mean	**4.00**	**5280**	**352**	**14000**	**935**	**44600**	**2970**	

Study MW2010-03-02

Study MW2010-03-02 is a Phase 3, multi-center, multi-national, randomized, controlled, assessor-blinded, 3-arm study. Of the 175 patients enrolled in the study, PK blood samples were collected from 36 out of 77 NexoBrid treated patients. Patients received NexoBrid in 2 separate sessions if the burned wound area was more than 15% TBSA (planned 2 application) or if the debridement of the first application was not complete and another treatment session was required. Of the 36 patients with PK data, only 1 received planned second application.

Of the 36 patients enrolled, 22 patients treated with single application and 14 patients treated with two consecutive applications of NexoBrid. Each subject received NexoBrid at a dose of 2 grams or 5 grams of NexoBrid sterile powder that were mixed in 20 grams or 50 grams of sterile Gel Vehicle respectively (ratio of 1:10) to obtain NexoBrid Gel. Twenty (20) grams of NexoBrid gel was applied on 1% of TBSA for four hours. NexoBrid was not applied to more than 15% TBSA in any one session. Subjects received NexoBrid in two separate sessions if the burned wound area was more than 15% TBSA or if the debridement of the first application was not complete and another treatment session was required.

PK Sampling and analysis: Blood samples were taken from each subject to measure NexoBrid absorption. For subjects with one single application (for patients with ≤15% TBSA), blood samples were taken prior to NexoBrid treatment, 0.5, 2, 4, 12, 24, 48, and 72 hours post application. In patients requiring 2 planned applications, PK samples were taken prior to the first application, and 0.5, 2, and 4 hours post first application. Following the second application, PK samples were taken prior to application, 0.5, 2, 4, 12, 24, 48, and 72 hours after the second application.

Samples were analyzed at the (b) (4) site using a validated ECL method (see section 19.4.1). The serum stability of NexoBrid has been determined to be 93 days at -20°C and 561 days at -80°C. In this study, there were samples that were stored for more than 93 days at -20°C and/or more than 561 days at -80°C. These samples were analyzed and defined as an exploratory analysis and were not included in the final PK parameter assessment.

Summary of pharmacokinetics:

Following topical administrations of NexoBrid, evidence of systemic serum exposure was observed in all of the 21 patients for which valid PK samples were available (main analysis). There were an additional 15 patients for which the PK samples were analyzed later than the stability period. These samples that were evaluated from an exploratory status also demonstrated systemic serum exposure (See section 6.3.2 for additional discussion).

Table A5 summarizes the individual and mean NexoBrid PK parameters from study MW2010-03-02 (main analysis). Table A6 summarizes the individual and mean NexoBrid PK parameters

for the 15 patients who samples were analyzed later than the established stability limit of 561 days at -80 °C or 93 days at -20 °C.

Table A5. Individual and mean NexoBrid PK parameters from study MW2010-03-02 (main analysis)

Treatment #	Subject ID	Wound Depth	%BSA Treated	Dose (g)	T_{max} (h)	C_{max} (ng/mL)	C_{max} / Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4} / Dose (h*ng/mL/g)	AUC_{0-24} (h*ng/mL)	AUC0-24 / Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last}/ Dose (h*ng/mL/g)
1st	(b) (6)	MIXED	5.0	12	2.0	444	37.0	1260	105	4470	373	5980	498
		MIXED	4.5	9.0	4.0	69.1	7.68	201	22.3	580	64.4	518	57.6
		ALL DPT	5.0	10	4.0	90.1	9.01	287	28.7	647	64.7	287	28.7
		MIXED	5.3	11	4.0	106	9.81	193	17.8	1090	101	1480	137
		ALL DPT	3.0	6.0	4.0	223	37.2	223	37.2	1820	303	2290	381
		MIXED	3.0	6.0	2.0	30.7	5.12	96.5	16.1	326	54.4	259	43.1
		MIXED	4.0	8.0	4.0	175	21.9	479	59.8	2380	297	3770	472
		MIXED	7.0	14	4.0	112	8.00	287	20.5	999	71.4	999	71.4
		MIXED	7.7	15	12	202	13.1	135	8.74	2960	192	4960	322
		MIXED	5.3	11	4.0	77.1	7.34	203	19.4	1010	96.2	1010	96.2
		ALL DPT	3.5	7.0	4.0	69.6	9.94	215	30.7	933	133	933	133
		ALL DPT	3.0	6.0	4.0	151	25.2	382	63.6	1650	275	2160	360
		ALL DPT	4.0	8.0	4.0	327	40.9	733	91.6	4790	599	6270	784
		ALL DPT	7.0	14	4.0	156	11.1	359	25.6	1610	115	1610	115
		ALL DPT	6.0	12	4.0	151	12.6	368	30.7	1860	155	1860	155
		MIXED	3.5	7.0	4.0	45.3	6.47	115	16.4	296	42.3	115	16.4
		MIXED	15	30	4.0	309	10.3	956	31.9			956	31.9
		MIXED	11.0	22	4.0	830	37.7	2350	107	7150	325	7900	359
		MIXED	8.0	16	4.0	233	14.6	782	48.9	2690	168	4340	271
		ALL DPT	3.5	7.0	0.50	36.3	5.19	69.7	9.96	117	16.8	69.7	9.96
		MIXED	13.5	26	2.0	360	13.8	1140	43.7	3180	122	4700	181
				N	**21**	**21**	**21**	**21**	**21**	**20**	**20**	**21**	**21**
				Mean	**3.93**	**200**	**16.4**	**516**	**30.8**	**2030**	**178**	**2500**	**215**
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				CV%	**53.4**	**92.0**	**72.7**	**106**	**74.7**	**88.1**	**80.8**	**93.2**	**94.0**
				Min	**0.500**	**30.7**	**5.12**	**69.7**	**8.74**	**117**	**16.8**	**69.7**	**9.96**
				Median	**4.00**	**151**	**11.1**	**287**	**30.7**	**1630**	**128**	**1610**	**137**
				Max	**12.0**	**830**	**40.9**	**2350**	**107**	**7150**	**599**	**7900**	**784**
				Geometric Mean	**3.46**	**143**	**13.1**	**340**	**31.3**	**1340**	**130**	**1360**	**126**
				Geometric CV%	**62.1**	**103**	**74.2**	**115**	**81.0**	**137**	**106**	**220**	**180**
				CI 90% Lower Mean	**3.14**	**131**	**11.9**	**310**	**28.6**	**1340**	**123**	**1620**	**139**
				CI 90% Upper Mean	**4.72**	**269**	**20.9**	**721**	**51.0**	**2720**	**234**	**3370**	**292**
2nd	(b) (6)	MIXED	6.1	12	4.0	183	15.0	618	50.6	3020	248	6010	492
				N	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
				Mean	**4.00**	**183**	**15.0**	**618**	**50.6**	**3020**	**248**	**6010**	**492**

Table A6. Individual and mean NexoBrid PK parameters from study MW2010-03-02 (exploratory analysis for samples analyzed beyond the established stability period)

Subject ID	Wound Depth	% TBSA	Dose (g)	T_{max} (h)	C_{max} (ng/mL)	C_{max} / Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4} / Dose (h*ng/mL/g)	AUC_{0-24} (h*ng/mL)	AUC_{0-24}/ Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last}/ Dose (h*ng/mL/g)
(b) (6)	ALL DPT	8.0	14	4.0	89.2	6.37	216	15.5	782	55.9	657	46.9
	ALL DPT	5.0	12	12	150	12.5	439	36.6	2530	211	1630	136
	MIXED	5.5	11	2.0	247	22.5	698	63.5	2470	225	3290	299
	ALL FT	4.0	10	4.0	179	17.9	510	51.0	1660	166	1660	166
	ALL DPT	11.0	22	2.0	245	11.1	815	37.0	2420	110	2890	131
	ALL DPT	2.0	4.0	4.0	319	79.8	746	187	3460	864	5680	1420
	ALL DPT	11.0	22	4.0	156	7.09	500	22.7	1760	80.2	1760	80.2
	ALL DPT	8.0	16	2.0	98.0	6.13	315	19.7	1030	64.4	1030	64.4
	ALL DPT	6.0	20	4.0	379	19.0	986	49.3	5700	285	8510	426
	MIXED	4.0	8.0	4.0	109	13.6	275	34.4	1910	239	275	34.4
			N	10	10	10	10	10	10	10	10	10
			Mean	4.20	197	19.6	550	51.6	2370	230	2740	280
			SD	2.90	97.9	21.9	254	49.7	1400	237	2560	419
			CV%	69.0	49.6	112	46.1	96.3	59.2	103	93.5	149
			Min	2.00	89.2	6.13	216	15.5	782	55.9	275	34.4
			Median	4.00	168	13.1	505	36.8	2160	188	1710	133
			Max	12.0	379	79.8	986	187	5700	864	8510	1420
			Geometric Mean	3.63	176	14.1	495	39.6	2050	165	1820	146
			Geometric CV%	57.3	53.2	88.8	53.4	80.0	61.6	98.2	133	158
			CI 90% Lower Mean	2.52	140	6.92	403	22.8	1560	92.8	1250	37.6
			CI 90% Upper Mean	5.88	254	32.3	697	80.4	3190	367	4220	523

19.5. Additional Clinical Outcome Assessment Analyses

None.

19.6. Deaths in the Clinical Development Program

1. **Subject:** (b) (6) (2010-03-02; Romania) DETECT
   Event: Acute respiratory failure (Acute respiratory failure)

An 18-year-old female sustained fire/flame burns (indoors), with total burn surface area (TBSA) of ~24% on (b) (6). She was admitted on (b) (6), and wounds were cleansed in the operating room under intravenous anesthesia the same day. She was randomized to study treatment on (b) (6) and target wounds (TWs) represented 21% TBSA: 3% each thigh; 15% anterior trunk. (Note: Per Listing 16.2.4.2.2.1, "Description of General Burn Injury Wounds at Registration," burns also involved her face and hands. Therefore, it appears that the remaining ~3% TBSA burn injuries were at those sites, with the %TBSA distribution unclear.) NexoBrid was applied to 15% TBSA (anterior trunk) on (b) (6) under general anesthesia; she was extubated and monitored in the intensive care unit. On (b) (6), NexoBrid was applied on 6% TBSA (both thighs) under general anesthesia and removed after 4 hours. Her

pulse was 105 beats/minute (apparently following removal of NexoBrid and an unspecified time before the respiratory failure). "Five and a half hours later," she became cyanotic "with desaturation" (acute respiratory failure), and ECG showed right bundle branch block (RBBB). Initially, pulmonary embolism was suspected, and heparin was administered. She was intubated and received external cardiac massage. Thoracic CT scan on (b) (6) showed findings densification of the inferior and superior lobes of the left lung (suggestive of bronchopneumonia) and fluid in both pleurae. Pulmonary arteries were clear. Cardiology and surgery were consulted (and thoracic surgery on (b) (6)); however, the narrative did not include their findings. ECG earlier on (b) (6) apparently did not show evidence of RBBB. On the same day, d-dimer was 2.71 µg/mL, cardiac markers were unremarkable (reported as troponin of 0.003 ng/mL; normal CK-MB). However, her potassium level was low (value not specified). On (b) (6), arterial blood gases suggested acidosis ("increase of pCO2; decrease in pO2"). That same day (Study Day 4), she underwent thoracentesis, but later that day suffered cardiac arrest and was not resuscitated (timeframe of events to the arrest is unclear). Although an autopsy was performed, the findings were not provided for the study report (following multiple requests for the report). The Investigator, the DSMB and the Applicant concluded that the cause of death was probably "a pulmonary complication which could have been related to the mechanical ventilation procedures or aspiration." Delayed smoke inhalation injury was also considered a possibility.

Additional history: Hemoglobin was 12.7 g/dL pre-first NexoBrid application and 9.9 g/dL post application (reference range [RR]: 12.0 to 15.6 g/dL); hematocrit decreased from 0.397% to 0.332 (RR: 0.35 to 0.46%). She received transfusions of packed red blood cells between the first and second applications. Post second application, her hemoglobin was 10.1 g/dL, and hematocrit was 0.313. She also received fresh frozen plasma during the two days of the applications ((b) (6)). Blood culture pre-first application grew *Streptococcus mitis*; post first application ((b) (6)) grew *Staphylococcus epidermidis* (assessed as contaminant by the investigator). Blood culture post second application was negative. One wound culture grew *Candida albicans* post second application ((b) (6)), and another grew *Enterococcus faecalis*, both were assessed as "not clinically significant" by the investigator.

Comment: This subject died ~ 6 days after sustaining a serious burn injury indoors, involving ~ 25% body surface area, including to her face. She received 2 applications of NexoBrid, both under general anesthesia. Pulmonary embolism seems a reasonable initial thought, given the acute respiratory failure, tachycardia, and apparently new RBBB. Pulmonary arteries were "clear." Her culture results appear to make sepsis unlikely (negative after 2nd NexoBrid treatment, apparently in timeframe of onset of crisis). A role the possible bronchopneumonia cannot be excluded. Delayed inhalation injury could be a possibility, given that she did sustain the burn injuries indoors, and the burns involved her face (location(s) not further specified). The acute onset and nature of her symptoms, relative to when she received NexoBrid treatments, would not appear to suggest a clear role for those treatments in causation, mechanistically. The Applicant's assessment, that the death of this teenager was due to a "pulmonary complication," is vague and not clinically interpretable. In response to an Information Request regarding the autopsy report, the Applicant detailed their efforts to obtain the report and stated, "All the

information available to MediWound on this death case was included in the BLA" (SN-0015; 12/18/2020).

2. Subject: (b) (6) (2010-03-02; United States)
   Event: Death unknown cause (Death)

A 66-year-old quadriplegic male sustained a contact burn of 4% TBSA (anterior trunk: 0.5% and left anterior thigh: 3.5%) on (b) (6), and all wound were designated as TWs. His medical history was significant for multiple problems, including type 2 diabetes mellitus, hypertension, neurogenic bladder, indwelling urinary catheter, recurrent urinary tract infection, neurogenic bowel, colostomy, protein malnutrition, anemia of chronic disease, decubitus ulcer, depression, hypernatremia, hypokalemia, and gastroesophageal reflux disease.

He was randomized on (b) (6) and received the following eschar removal procedures for his burns:

- (b) (6): NexoBrid to both TWs (trunk and thigh) with complete eschar removal of trunk TW
- (b) (6): Surgery (tangential) to thigh TW for residual eschar; this procedure completed the eschar removal for the thigh lesion.

Both wounds were covered with allografts between (b) (6) and (b) (6) and autogratfted on (b) (6). He was discharged on (b) (6). On (b) (6) (43 days after the first study treatment application), he presented with new burns to the scrotum and medial aspect both thighs, reportedly from "hot coffee spills." These burns were assessed as being deep DPT burns covering 3% TBSA (previous burn site on left anterior thigh was not involved). Excision, debridement, and split thickness skin grafting were performed on the new burns on (b) (6). He was discharged on (b) (6).

Additionally, the subject required hospitalization for the SAEs presented in the following table:

SAE	Start date	End date
Urosepsis	(b) (6)	
Osteomyelitis of right ischial tuberosity		
Sepsis secondary to right ischial osteomyelitis		
Reconstructive surgery of decubitus ulcer		

The decubitus ulcer was "ongoing" since (b) (6); the site of the decubitus ulcer was not found in the narrative (?right ischial tuberosity). On (b) (6) (267 days after the first NexoBrid application), he was found dead in his wheelchair. His family declined an autopsy.

Comment: This subject received surgical treatment for the TWs within 2 days of NexoBrid treatment, which could compromise an assessment of relatedness to a particular treatment. The narrative includes no discussion of lingering, post-treatment wound complications. Additionally, he sustained new burns and experienced other serious medical problems, including significant infections, in the interval between study treatment and death. Therefore, this history and the temporal distance between study treatment and death would appear to support a conclusion that his death was unrelated to study treatment.

This subject's medical status was generally fragile. The occurrences of 2 separate burn incidents, ~6 weeks apart, in this elderly quadriplegic may raise a question of neglect (or abuse), particularly as the last wounds were said to have resulted from coffee "spills" (plural). Questions regarding the quality of his care may be further raised by the presence of a decubitus ulcer.

3. Subject: (b) (6) (2004-11-02; Romania)
   Event: Cardiac arrest (Cardiac arrest)

A 51-year-old male was hospitalized on (b) (6), after sustaining flame burns (that day) of 22% TBSA as a result of an explosion of gun powder that he was carrying in his hands. The burns involved his head (face, scalp), neck, right arm, both hands, both thighs, and the left leg. On (b) (6) he received a single Debrase Gel Dressing (now NexoBrid) treatment to 17% TBSA: right arm, both hands, both thighs, and the left leg. However, he subsequently underwent "repeated debridement," with dates, sites, and treatments unspecified in the narrative. (b) (6), 7 days after application of the Debrase, he experienced sudden onset of dyspnea, which necessitated transfer to the intensive care unit (ICU), with intubation and mechanical ventilation following. Chest x-ray showed a pleural effusion, with "no bacterial growth" on culture. Partial pressure of oxygen was 80-91 %, and blood pressure was 160/80 mmHg. CT scan on (b) (6), showed "hazy infiltrates compatible with pleural effusion with/without acute respiratory distress syndrome." Bronchoscopy on (b) (6) revealed "swollen bronchial mucosa, narrowed lumen and dark 'bile-like' thick mucus." By (b) (6), his pulmonary status had improved, and chest X-ray on (b) (6) showed clear pulmonary fields. However, on (b) (6), he suffered cardiac arrest. He was resuscitated but suffered a second cardiac arrest on (b) (6) and died that same day. Reported autopsy findings (autopsy performed on (b) (6)), cited the causes of death as septic shock and multi-organ failure. He reportedly presented no signs or symptoms of sepsis, with the condition only being diagnosed postmortem. From the narrative in the study report, postmortem evaluation of the upper respiratory tract mucosa was described as follows: "Macroscopic examination revealed morphological modifications of the upper respiratory tract mucosa, described as possibly due to upper respiratory tract burn. The upper respiratory tract was permeable, with grey-violet mucosa and ulcerations covered by mucus on the larynx and cervical trachea, with significant blood content in the mucus." Presented histopathology findings of the lung were: "incipient bronchopneumonia; aspects of vascular leukostasis; relatively extended areas of edema; areas of atelectasis and pulmonary scleroemphysema, changes in the upper respiratory tract mucosa compatible with burns to the bronchi." Other

histopathology findings included “myocardial fibrosis, with acute myocardial hypoxemic changes” and “evidence for chronic active hepatitis, and diffuse atherosclerotic changes in the vasculature in many organs.”

Comment: The cited causes of death were septic shock (sepsis was only diagnosed postmortem) and multi-organ failure. The events that appear to mark the beginning of his downward course (starting 7 days post application of Debrase) were pulmonary related and could reflect the respiratory tract injury suffered during the burn event, but may also have been indicators of sepsis (or both). He had also undergone “repeated debridement” in the same timeframe as the events; therefore, NexoBrid treatment may not have been the only potential source of infection. The acute pulmonary dysfunction and dyspnea may have been indicators of sepsis.

4. Subject: (b) (6) (2004-11-02; Brazil)
   Event: Homicide (Murdered)

A 24-year-old male sustained fire/flame burns to 13.5% TBSA on (b) (6), DPT burn injuries: right and left lower arms (3% and 1%, respectively) and right and left hand (1% each). Standard of care treatment (surgical and nonsurgical) was begun on (b) (6) to his wounds. He was discharged on (b) (6). On (b) (6), he was shot multiple times and was pronounced dead on arrival at the hospital.

5. Subject: (b) (6) (2002-04-01; United States)
   Event: Multiple organ dysfunction (Multiorgan failure)

A 69-year-old male sustained second and third degree burns of 28.5%TBSA on (b) (6) after falling into a fire pit. The burns affected his head/neck, right hand, both arms, both aspects of the trunk and both thighs/legs. He had soot in his nostrils, and on his tongue and posterior pharynx. Per the study report narrative, he “sustained significant inhalation injury.” His medical history included smoking (>30 cigarettes/day) for 50 years, emphysema, hypertension, hepatitis C, bleeding episodes of peptic ulcer, diabetes mellitus type 2, mild von Willebrand's disease, and hypercholesterolemia. From (b) (6) to (b) (6), he received Debrase (now NexoBrid) to 4% TBSA (left thigh and leg), designated as TW. The remaining burns (24.5% TBSA) were treated with SOC. The target wound was covered with xenograft on (b) (6). On (b) (6), he underwent surgical debridement and grafting of wounds on his face, hands, and fingers. He remained intubated postoperatively. No additional information regarding his hospital course is provided until (b) (6), when he underwent another debridement of his right hand and received a tracheostomy. From (b) (6) (b) (6) to (b) (6), he underwent a series of SOC debridement procedures as well as grafting procedures (including grafting of portions of the TW on the left leg). On (b) (6) (there was no discussion of his course between (b) (6)), dialysis was begun (acute renal failure per study report narrative), and he received massive transfusions due to a GI bleed from a duodenal ulcer. On this same date, the following events were reported: sepsis due to methicillin-resistant *Staphylococcus aureus*, encephalopathy, disseminated intravascular coagulation, “leading ultimately to multiorgan failure.” On (b) (6), all therapeutic

measures were discontinued, and he died the following day ([(b) (6)]), 69 days after Debrase treatment. An autopsy was not performed.

Comment: There are gaps in the narrative history. However, this elderly male had multiple, significant, preexisting medical problems onto which serious burns and "significant inhalation injury" were superimposed. Based on his medical history, he seemed at increased risk for a poor outcome. Most of his wounds (86%) were treated with SOC, and the narrative included no information describing the status of any of the burn sites posttreatment. Based on the available information, it would be difficult to assess or assign relatedness to NexoBrid in the multiple medical complications and, ultimately, fatal outcome.

6. Subject [(b) (6)] (2002-04-01; India)
   Events: Respiratory failure (Acute on chronic hypercapnic respiratory failure)
   Lung injury NOS (Acute lung injury)

A 45-year-old male sustained burns of 13% TBSA (right arm, neck, left arm, and anterior trunk), "while cooking under the influence of alcohol" on [(b) (6)]. That same day, he was hospitalized and randomized to study treatment with Debrase. Past medical history included chronic alcohol use, being a "heavy smoker for more than 25 years," and COPD. On presentation, he showed no signs of smoke inhalation injury, but did have a 3-4 day history of cough with mucopurulent "expectoration," and he had bilateral wheezing and rhonchi on auscultation. His white blood count (WBC) was ~32,000 with 95% neutrophils and his temperature was 37.6°C (99.7°F). On the day of admission ([(b) (6)]) Debrase was applied to 7% TBSA TW (wounds not specified); the remaining 6 % TBSA burns received SOC treatment. Prior to the Debrase treatment, he received pentazocine, promethazine, and pethidine. An hour post-application of "debridement dressing," he reported pain (grade 7), and he was experiencing "heavy breathing" (respiratory rate: 25/min). He was placed on theophylline and hydrocortisone. He was unchanged the following day, and terbutaline nebulizer was added to his regimen. He continued to have rhonchi, and his temperature remained 37.6°C . On [(b) (6)] [(b) (6)], his respiratory rate was 28/min; rhonchi and temperature were unchanged from [(b) (6)] [(b) (6)] his WBC count was 30,400. Also, wound culture (wound not specified) grew *Streptococcus pyogenes*; blood culture was negative. Additional treatment included several antibiotics. The next date for report of information was [(b) (6)] (8 days after Debrase): The respiratory distress worsened; he was admitted to the ICU. He was intubated on [(b) (6)] [(b) (6)]. At some point, he was noted to be responsive only to deep painful stimuli, and he was in respiratory failure and severely acidotic (pH 7.26, pO2 65, O2 saturation 87.5%, pCO2 90). The recorded diagnosis was "COPD with acute on chronic respiratory failure with possible aspiration pneumonia and septicemia." On [(b) (6)], chest X-ray showed bilateral infiltrates, and tracheobronchial secretion culture grew Klebsiella species. The next day, the acidosis had worsened, and blood pressure had fallen to 90/60 mm Hg. On [(b) (6)] (14 days post Debrase; study day 15), he experienced cardiac arrest, and resuscitation efforts were unsuccessful. Reported autopsy findings and conclusions included the following: "The pleural cavity contained 400 ml of straw-colored fluid. Both lungs were congested and edematous, with patchy consolidation and multiple air-filled bullae present. A cut section of lung showed oozing

of frothy fluid mixed with blood…the cause of death was septicemia as a consequence of infected burn wounds, a provisional diagnosis based on clinical findings of increased white blood count and neutrophils, development of hypotension requiring dopamine infusion and respiratory failure as seen from blood gas analysis." Post-mortem blood and lung cultures were not done.

Comment: This reported "heavy smoker" with COPD may have had a pneumonia at presentation and pre-Debrase treatment. Worsening of his pulmonary status began an hour after application of "debridement dressing"*; however, it is not clear what part of the Debrase process this represents. Additionally, this subject received Debrase and SOC treatment for his burn injuries. Therefore, although a wound infection was diagnosed, the treatment that the infected wound received was not specified i.e., Debrase or SOC. Although his septicemia was attributed to "infected burn wound," it seems the apparent pneumonia at study entry could have been a possible alternative source. Therefore, relatedness of the septicemia to Debrase treatment is unclear, based on the available information.*

7. Subject: (b) (6) (2002-04-01; India)
   Events: Respiratory failure (Respiratory failure); Pneumonia aspiration (Aspiration pneumonitis)

A 40-year-old male sustained burns of 29.5 % TBSA (head/neck, both hands, both arms, anterior trunk, and both thighs/legs) on (b) (6) (no additional information was provided on the history of the burns). He was not taking any medications; per the case report form, the review of systems was negative at screening. He was hospitalized and randomized to study treatment the same day. On (b) (6), Debrase was applied to burns on 12.5%TBSA TW: Lt Upper Arm (1.5 %TBSA) and the entirety of the burn on the anterior trunk (11% TBSA). The remaining non-TW burns (17 %TBSA) were treated with nonsurgical SOC. On (b) (6), he was noted to have "mild" abdominal distention and was tachypneic (30/min). Later that day, "while sleeping," he experienced an episode of "severe projectile vomiting" and aspirated vomitus. His respiratory rate was 40/min, and bilateral crepitations were noted. He was intubated. ABG's showed pH 7.33; pCO2 33.7 mm Hg; pO2 68.2 mm Hg; O2 saturation 89.1%. Treatment included hydrocortisone, atropine, adrenaline, and cardiac massage. Resuscitation efforts (90 minutes) were unsuccessful, and he was pronounced dead on (b) (6), the day of aspiration (2 days post Debrase; study day 3). The autopsy was reported to have documented the cause of death as "respiratory failure following aspiration pneumonitis in a case of 29.5 % infected thermal burns."

Culture Results*

Date (time point)	Site(s): Results
(b) (6) (Screening)	Blood and wound: "scanty anaerobic organisms," later identified as *Klebsiella pneumoniae*
(b) (6) (Pre-debridement)	Blood: "scanty aerobic organisms"

	Wound: gram-negative organisms, later identified as *Klebsiella pneumoniae.*
[redacted] (24 h. Post-debridement)	Blood: anaerobic and aerobic organisms Wound: anaerobic organisms, later identified as *E. coli* and *P. aeruginosa*
[redacted] (48 h. Post-debridement)	Blood: no organisms Wound: "scanty gram-negative organisms," later identified as *E. coli* and *P. aeruginosa*

*Wounds not specified; culture results are as presented in the narrative

Comment: The autopsy-reported cause of death, "respiratory failure following aspiration pneumonitis," appears to be consistent with the limited history.

8. Subject: [redacted] (India) 2002-04-01
   Event: Acute respiratory failure (Acute respiratory failure)

A 21-year-old female sustained self-inflicted kerosene burns of 27% TBSA (head, neck, anterior and posterior trunk, both hands, and both arms) on [redacted]. She inhaled kerosene fumes; however, acute smoke inhalation injury was not diagnosed, and labs and chest x-ray were normal. Per the case report form, the review of systems was negative at screening. She was randomized into the study on [redacted] and Debrase was applied to 7% TBSA TW (right arm) on [redacted]. The remaining wounds (20%) were treated with surgical SOC on [redacted] Her course was reported to have been uneventful until [redacted] (10 days post Debrase; 8 days post-surgery), when she experienced acute tachypnea (respiratory rate of 28/min), with pulse 110/min and systolic blood pressure of 100 mm Hg. She was also noted to have "mild" abdominal distension. Treatment included oxygen, and fluconazole was initiated (prophylactically per case report form. She experienced respiratory arrest ~6.5 hours after the onset of tachypnea, could not be resuscitated, and was pronounced dead (on [redacted], 10 days post Debrase; study day 11). The extent of information provided from the autopsy report was that, "there was evidence of chronic obstructive pulmonary disease, with pulmonary hypertension and with intra-alveolar hemorrhages and acute respiratory failure leading to hypoxic encephalopathy. There was no evidence of septicemia."

Comment: Most of her wounds (74%) were treated with surgical SOC. Therefore, any attribution of the fatal outcome to study treatment would have to include SOC. Limited information was provided from the autopsy report. However, the report was said to describe preexisting pulmonary disease, and the role of the inhaled kerosene fumes on her underlying disease in precipitating her acute respiratory distress and failure is unclear.

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MOHAMED A ALOSH on behalf of KATHLEEN S FRITSCH
06/24/2021 05:14:04 PM
I am signing for Kathleen Fritsch

MOHAMED A ALOSH
06/24/2021 05:15:34 PM

BRENDA CARR
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SNEZANA TRAJKOVIC
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