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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NexoBrid

Concentrate of proteolytic enzymes enriched in bromelain

Procedure No. EMEA/H/C/002246

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

aa	amino acid
BLQ	below the Limit of Quantitation
BSA	Bovine Serum Albumin
CDU	Casein Digestion Unit
CFU	Colony Forming Unit
c.f.	compare (abbr. also: cp. from Latin: confer, "compare")
cm	Centimeter
CoA	Certificates of Analyses
CPMP	Committee for Proprietary Medicinal Products
CPP	Critical Process Parameter
curr. Ed.	Current Edition
CV	Column Volumes
Da	Dalton
DF	Diafiltration
DIN	Deutsches Institut für Normierung German Industrial Standard
DP	Drug Product
DS	Drug Substance
EDTA-Na2	Ethylenediaminetetraacetic acid Disodium salt
EC	European Commission
EP	European Pharmacopoeia
g	gram(s)
GACP	good agricultural and collection practice
GMP	Good Manufacturing Practice
HACCP	Hazard analysis and critical control point
HAV	Hepatitis-A virus
HVAC	Heating, Ventilating, and Air Conditioning
HCl	Hydrochloric Acid
HMPC	Committee on Herbal Medicinal Products
HPLC	high performance liquid chromatography
hrs	Hours
ICH	International Conference on Harmonisation
ICP	inductively coupled plasma
IPA	isopropyl alcohol
IPC	In- Process Controls
IR	infrared
ISO	International Organization for Standardization
kDa	Kilodalton
kg	Kilogram(s)
l	litre(s)
LAL	Limulus Amoebocyte Lysate
LFGB	Lebensmittel-, Bedarfsgegenstände- und Futtermittelgesetzbuch Law for foodstuffs, consumer goods and feeding stuff (Germany)
LOD	Limit of Detection
LOQ	Limit of Quantitation
MAA	Marketing Authorisation Application
mg	milligram(s)
ml	millilitre(s)
min	minutes
mM	Millimolar
MVD	Maximum Valid Dilution
Mw	Molecular Weight
NaCl	Sodium chloride
NaHSO3	Sodium bisulfite
NaOH	sodium hydroxide
NGD	NexoBrid
NIR	Near- Infrared Analysis
nm	Nanometer
NOAEL	No Observed Adverse Effect Level
NoV	Norovirus

OOS	Out of Specification
OD	Optical Density
OP	Operating Parameter
Pa	Pascal
PAMP	pathogen-associated molecular pattern
PBS	phosphate buffered saline
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
pH	power of hydrogen (scale measuring acid / alkaline nature of solution)
ppm	parts per million
PTWI	Provisional Tolerable Weekly Intake
QL	Quantitation Limit
QP	Qualified Person
q.s.	quantum satis
QWP	Quality Working Party
resp.	respectively
RH	Relative humidity
RPM	Revolutions per minute
RS	Reference Standard
RSD	Relative Standard Deviation
RT	Room Temperature
RT	Retention Time
SD	Standard Deviation
SM	Starting Material
SPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
UV	Ultraviolet
V	Volt
WFI	Water for Injection
WHO	World Health Organisation
w/v	weight/volume
w/w	weight/weight

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma GmbH submitted on 29 October 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for NexoBrid, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 December 2009.

NexoBrid was designated as an orphan medicinal product EU/3/02/107 on 30 July 2002. NexoBrid was designated as an orphan medicinal product in the following indication: Treatment of partial deep dermal and full thickness burns.

The applicant applied for the following indication: Timely, selective removal of eschar in patients with deep partial- and/or full-thickness burns.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/227/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000142-PIP02-09 was not yet completed as some agreed measures were deferred.

Information relating to orphan market exclusivity

NexoBrid has an Orphan Drug designation.

On 30 July 2002 orphan designation (EU/3/02/107) was granted by the European Commission for purified Bromelain for the treatment of partial deep dermal and full thickness burns.

Upon request by the MAH a revised opinion was edited in June 2010 (*14 June 2010 EMA/COMP/1413/2002 Rev.2*). According to the conclusion of this opinion the prevalence of the partial deep dermal and full thickness burns affected approximately 1 in 10,000 people in the European Union (EU).

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance concentrate of proteolitic enzymes enriched in bromelain contained in the above medicinal product to be considered as a new active substance in itself.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP in NexoBrid on 14 June 2005, 14 May 2008, 18 December 2008 and 19 February 2009. The Protocol Assistance pertained to quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: RobertJames Hemmings

- The application was received by the EMA on 29 October 2010.
- The procedure started on 17 November 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 February 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 04 February 2011.
- During the meeting on 17 March 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 March 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 11 October 2011.
- The summary report of the inspection carried out at the following sites: MediWound Ltd., 42 Hayarkon St., 81227 Yavne, Israel between 22 and 25 August 2011 and Analyst Research Laboratories, 12 Hamada St, 76703 Rehovot, Israel on 23 August 2011 was issued on 26 September 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 November 2011.
- During the CHMP meeting on 12-15 December 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 9 March 2012.
- During a meeting of an Ad-hoc Expert group on 7 March 2012, experts were convened to address questions raised by the CHMP.

- During the CHMP meeting on 12-15 March 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 12-15 March 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 24 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 9 May 2012.
- During the CHMP meeting on 21-24 May 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the CHMP meeting on 18-21 June 2012, the CHMP agreed on a third list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the third CHMP List of Outstanding Issues on 28 June 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the third List of Outstanding Issues to all CHMP members on 11 July 2012.
- During the CHMP meeting on 16-19 July 2012, the CHMP agreed on a fourth list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the fourth CHMP List of Outstanding Issues on 17 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the fourth List of Outstanding Issues to all CHMP members on 7 September 2012.
- During the CHMP meeting on 20 September 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 17-20 September 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to NexoBrid on 20 September 2012.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of NexoBrid as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find Medicine/Human medicines/Rare disease designations.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Debridement of eschar is essential to initiate the wound healing process and prevent further complications. Technology for this treatment in severe burns has not advanced significantly in the past few decades. Traumatic surgical debridement in burn wounds with sacrifice of healthy tissue and subsequent skin grafting may be considered in some cases to constitute over-treatment. On the other

hand, the conservative treatment modality with antimicrobial agents or inefficient chemical debridement results in a lengthy sloughing period and delayed healing process, and may therefore be considered to constitute under-treatment.

An effective enzymatic debriding agent can change this suboptimal treatment paradigm and provide the basis for first-line minimally invasive treatment.

Eschar is thick, leathery, black necrotic tissue that has dried out. Debridement is essential to wound healing. Removing necrotic tissue reduces the wound's biologic burden, clears debris that prevents or slows cell movement necessary for healing, and helps prevent infection. "Unroofing" a wound also lets health care providers see the wound walls and base; without debridement a burn wound cannot be staged. Enzymes that act on necrotic tissue are categorized as proteolytics, fibrinolytics, and collagenases, depending on the tissue component they target.

2.1.2. About the product

NexoBrid is an enzyme-based debriding agent that has been developed to be used for timely, selective removal of eschar in patients with deep partial and/or full thickness burns and is for cutaneous use.

The product consists of a partially purified mixture of proteolytic enzymes enriched in bromelain extracted from the stem of the pineapple plant (*Ananas comosus*) containing mainly proteases, in an acetic acid and ammonium sulphate solution

The finished product is presented as a lyophilised powder to be mixed with a sterile gel vehicle before application. Within 15 minutes after mixing, the product is topically applied under sterile conditions for a maximum of 4 hours to the burn wound, at a dose of 0.02 g/cm^2. In most cases a single application is sufficient, however, it may be applied for a second time to the same burn area if medically warranted.

NexoBrid should be applied topically to a clean burn wound by a trained healthcare professional in a specialised burn centre. It can be applied as soon as the wound has been cleaned in accordance with the instructions described in the product information. NexoBrid should not be applied to more than 15% Total Body Surface Area (TBSA) in one session and should be left in contact with the burn for a duration of 4 hours.

Before NexoBrid application, a dressing soaked with an antibacterial solution should be applied for 2 hours. Preventive pain management should be used as commonly practiced for an extensive dressing change. This should be initiated at least 15 minutes prior to NexoBrid application. After removal of NexoBrid and the dissolved eschar from the wound, a dressing soaked with an antibacterial solution must be applied for an additional 2 hours.

NexoBrid is not indicated for use in the paediatric population. The experience with NexoBrid in elderly patients (>65 years) is limited.

2.1.3. Type of Application and aspects on development

This is a complete application for approval of a new active substance, according to the Article 8(3) of Directive 2001/83/EC, through the centralised procedure.

Regarding the nomenclature for the active substance, the WHO confirmed to the Applicant that an INN cannot be assigned to an heterogeneous mixture of proteolytic enzymes, in accordance with the current INN. As 'No INN' is applicable to this substance, the common name 'concentrate of proteolytic

enzymes enriched in bromelain' is considered appropriate to describe the active substance of the product.

The early development was conducted with the first generation product.

Improvements in the manufacturing process eventually led to the current to-be-marketed formulation.

CHMP provided scientific advice on various aspects of the development of NexoBrid. The clinical development plan has been adjusted to align with the given advice.

NexoBrid has received on an Orphan Drug designation.

A Paediatric Investigation Plan (PIP) has been agreed. The obligation to submit the results of studies with NexoBrid in one or more subsets of the paediatric population has been deferred. The planned date of completion of the PIP is March 2019.

2.2. Quality aspects

2.2.1. Introduction

NexoBrid active substance (AS) is a concentrate of proteolytic enzymes enriched in bromelain extracted from the stems of the pineapple plant (*Ananas comosus*). NexoBrid AS contains mainly proteases.

The finished product is presented as a lyophilised powder containing the concentrate of proteolytic enzymes enriched in bromelain and a sterile gel vehicle, for preparation of a gel for cutaneous use. The powder is off-white to light tan. The gel is clear and colourless.

Following mixing of the powder with the gel, each gram of the prepared medicinal product contains 0.09 g concentrate of proteolytic enzymes enriched in bromelain.

The composition of the finished product is summarised in the following table:

Composition of Nexobrid Finished Product

Component	Grade
Nexobrid Active Substance	In-house
Acetic Acid	Ph. Eur.
Ammonium Sulphate	Ph. Eur.
Water for Injections	Ph. Eur.

Composition of Gel Vehicle

Component	Grade
Carbomer 980	Ph. Eur.
Di-sodium hydrogen phosphate, anhydrous	Ph. Eur.
Sodium hydroxide	Ph. Eur.
Water for Injections	Ph. Eur.

The lyophilised powder is formulated in 50 ml type II glass vials and the sterile gel vehicle is presented in 100 ml type I borosilicate glass bottles used to re-suspend the powder.

Two packaging sizes are proposed: 2 g NexoBrid powder in 20 g gel vehicle, applied to a burn wound area of 100 cm^2 and 5 g NexoBrid powder in 50 g gel vehicle, applied to a burn wound area of 250 cm^2, under occlusion.

After mixing the lyophilized powder with the vehicle in a 1:10 ratio, the product is topically applied within 15 minutes and for a maximum of 4 hours to burn wound area, at a dose of 0.02 g/cm^2.

2.2.2. Active Substance

NexoBrid active substance is derived from bromelain. The bromelain is obtained by extraction from the stem of the pineapple palnt (*Ananas comosus*). This is subject to further partial purification resulting in a complex mixture of proteolytic enzymes, mainly comprising cysteine proteases, such as stem and fruit bromelain as major components and ananain and comosain in minor amounts. Other enzymes and bromelain inhibitors may also be present in minor amounts.

The ratio of proteolytic enzymes in this product is different compared to bromelain herbal medicinal products marketed in some EU member states, which contain a heterogeneous mixture of a wide range of molecules. In addition, for a complex biological product such as NexoBrid, it is considered that the quality of the product is strictly dependent on the manufacturing process and its control. In view of the significant differences between the manufacturing processes of NexoBrid and bromelain products, which result in a different composition of the mixtures of substances, it is concluded that the active substance contained in NexoBrid is to be qualified as a new active substance in itself, in accordance with Directive 2011/83/EC.

Given that this product is derived from botanical starting materials and contains biologically active components, including proteolytic enzymes, it is appropriate that relevant herbal and biological guidelines are both applied.

WHO confirmed on 16th December 2010 that an INN is not applicable in this case, as it could not be assigned to a heterogeneous mixture of proteolytic enzymes. Therefore the CHMP considers the following common name to be the most appropriate to describe NexoBrid active substance: 'concentrate of proteolytic enzymes enriched in bromelain'.

The applicant presented comprehensive characterisation data, which allow identification and quantification of key of components of NexoBrid. HPLC analysis demonstrated that the product contains the proteolytic enzymes required to support the proposed mechanism of action. HPLC analysis also showed to determine the relative proportions of each of the key of constituents in terms of their structure and function, not only for proteolytic enzymes but also enzyme degradation products. This data also allowed identification of key markers for the potency assay. The development of a potency assay further substantiates the theory that the eschar produced by burning of the skin is a key substrate for debriding activity of the product, and that debriding results from stem bromelain and ananain components.

Manufacture

Taking into account the definition of starting materials for biological medicinal products (Annex I to Directive 2001/83/EC, as amended) and the relevant herbal guidelines (CPMP/QWP/2819/00 Rev 1 and CPMP/QWP/2820/00 Rev 1), the pineapple stems are defined as the herbal starting material and Bromelain as an intermediate product for the manufacture of NexoBrid active substance.

The overall manufacturing process of NexoBrid active substance is divided into two stages. The first stage is extraction of juice from peeled pineapple stems and further manufacturing to yield Bromelain,

which is done at a subcontracted site. The second stage is further processing of Bromelain into NexoBrid active substance which is done at site MediWound Ltd., Israel.

The manufacturing process of NexoBrid active substance starts at a subcontracted site with peeling of the pineapple stems. The stems are crushed, the juice is extracted and after further processing the extract is lyophilised to obtain the bromelain. This powder is packed and stored. In summary, the manufacturing process of Bromelain from pineapple plant stems consists of eight steps as detailed below:

1. Peeling of the pineapple stems and Transfer
2. Crushing
3. Juice Extraction
4. Separations
5. Filtration
6. Concentration
7. Lyophilisation
8. Packaging and Storage

After shipping the Bromelain to MediWound Ltd., the manufacturing process of NexoBrid active substance continues with the following steps:

1. Suspension
2. Filtration through filter
3. Separations
4. Re-suspension
5. Filtrations
6. Concentration

Bromelain is suspended. Following filtration, the solution goes through separations and filtrations. The solution is concentrated to become NexoBrid active substance. Following filtration steps NexoBrid active substance is stored. Reprocessing is not applied for.

Process Controls

Process-related and product-related in-process controls (IPCs) and operational parameters together with the respective acceptance criteria were described, and reviewed.

The applicant has summarised all IPCs of the active substance manufacturing process indicating the critical IPCs and has justified which IPCs have binding acceptance criteria and those ones having action limits. Acceptable rationale and justification for the classification of the IPCs in critical and non-critical process controls as well as a definition for IPCs, operating parameters and critical operational control parameters are considered acceptable.

Control of Materials and Starting Material

All reagents and solvents used during NexoBrid active substance manufacture starting from the pineapple plant are Ph. Eur. grade. There are only two non-compendial raw materials used in the Bromelain manufacturing process.

The procedures involved in cultivating and harvesting of the pineapple plant stems adhere to the concept of Good Manufacturing Practice for the herbal starting material based on the requirements of the Guideline EMEA/HMPC/246816/05 "Good Agricultural and Collection Practice for starting materials

of Herbal Origin". Procedures and tests used to control the quality of herbal starting material are comparable and consistent with the requirements of the Ph. Eur. Monograph "Herbal Drugs: 1433" and the relevant herbal guidelines.

A detailed description of the manufacturing process of Bromelain including the respective IPCs, information on quality and quantity of all materials and reagents used as well as on storage and shipping conditions was provided. The concentrations of the reagents used in the manufacturing process of Bromelain are comprehensible and justified.

An adequate specification for Bromelain set by the manufacturer, as well as the specification of the material on receipt at MediWound Ltd. is presented. The acceptance criteria for Bromelain specification have been adopted according to the requirements of the Ph.Eur. 5.1.4. The testing for impurities such as pesticides, toxic (heavy) metals and aflatoxins in the release of the active substance instead of the starting material is considered acceptable.

Process Validation

Appropriate validation data for the entire active substance manufacturing process was provided to demonstrate that the proposed manufacturing process is reproducible and capable of consistently producing the active substance, meeting predefined in-process parameters and a predefined specification.

Process validation data comprise the manufacturing processes of the bromelain starting with the extraction of the pineapple stems. Process validation data of consecutive manufacturing validation runs of the Bromelain manufacturing process and of consecutive validation batches of NexoBrid active substance manufacturing process were provided. Additionally, sufficient data is presented which confirm product consistency by analytical evaluation of key marker constituents by HPLC assays as well as potency indicating assays. This is considered adequate to demonstrate process consistency.

Process Development

The manufacturing process of NexoBrid was first established in the 1980's. Following several transfers in 2001 the product was finally transferred to MediWound Ltd. where it was renamed Debrase and then NexoBrid.

Since the forerunner materials were only used for some of the non-clinical studies, a detailed comparability exercise relating to these manufacturing processes is not considered relevant. The MediWound process was installed in 2001 and some process changes had been reported since January 2006 up to July 2010. Since 2002, the analytical methods and specifications used to release the active substance and the finished product have been continuously changed and/or improved. Clinical studies have been performed with NexoBrid batches manufactured in a period ranging from 2002 to April 2009. Manufacturing changes as well as changes in the analytical procedures have been indicated and their impact on product quality has been thoroughly studied and explained. The applicant provided evaluation of comparability of pre and post change material as well as evaluation of comparability or interchangeability of analytical methods.

Based on the data provided, it can be concluded that material manufactured with the commercial manufacturing process is within or close to the qualified acceptance limits of the clinical material. There is a slight trend towards higher purity in the commercial batches compared to the clinical batches.

Characterisation of the active substance

The majority of characterisation studies have been performed with the lyophilised NexoBrid finished product. The presence of different constituents in the heterogenous mixture of proteolytic enzymes has

been demonstrated by testing with several analytical methods. The identity of the chromatography peaks have been extensively investigated using two orthogonal methods, through which the applicant was able to quantify the relative proportions of the key constituents. Protein size distribution by HPLC and information on characterisation of the main peaks, which form the fingerprint of the profile, were also provided.

The heterogeneity pattern, i.e. the relative ratio of the main components and thus the consistency of product composition can be monitored by the establishment of validated HPLC assays that were introduced into the release specification.

It is concluded that the applicant has identified and can control key components relevant to product quality.

Further analysis of NexoBrid finished product have been performed.

The glycoprofile of NexoBrid active substance is considered sufficiently investigated. Data on the Total monosaccharides, the most abundant monosaccharide and on N-glycan in NexoBrid active substance were investigated and provided.

The potency of NexoBrid finished product was tested by several methods. The relevance and adequacy of the limits for the potency assays are considered acceptable at present. One assay has been introduced only recently and the number of batches available to be tested is as yet limited.

Several process-related impurities were found below the respective limits of detection and are considered not necessary to be controlled at release. Other process-related impurities are adequately controlled through the specifications. Concentration of one reagent is significantly below the recommended upper limit for exposure. Control of heavy metals and testing of pesticide residues and aflatoxins will be performed at the level of the finished product. Potential carry-over of components used in the manufacturing process of Bromelain into NexoBrid active substance has been investigated. Therefore, it is concluded that the active substance manufacturing steps are resulting in removal of the reagents to relatively low levels with a wide margin of safety.

Specification

The active substance specifications have been updated according to the CHMP's various requests during the marketing authorisation procedure to include new tests and acceptance limits for purity and tightened pH limits. References to the analytical methods were included for each test parameter. All analytical methods have been appropriately validated.

To control product-related impurities, HPLC analyses have been included in the active substance specification. Control of process-related impurities, residuals, toxic (heavy) metals, pesticides and aflatoxins, are performed at the level of the finished product and it is considered acceptable. Bioburden determination has been also included into the active substance specification.

The justification for specification is considered adequate to control the active substance. However, the applicant is recommended to re-evaluate the active substance as well as the finished product specifications after testing of 20 batches manufactured according to the current processes. The review should include the procedures for qualification and implementation of the in-house reference standard. Depending on the outcome of the re-evaluation, specifications for the active substance and finished product should be updated to introduce new limits through a variation procedure.

Stability

NexoBrid active substance is intended to be directly processed to the finished product.

2.2.3. Finished Medicinal Product

NexoBrid finished product is provided as a lyophilised powder of NexoBrid active substance in a 50 ml type II glass vial stoppered with a type I bromobutyl rubber lyophilisation stopper and sealed with an aluminium cap. The excipients in NexoBrid finished product are acetic acid and ammonium sulphate. NexoBrid finished product is reconstituted with a gel vehicle presented in 100 ml glass bottles.

Two different dose sizes are supplied: 2 g of lyophilised powder and 20 g of gel vehicle, and 5 g of lyophilised powder and 50 g of gel vehicle.

Pharmaceutical Development

The formulation of NexoBrid finished product was not changed from pivotal toxicology studies, clinical development programme through to the final commercial process. The current gel vehicle formulation was used for the Phase III trials, Compatibility of NexoBrid finished product and gel vehicle had not been satisfactorily demonstrated in the initial quality dossier. New compatibility (in-use stability) studies at 25°C and 37°C have been performed demonstrating that NexoBrid degrades within hours after mixing. The applicant's conclusion that the product should be used immediately after mixing is therefore supported.

Manufacture of the product

The site MediWound Ltd., Israel is responsible for manufacture of NexoBrid active substance, NexoBrid finished product and for the gel vehicle. European release testing of NexoBrid finished product and gel is intended to take place at Teva in Gödöllő, Hungary, and batch release for the EEA at Teva in Haarlem, The Netherlands.

The manufacturing process consisting of sterile filtration of the active substance solution, aseptic filling and lyophilisation underwent adjustments throughout development. Changes comprised two fold scale-up, supplier of rubber stoppers, analytical methods, specifications and lyophilisation cycle. The current cycle was applied for all Phase III clinical trial supplies, the developmental lyophilisation conditions were applied in the manufacture of some Phase II clinical batches.

A recent change of the finished product manufacturing process was investigated on its relevance for the clinical data. A comparability exercise showed results for the commercial batches within or close to the range of experience of the clinical batches, thus demonstrating that the clinical data are still relevant in this regard.

The manufacture of NexoBrid finished product is performed in two scales.

For the finished product manufacturing process, additional limits have been included in the list of in-process controls for the finished product upon request. Insufficient validation data for the previous manufacturing process had been classified as major objection during the procedure. The revised manufacturing process has been validated for the 5 g presentation and for the 2 g presentation. Based on the presented validation data, the revised finished product manufacturing process is considered robust and consistently resulting in a finished product conforming to the pre-defined specifications.

Product specification

The applicant provided a specification for the NexoBrid finished product as well as for the NexoBrid powder and gel vehicle mixture for routine batch release and stability testing. The finished product specifications have been reviewed and revised during the marketing authorisation procedure, in the light of additional characterisation information. The HPLC test for composition has been appropriately validated and considered suitable for purpose. Likewise the potency assays are acceptable markers for consistency. A detailed description of the newly introduced potency assay to determine activity is missing but a validation study has been reported. The batch data available for this potency assay is limited. Further justification should be provided for the adequacy of the chosen potency markers and their assays to determine the overall debriding activity of this complex mixture in the absence of a standardised *ex vivo* or *in vitro* assay, see section "Recommendation(s) for future quality development".

Purity, activity, and limits for residuals in accordance with the requirements of the preclinical assessment have been implemented in the finished product specification. However, the limit of one residual needs re-evaluation, see section "Recommendation(s) for future quality development". Endotoxin control is ensured throughout the manufacturing process, based on control of materials used in the process and a strict bioburden control at all stages of the manufacturing process. Test on reconstitution time of the lyophilisate in the gel vehicle have been implemented in the specification for NexoBrid finished product and gel vehicle mixture. For heavy metals, more stringent limits than for oral exposure are applied. The specification for toxic (heavy) metal has been revised. Also, the acceptance limits for mercury and arsenic have been tightened in line with the batch data respectively by using a more sensitive analytical method.

The limits of all specifications for composition and potency, should be reviewed once more data is available, particularly potency/activity assay. Qualification and implementation of the new reference standard according to the latest procedures, and including the potency assay, should be included in the review. This review may be completed as a post-approval commitment, see section "Recommendation(s) for future quality development".

All release batch data provided comply with the proposed specification and for those tests available at the time of testing, the methods are deemed suitable and validated. The approach of measuring impurities at the finished product level, but not at the active substance level is considered acceptable although some quantitative differences are expected.

Container Closure System

The commercial container closure system for both presentations of the finished product comprises a 50 ml clear Type II glass vial with a 32 mm neck and a siliconised bromobutyl rubber stopper complying with the respective Ph. Eur. requirements. The current rubber stopper was not used for clinical supplies; however the previous stopper also consisted of bromobutyl rubber. Batch results and stability testing results of NexoBrid finished product with previous and current rubber stopper showed no significant differences. Extractables studies for the current rubber stoppers were performed. Leachable studies for the container closure system which were omitted in the primary quality documentation have now been presented. None of the potential leachables were detected. The choice of the container closure system is adequate with respect to the use of the product. The 32 mm neck of the vial should provide sufficient space to remove NexoBrid finished product for mixing in the bottle containing the gel vehicle. The vials are also considered adequate to support the stability of NexoBrid finished product based on the data provided for leachable studies, container closure integrity tests, manufacturing process validation and stability studies.

Stability of the product

The applicant proposes a finished product shelf-life of 36 months at 5±3°C. After reconstitution the product should be used immediately (i.e. within 15 minutes).

Four stability studies with finished product batches produced according to the previous manufacturing process had been performed at real-time conditions of 5±3°C and accelerated conditions of 25°C/60% RH reflecting development progress. The stability data reported in the original dossier is in principle considered relevant for the revised finished product. However, the originally provided data did not comprise all stability indicating tests, e.g. the test on purity with HPLC was missing in all stability studies. Updated results for the ongoing previous stability studies had been provided. Though results for the newly introduced stability indicating tests are limited, the stability data of batches manufactured with the previous manufacturing process is considered relevant for the commercial drug product.

Three batches of each presentation of the revised commercial manufacturing process using the current container closure system were submitted into a real time stability study (5±3°C), in both upright and inverted positions. For accelerated stability studies (25 ± 2°C/ 60 ± 5% RH) one batch of each presentation was submitted into a stability study in both the upright and inverted positions. The previously missing tests such as activity assay have been also included into the stability protocols.

Three months stability data are presented for all batches of the NexoBrid finished product. There was an out-of-specification result after one month for one batch stored at 2-8°C in inverted position with respect to HPLC testing. However it was found to be a typographical error.

The current stability results are in general stable was found over time, but there are out-of-specification results with respect to water content and pH in water. However, there does not appear to be a trend and the out-of-specification results are sporadic. The cause is currently not known. Water contents in the previous stability studies were well within the specification limits with no obvious trend.

The proposed shelf-life for both presentations of the drug product of 36 months when stored at 5 ± 3°C is accepted based on all available stability data. However, the applicant is advised that the shelf-life may have to be altered depending on further investigations on possible causes of the out-of-specification results and the results of the ongoing stability studies. In accordance with EU GMP guidelines any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Photostability testing shows that a "Protect from Light" statement is not required in the product information.

New in-use stability studies with samples produced in accordance with the revised manufacturing process demonstrate that the digestive potency of the product decreases steadily following mixing. This finding is included in the labelling texts.

Gel Vehicle

The formulation of the current gel is derived from a historical formulation and the choice of the composition is comprehensible and acceptable. The constituents are appropriate for the required pH range and are suitable for the administration in the wound scenario. The excipients used are in accordance with pharmacopoeia quality.

Two different presentations are available according to the different sizes of the finished product. In both cases, 20 g and 50 g size, the gel is presented in 100 ml glass bottles.

The overall volume of the bottles is sufficient for effective mixing with NexoBrid finished product and for removal of the constituted gel for administration. The applicant demonstrates that the mouth of the glass bottles is wide enough to facilitate extraction of the final, mixed product. The glass bottles and polypropylene screw caps are manufactured with reference to the Ph. Eur. Studies on extractables and leachables were performed taking into account the conditions of the intended use. Small quantities of extractables and leachables were found and it is justified that the amounts found do not give rise to concerns.

During the manufacturing process development the batch size was scaled up. The scale-up process was confirmed by sufficient batch data.

The sterilisation process for NexoBrid gel vehicle was modified during the marketing authorisation procedure. The manufacturing of the gel vehicle is a conventional process. The manufacturing of the gel vehicle is a conventional process.

Suitable operating parameters and IPCs with appropriate acceptance criteria were defined for the manufacturing steps. In view of the process changes full validation of the revised, commercial process was performed. Validation on the basis of two batches of the 50 g presentation and one batch of the 20 g presentation of gel vehicle is reasonable. Review of critical manufacturing steps, accuracy of filling process, homogeneity and bioburden during filling process and release testing of the validation batches of gel vehicle ensures the validity of the revised manufacturing process.

Due to the change in the manufacturing process, the formulation of the gel vehicle and the fill weights have been revised, in order to achieve comparability with the gel vehicle used for clinical trial supplies.

The test methods and the proposed specifications for the routine batch release and stability testing of the gel vehicle are described in the table below.

The parameter extractable weight is added in the release and shelf-life specification of gel vehicle with a specification which is sufficient to control and define the dosage. The proposed pH range has been revised. The specification for the parameter viscosity is also tightened to reflect the improvements in the manufacturing process. A risk assessment regarding potential impurities or degradation products arising from the manufacturing process in the gel vehicle is provided and it is considered that the criterion of viscosity of the final gel vehicle provides the control necessary to ensure consistency of the vehicle in terms of the degree of degradation during the terminal sterilisation step.

Since the submission of results of clinical trials in paediatric patients has been deferred in the PIP, the calculation of endotoxin limits for this population can also be postponed until the PIP has been completed.

A comprehensive programme of stability testing on gel vehicle under the proposed storage conditions, for the full proposed shelf life of 36 months is presented. The gel vehicle was stored in the upright position only. However, a supportive stability study was performed which investigated both upright and inverted position. No trends towards increasing or decreasing values were observed for any of the test parameters. Additionally, a stability study using batches of gel vehicle manufactured according to the current commercial process was initiated, stored in the upright and inverted positions.

A photostability study was performed using representative batches of both the (20g and 50g presentation. The test criteria sufficiently identify instability of the gel vehicle. Based on the photostability study, a warning to protect the gel vehicle from exposure to light has been included in both the Summary of Product Characteristics and the package leaflet. The proposed warning states: "*NexoBrid must be stored upright to keep the gel at the bottom of the bottle and in the original package to protect from light*".

The additional advice to always store the package in the upright position is justified to be on the safe side. The shifting of the gel into the top of the bottle would not affect the performance of the product

but scraping off the gel may be inadequate for the use. Additionally, it is confirmed that on all outer packaging used for the shipping and/or distribution of NexoBrid it will be clearly state "Store in an upright position".

A shelf-life of 36 month stored at 5 ± 3°C for the gel vehicle is acceptable as confirmed, by the results of the pivotal stability studies and the supportive stability studies.

Adventitious Agents Safety Evaluation

No raw materials of animal or human origin are used during the production of NexoBrid finished product. The only biological materials used are the pineapple stems. The risk of viral contamination of the pineapple stems was assessed and found to be mainly attributable to the environmental exposure (cultivation and storage of harvest in open field conditions) and the exposure to workers. The transmission of zoonotic viruses by animals or of human pathogenic viruses transferred through the direct contact of infected workers with the plant constitutes a risk which should be controlled as far as possible, particularly considering the extensive systemic exposure through the wound bed of this product in immunologically unbalanced patients. The virus inactivating capacity of the active substance manufacturing process has been determined by conducting a virus validation study. The results of the study demonstrate that the process is solely effective in inactivating some viruses but ineffective for other viruses. This is a rather critical finding, since the viruses which were not sufficiently inactivated are viruses associated with food contamination. They are listed in the FDA "Guidance for Industry: Guide to Minimize Microbial Food Safety Hazards of Fresh-cut Fruits and Vegetables" both as foodborne pathogens associated with fresh fruits and vegetables and pathogens transmitted by food that has been contaminated by infected employees. The active substance manufacturing process does not offer a safety margin for virus inactivation in case of a potential contamination with these or other even more resistant viruses.

The Applicant has performed a more in-depth risk assessment focusing on the exposure of the pineapple stems to a direct contamination source such as infected workers or animals. Data on the tenacity of relevant viruses on peeled and unpeeled stems have not been provided, which would have been helpful to assess the actual risk for transmission. Nevertheless, as requested during the procedure, a step-wise risk mitigation strategy has been proposed and integrated into the process to ensure the virus safety of the product as also requested by the Guideline on the Quality of Biological Active Substances Produced by Stable Transgene Expression in Higher Plants (EMA/CHMP/BWP/48316/2006). Key features of this strategy are the storage of the pineapple stems during harvest and transportation in dedicated closed containers, harvesting farmers using protecting wear (including gloves) and routine testing of Bromelain for such viruses performed by MediWound. Furthermore, the applicant has investigated the feasibility of modifying the manufacturing process through introduction of a nanofiltration step for clearance of adventitious viruses. However, the Applicant does not consider the risk of potential viral contamination such as to warrant the introduction of such a step. This is deemed acceptable, although the applicant is encouraged to consider implementing this step in the future, since this would confer a considerably higher level of virus safety for the product and patient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has provided a satisfactory quality dossier for NexoBrid, both for the active substance, the powder and the gel vehicle including product characterisation, the choice of parameters to determine potency and biological activity and evaluation of batch to batch consistency. The virus safety

has been addressed satisfactorily by an extensive risk assessment and the implementation of a step-wise risk mitigation strategy.

In accordance with the relevant herbal guidelines the pineapple plant/stems are defined as the starting material and Bromelain as an intermediate in the active substance manufacturing process. Extensive additional characterisation has been performed, allowing the choice of parameters to determine relative composition of key constituents and markers for potency to be identified and employed for the evaluation of batch to batch consistency. Validation and thus reproducibility and consistency of the proposed NexoBrid active substance manufacturing process starting with the extraction of the pineapple stems, has been confirmed.

The finished product manufacturing process has been revised to ensure a constant concentration of active substance and excipients in the finished product. Furthermore, manufacturing process validation demonstrates that the process is robust and consistently resulting in a finished product conforming to the pre-defined specifications. The change of the finished product manufacturing process does apparently not impact the relevance of the clinical data, as shown by a comparability exercise.

Review and amendment, if applicable, of both active substance and finished product specification limits is recommended once more data has been generated for the final commercial product.

The proposed shelf-life of 36 months for the drug product when stored at 5 ± 3°C is accepted based on all available stability data and explanations. However, the company is advised to strictly follow its commitment to monitor the ongoing stability studies and to remain vigilant for any trends.

For the gel vehicle, the manufacturing process including the sterilisation process has been modified and optimised to ensure a reproducibility.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the Summary of Product Characteristics. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Re-evaluation of the active substance and finished product specifications after testing of 20 batches manufactured according to the current processes. The review should include the procedures for qualification and implementation of the in-house reference standard for the newly introduced potency assay. Depending on the outcome of the re-evaluation, specifications for the active substance and finished product should be updated to introduce new limits through a variation procedure.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical pharmacodynamic package for NexoBrid consists of primary pharmacological investigations the forerunner bromelain product, and 5 studies with NexoBrid (2 study reports; 3 literature references). In the absence of an establishment of similarity between Nexobrid and the forerunner bromelain product the data with the latter are only seen as supportive. Further, to support the clinical development of NexoBrid, a dose finding study in a pig burn wound model was conducted where a VAS scale was used for assessment of debriding activity.

For the evaluation on non-clinical pharmacokinetics data from 6 in vivo studies (including 3 toxicokinetic studies) is available characterizing the absorption of NexoBrid in Sprague-Dawley rats, New Zealand White (NZW) rabbits and Gottinger minipigs. In all studies, NexoBrid was administered intravenously. The serum disposition of NexoBrid has been investigated in pregnant rats and rabbits in association with embryo-foetal development studies in these species and in minipigs in association with a single dose toxicity study.

The non-clinical toxicology program included single dose toxicity studies (minipig and domestic pig), genotoxicity and reproductive and developmental toxicity studies. An additional study evaluated the effect of NexoBrid on sensitization.

The preclinical safety studies in this application (general toxicity studies, reproductive toxicity studies, genotoxicity studies and an antigenicity study) were conducted following GLP principles. No concerns over GLP compliance are raised in relation to these studies.

2.3.2. Pharmacology

As most of the burn eschar is denatured proteins, enzymatic activity in the product is crucial. In order to use a bioassay which is the most relevant to the NexoBrid therapeutic outcome and clinical activity, the enzymatic activity of NexoBrid was the target of such development. A validated bioassay to determine enzymatic activity was provided and a definable linear dose-concentration relationship was found. By digesting the eschar, its removal is aided to confer benefit in wound recovery.

Primary pharmacodynamic studies

The dose range study was performed in pigs. The debriding activity was determined after a 4 h exposure based on a 6 point VAS scale where the amount of eschar remaining and the number of viable patent vessels and punctuate bleeding spots was assessed. When applied on deep burn wounds at concentrations of 5, 10 or 20%, the most consistent and efficient debriding activity was observed with the 10% preparation, even if the best concentration was not as clear as preferable. It could not be clearly shown if the average VAS of 4.18 (10%) is really statistically significant better than the average VAS of 4.06 (20%). From literature it is known that 35% bromelain in a lipid phase ointment was used to achieve debridement of wounds (e.g. Maurer 2001) and Wang et al. (2009) described that burn healing is dependent on burn site.

Within the acute dermal toxicity study the time setting compared to the dose range study was changed. While in the first study the burned wounds were treated with NexoBrid for 4 h in the acute toxicity study (GLP) the treatment interval includes 2 x 4 h treatment. It was not shown, why the time setting (2 times 4 h) the most effective and safe setting is.

In response to questions raised by the CHMP during the assessment the applicant submitted data from two additional animal studies using the pig burn wound model to support completeness and selectivity of debridement where histology results were provided by a blinded dermatohistopathologist.

Visual and histological results from Study A suggested that post NexoBrid treatment no eschar could be detected, intact skin was unharmed and that remaining dermis was similar in thickness and structure to that seen in wounds treated with a control agent. Results from Study B appeared to corroborate these findings. However, very little quantitative data (in comparison to study A) were provided with regard to depth of remaining dermis and comparison to controls for this study.

Overall the Applicant has shown to an acceptable degree in the animal studies that NexoBrid does not remove healthy tissue and fully removes eschar from wounds. However, these data are only considered supportive in nature and generally animal data should not be used where it is feasible to generate human data.

Further literature references[1] [2] were added. The first literature reference demonstrated efficient debriding activity and selectivity (effect limited to damaged or denatured collagen with no effect on normal or native collagen). The most important limitation of this study is the fact that the study was limited to the first 48 h after injury. The second literature study has demonstrated that rapid enzymatic debridement of deep partial-thickness burns with NexoBrid results in earlier reepithelialisation and cellular proliferation in pigs, when compared with the Vehicle Gel and topical antibiotic dressing alone. The most important limitation of that study was that most burns were deep dermal, and the results may differ in both deeper and less superficial burns. Obviously, healing of the exposed dermis greatly depends on the dressing used to protect the dermis and the epithelialisation process. This is confirmed by Wasiak et al. (2008)[3] which compared clinical studies with different wound dressings. They concluded that a number of dressings appear to have some benefit over other products in the management of superficial and partial thickness wounds.

Secondary pharmacodynamic studies

No secondary Pharmacodynamic studies have been conducted with NexoBrid. The general pharmacological properties of different bromelain products have been reviewed in the published literature. In addition to the debriding effect, main pharmacological activities explored for therapeutic use include anti-inflammatory, antithrombotic and anticoagulant effects as well as anti-tumour activities and support of digestion. All of these latter activities have been investigated using the oral route of administration and with repeated dosing. Therefore, use of bromelain (orally) can be considered to be well-established. Therefore, no further studies are deemed necessary.

Safety pharmacology programme

No standard safety pharmacology studies have been conducted with NexoBrid. NexoBrid consists of plant-derived proteases that are to be applied dermally for a limited time period and that the acute toxicity study performed in minipigs did not show any effects on vital organ system. Clinical safety data on vital organ systems was obtained from early clinical investigations and thereafter. Patients requiring NexoBrid treatment are closely monitored and the restriction of the body area which can be

[1] Singer AJ, McClain SA, Taira BR, Rooney J, Steinhauff N, Rosenberg L. Rapid and selective enzymatic debridement of porcine comb burns with bromelain-derived NexoBrid: acute-phase preservation of noninjured tissue and zone of stasis. J Burn Care Res. 2010 Mar-Apr;31(2):304-9.
[2] Singer AJ, McClain SA, Taira BR, Rooney J, Steinhauff N, Rosenberg L. The effect of rapid enzymatic debridement of deep partial-thickness with NexoBrid on wound reepithelialization in swine. J Burn Care Res. 2010 Sep-Oct; 31 (5): 795-802.
[3] Wasiak J, Cleland H, Campbell F. Dressings for superficial and partial thickness burns. Cochrane Database Syst Rev. 2008 Oct 8;(4):CD002106. Review.

treated as well as the number of treatment courses will decrease the plasma levels of bromelain and therefore the risk associated with NexoBrid treatment. The available clinical data did make further nonclinical safety pharmacology data not necessary.

Pharmacodynamic drug interactions

The potential pharmacodynamic interaction at the site of application was investigated between the forerunner product and antibiotics (gentamycin, silver sulfadizine, mafenide acetate) and /disinfectants (povidoneiodine, silver nitrate). No negative influence on the efficacy was observed when these substances were used prior to the debridement. A lower degree of debridement was observed when silver sulfadizine and povidone-iodine was given concomitantly to the forerunner product.

Proteolytic substances for wound care showed often that antibiotics or antiseptics (in acidic range) might alter the effectiveness of this enzymatic debridement. This was also shown for some antiseptic wound dressings which had influence on collagenase and papain activity (Shi et al. 2010). On the other hand there are some information that using debridement agents no concomitant topical antimicrobials are needed in chronic-infected wounds (Payne et al. 2008)4.

No specific nonclinical pharmacodynamic drug interaction studies have been conducted with NexoBrid. However, the studies concerning pharmacodynamic drug interactions conducted with the forerunner product were considered sufficient to assess the potential for drug interactions on the wound site. The SmPC provides adequate guidance.

2.3.3. Pharmacokinetics

The absorption of NexoBrid after IV administration was investigated in Sprague-Dawley rats, New Zealand White (NZW) rabbits and Gottinger minipigs. The i.v. route was considered adequate as it allows one to reach much higher exposures than dermal application (to evaluate the safety profile of higher systemic exposures).

The serum disposition of NexoBrid has been investigated in pregnant rats and rabbits in association with embryo-foetal development studies in these species and in minipigs in association with a single dose toxicity study using a detection and quantification method.

In all species used, the elimination from the serum after a single dose appeared to be bi-phasic or multi-phasic with a terminal elimination half-life generally in the range of 7-10 h in rats and rabbits and 12-16 h in minipigs. Serum clearance was in the range of 100-130 ml/h·kg in rats and rabbits and 130-170 ml/h·kg in minipigs and independent of dose.

There was no gender difference in the kinetics of NexoBrid when this was examined in minipigs, while in rats and rabbits only female animals were examined. The observation of a significant increase in the systemic clearance of NexoBrid after repeated dosing to pregnant rats and rabbits was suggest to be due to the pregnancy state of the animal because this phenomenon was not seen in the repeat dose i.v. administration to minipigs. In this minipig study it could be shown that the clearance was maintained at about the same level in both male and female animals for the duration of the study (3 administrations a week for 2 weeks). However in the absence of other (confirming) information (e.g. of anti-drug antibody levels) this is so far only an assumption. The development of anti-NexoBrid antibodies has been included as important missing information into the RMP and further clinical data is planned to be generated in the phase III study (MW2010-03-02).

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4 Payne WG, Salas RE, Ko F, et al (2008). Enzymatic debriding agents are safe in wounds with high bacterial bioburdens and stimulate healing. *J Plast Surg* **8:** 151–6

Proteinases similar to bromelain are rapidly complexed with antiproteinases, mainly with α2-macroglobulin and α1-antitrypsin. Therefore for the proteases of NexoBrid the information are sufficient as well as the general information concerning their metabolism and excretion.

According to the quality dossier also other constituents are present in the NexoBrid powder (monosaccharides, N-linked Oligosaccharides, sterols, fatty acids). For some constituents knowledge concerning distribution, metabolism and excretion is available, these data were provided. For some other constituents (sterol, fatty acids) their amounts within the NexoBrid powder were defined and because of their small amount the estimation of safety done by the Applicant can be accepted without further knowledge of metabolism etc.

The Applicant expected no pharmacokinetic interactions affecting the efficacy of the product due to the nature of the product (protease enzyme) and the method of administration (dermal application on burn wounds). Nevertheless since Bromelain consists of cysteine proteases, it cannot be excluded that they, if present in sufficiently high circulation concentrations, could inhibit drug metabolising enzymes. In one literature report[5] it was shown that CYP2C9 is strongly inhibited by bromelain, however this activity was seen when pineapple juice was added to human liver microsomes. Inhibition studies with NexoBrid were conducted assessing potential inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5 using pooled human liver microsomes. At all concentrations tested (0.15 to 150 µg/ml), NexoBrid caused complete or near complete loss of activity of all these enzymes. When tested in human hepatocytes, NexoBrid showed a different profile and showed little or no evidence of time-dependent and/or concentration-dependent inhibition of CYP2C9, or CYP1A2, CYP2B6, CYP2C19, CYP2D6 or CYP3A4/5. In human hepatocytes, NexoBrid did inhibit CYP2C8 and CYP2C9 with IC50s of 30 and 129 µg/ml, and CYP3A4/5 with an IC50 of 133 µg/ml. For the other enzymes an IC50>150 µg/ml was determined. As the highest reported Cmax in the clinical setting is 13.5 µg/ml and it is also reported that there is inhibitory activity of α2-macroglobulin on the proteolytic activity of NexoBrid, the results overall suggest that it is unlikely that NexoBrid will cause clinically significant inhibition of any CYP enzyme (see also below "Pharmacokinetics using human biomaterials"). However, this potential for cytochrome CYP2C8 and CYP2C9 inhibition should be considered in patients treated with substrates of CYP2C8 and CYP2C9, which is adequately reflected in the SmPC.

2.3.4. Toxicology

The recommended dose of 10% NexoBrid gel to be applied on the burn wound is 2 g powder per 100 cm^2 of skin (**20 mg/cm2**). The maximal recommended treatment area is given with 15% of TBSA. The average TBSA is given in literature with 1.7 m^2 so the maximal recommended treatment area is therefore 2550 cm^2. Following the initially proposed posology one burn wound area can be treated twice and 30% of the body area was treated (consecutively) in clinical trials. So for one treatment up to 51 g powder can be applied. All together 204 g (3.4 g/kg) powder could come in contact with the burned areas and treatment time might be up to 16 h.
In most studies minipigs were used for toxicity testing. The reason was given with the similar structure and enzyme activity of mini-pig/pig skin compared to human skin.

Single dose toxicity

In the dermal toxicity study a dosage of 15-18.5 mg/cm^2 was tested. Although the single dose dermal study in the pig wound model did not have the full monitoring program as per the standard repeat dose study, the haematology, clinical chemistry, urinalysis, organ weight measurement and the

[5] Hidaka M, Nagata M, Kawano Y, Sekiya H, Kai H, Yamasaki K, et al. Inhibitory effects of fruit juices on cytochrome P450 2C9 activity in vitro. Biosci Biotechnol Biochem. 2008 Feb;72(2):406-11

selected histology examinations did not reveal any indication of systemic toxicity. Dermal application of the test article to young pigs did not cause any local and systemic toxicological relevant findings when applied to burn wounds in the formulation and in the dosage regimen described. However, the concentration used was not the dosage recommended for human use. The Applicant discussed that due to the nature of this model and animal welfare issues only a limited burn area could be inflicted on the pigs. It was referred to the i.v. studies, were a much higher exposure compared to the dermal application (to evaluate the safety profile of higher systemic exposures) could be reached.

The following single-dose i.v. studies were conducted.
In the Rising Dose Tolerance Study NexoBrid-related clinical signs were essentially observed in the 24 mg/kg single dose group. The signs consisted of decreased activity, shivering, rapid breathing, impaired mobility, few faeces, decreased food intake, and discoloration in the abdominal region. Effects could be monitored until day 6 (m) and day 8 (f), respectively. Single i.v. doses of up to 12 mg/kg of NexoBrid powder were well tolerated with only minor signs of shivering and decreased activity observed. This is the 3 fold dosage compared to the maximum human dosage of 3.4 g/kg.

In the first Single Dose Toxicity Study (i.v.) NexoBrid-related clinical signs were limited to the 24 mg/kg dose group and included decreased activity, shivering (m only), few feces, and decreased food consumption. These signs persisted through day 7 (m) and day 2 (f), respectively. Clinical signs related to the dose administration were observed sporadically in all dose groups, including the control group, at the injection site and included scabs, reddened areas, skin discoloration and swelling. Based on the results obtained, the NOEL for a single dose of NexoBrid powder was determined to 12 mg/kg. The attained exposures (Cmax ~40 µg/ml and 75 µg·x·h/ml) at the NOEL was approximately 2.5-fold higher and 2-fold lower, respectively, than the maximally reported exposures in the clinical setting (Cmax ~15 µg/ml and 173 µg·x·h/ml). Even if not the intended route of administration these two studies might support the dermal toxicity study. Nonetheless it could not be shown if the clinical signs observed in i.v. studies are comparable with clinical signs to be expected with higher dosages in dermal toxicity studies.
In the second Single Dose Toxicity Study (i.v.) (1 animal per sex/group) minipigs were dosed i.v. with NexoBrid given to one male and one female at doses of 0, 24, 48 and 96 mg/kg as a single 2 h i.v. infusion. Minipigs were scheduled to be killed at day 8. There were unscheduled deaths of both pigs at the highest dose, with both dying at around 1 h and 15 min of the intended 2 h infusion. Generalised haemorrhaging was considered the cause of death in both pigs. All pigs given the lower doses survived to the intended termination. There were no test article-related changes in mean body weight, body weight gain, or organ weights during the study. Prothrombin time and activated PTT were slightly increased for 24 and 48 mg/kg/dose males and females on day 2, but returned to baseline values by day 8. Several test article-treated animals surviving to study termination had thrombi in the pulmonary artery or arterioles that were in various stages of organization. The most serious of these was the 24 mg/kg/day male that had a moderate early thrombus in a branch of the pulmonary artery as well as a smaller thrombus in an arteriole. The 48 mg/kg/day male and the 24 mg/kg/day female also had a small thrombus in a pulmonary arteriole. The remaining tissues/organs examined were essentially normal. Due to the slight, transient elevations of coagulation parameters in 24 and 48 mg/kg/dose animals and the pathological results (thrombi) no NOAEL can be supported. Furthermore the lack of equivalent sample size (1 animal per sex/group is not sufficient) does not allow a correct interpretation of the results.

Repeat dose toxicity

A 2-week, GLP conform, intravenous dose toxicity study was conducted. In this study, minipigs were dosed i.v. with NexoBrid given to four male and four female pigs at doses of 0, 4, 8 and 12 mg/kg three times weekly for 2 weeks followed by 2 weeks recovery period. There was one unscheduled

death in this study, with one pig at 8 mg/kg having convulsions and showing cyanosis on day 13 – it was killed on welfare grounds. All other pigs survived to the intended termination. In these pigs, convulsions, ataxia, laboured breathing and decreased food consumption were noted with no apparent dose-dependency but there were no notable findings on body weights, clinical pathology, ophthalmology or cardiology. At post mortem, there were increases in relative heart weight (12 mg/kg) and decreases in relative thymus weight (8 and 12 mg/kg) and there were findings of haemorrhages in multiple tissues, including in the thymus with cortical lymphoid depletion and pancreatic acinar cell degeneration. In recovery group animals, these findings had mostly resolved but there still remained minimal haemorrhage in the gall bladder and lymphoid depletion of the thymus. A NOAEL could not be determined.

Genotoxicity

NexoBrid was tested in a standard battery for genotoxicity. AMES and *in vitro* cytogenetic assays were negative. *In vivo* a statistically significant (p= 0.0317) increase in micronuclei frequency was measured in female mice in the highest tested dose of 2000 mg/kg. The statistical significance is mostly due to the low negative control value in females in this study. The mean negative control value was near the lower end of the historical negative control range. Also the mean MN frequency measured in the high dose group in females was still within the range of historical negative control, though near the upper end of the range. Therefore the statistical significance was not considered to also have biological relevance. It is concluded that NexoBrid does not show a relevant genotoxic potential and there are no concerns over any genotoxic potential.

Carcinogenicity

No carcinogenicity study has been conducted with NexoBrid and no such study has been identified with any stem Bromelain product. Die to the lack of any genotoxic activity of NexoBrid and the short-term use of the product, carcinogenicity studies are not required.

Reproduction Toxicity

The pivotal developmental studies were conducted in rats and rabbits. Both studies were preceded by dose range finding studies and, as no data from repeated dose studies were available, performed in non pregnant and pregnant animals, respectively. In all studies the compound was administered daily for 15 min via the i.v. route using infusion pumps. Vehicle control groups were treated with sodium chloride.

The dosages selected for the pivotal study in rats induced mortality in all dose groups. All remaining dams of the high dose group were euthanized on gestation day 8 to 10 due to adverse clinical signs (decreased body weight gain and food consumption, discoloration and swelling at the injection site). In the mid dose group discoloration and swelling at the injection site, scabbing, urine stained abdominal fur, ungroomed coat, low carriage, and decreased motor activity were observed. No effects on the number of corpora lutea, implantations, and live fetuses were noted. Fetal body weights and prenatal development were unaffected by treatment. Due to the fact that no maternal NOAEL could be established in this study, a bridging study was included consisting of another control and one group treated with 0.5 mg/kg/d. Similar to the previous study both groups contained 25 dams plus 6 dams for toxicokinetic investigations. In the bridging study neither effects on the dams nor on their offspring were detected. Thus the maternal NOAEL for this study is 0.5 mg/kg/d. The NOAEL for prenatal development is 4 mg/kg/d.

In the pivotal developmental toxicity study in rabbits one high dose rabbit was found dead on gestation day 13 without any clinical signs prior to death. One mid dose doe was euthanized on gestation day 11 due to severe clinical signs. At necropsy it was shown that in both rabbits the access ports were patent and properly located. While both rabbits showed mottled tan, red and/or dark red liver lobes in the doe from the mid dose group mottled red and dark red lung lobes and a pale white band encircling the ventricles of the heart were found. A pale white band encircling the ventricles and / or atrium was also observed in another mid dose doe as well as in one low dose doe. In the study reports of the dose range finding studies it is reported that microcirculation is disturbed by bromelain at 10 mg/kg/d given to rats intravenously, but the publication was not submitted. In the abstract of this publication (BAHDE et al. 2007) it is noted that bromelain given intravenously at a dose of 10 mg/kg/d to rats led to a disturbed microcirculation with increased leukocyte adherence, apoptosis rate, Kupffer cell activation, and endothelial cell damage. Uterine parameters and prenatal development was not affected. The maternal NOAEL derived from this study is 0.01 mg/kg/d and the developmental NOAEL is 0.10 mg/kg/d.

Toxicokinetic investigations performed after the first and last dose showed that exposure is much higher after single administration than after repeated dosing. No safety margins are available as higher dosages than those used in the pivotal studies were not feasible due to mortality and severe clinical signs, but in both species maternal toxicity occurred at low dosages without any effect on prenatal development at higher doses.

Toxicokinetic data

In the toxicokinetic Single Dose toxicity Study (i.v.) minipigs were given a 2 h i.v. infusion of NexoBrid at doses of 0, 24, 48 and 96 mg/kg but due to overt toxicity, blood was sampled only predose and at 0.5 h. Toxicokinetc results in this study indicated that at these doses the measured plasma concentration at 0.5 h after the end of dosing is 43,500/25,400; 66,600/63,900; and -/ 126,000 ng/ml in one male and one female minipig, with – indicating no sample. Within this study, the measured plasma concentration increased with dose, roughly in proportion.

Local Tolerance

Early local tolerance studies with the forerunner product showed that time and concentration dependent skin irritating effects of Bromelain products exist.

In studies with NexoBrid, the product was applied dermally to healthy minipigs at 10, 20 or 30% (intact skin and abraded skin). A control was also applied. The application area was ~0.5% of the body surface area. 20 and 30% caused significant behavioural responses interpreted as pain and this was relieved by buprenoprhine. Due to this response the initially planned dosing with these concentrations on subsequent dosing days was not continued. Erythema on abraded skin generally recovered within a week. Irritation and erythema were evident at all test concentrations and abrasion and scabbing of intact skin was seen at the application sites; there was a decrease in body weight at all concentrations. Microscopic examination indicated bacterial colonies, oedema, hyperkeratosis, epidermal hyperplasia, subacute inflammation, with rare instances of ulceration. However, all these changes were reversible. The data on local tolerability suggest that there is a potential for reversible local reactions when the gel is applied on intact skin and that contact with abraded skin could be irritating and painful. Within the SmPC it is clearly labelled, that the treatment area should be encircled with a sterile paraffin ointment adhesive barrier from surrounding area to protect intact skin. NexoBrid induced pain would be mitigated by the preventive analgesia medication as commonly practiced for an extensive dressing change.

A sensitization study (maximization method) in guinea pigs was conducted according to the OECD Guideline.The test article was administered at a concentration of 15, 30, and 100%. The challenge phase did not occur due to termination of the study after the topical induction phase due to the extensive adverse response exhibited by animals in the test and control article groups. As no irritation was observed in the irritation screen, treatment with sodium lauryl sulfate (SLS) was conducted five days post the intradermal induction dose. During the dermal induction dose unwrap, the skin ulcerations increased in size and severity in almost all animals. Animals had been treated with Buprenorphine twice per day in order to manage pain. By 48 h post the dermal induction dose, four test article animals had been found dead and another two were euthanized. Additionally, extensive clinical observations were noted in the majority of the test article group animals. In the best interests of the animals, the study was terminated on day 10. The Applicant stated that the use of the maximization method of determining sensitization with the use of SLS may not be the most appropriate model. The potential to cause sensitization in the clinical setting needs to be determined from the clinical use of the product. 4.4 of the SPC includes a warning that the potential of NexoBrid to cause sensitization should be taken into account when reexposing patients to bromelain-containing products at a later point in time.

Other toxicity studies

Available data for a reagent, which is used during the manufacturing process of NexoBrid with a presence in the NexoBrid powder did not reveal any concern

2.3.5. Ecotoxicity/environmental risk assessment

According to the „Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/ 4447/00) herbal medicinal products as well as medicinal products with active ingredients such as proteins and carbohydrates are exempted from the need to provide information on ecotoxicity/environmental risk assessment.

2.3.6. Discussion on non-clinical aspects

The pharmacological mechanism is assumed to be the enzymatic activity of the main components of the product. In a dose range study performed in pigs the debriding activity was determined after a 4 h exposure and the most consistent and efficient debriding activity was observed with the 10% preparation, even if the best concentration was not as clear as preferable.

Regarding the mechanism of action overall the applicant showed to an acceptable degree that in animal studies NexoBrid does not remove healthy tissue and fully removes eschar from wounds. However the selectivity of NexoBrid for dead eschar and not viable dermis was not sufficiently evidenced and despite further discussion of data from non-clinical burns models it was not considered that the evidence presented was sufficiently convincing to support the use of the term 'selective' in Section 4.1 of the SmPC. In addition to the debriding effect the main pharmacological activities explored for therapeutic use of different bromelain products include anti-inflammatory, antithrombotic and anticoagulant effects as well as anti-tumour activities and support of digestion.

Several studies characterize the absorption of NexoBrid in Sprague-Dawley rats, New Zealand White (NZW) rabbits and Gottinger minipigs. Specifity, sensitivity, and range of quantification of the bio-analytical method have been adaequately justified.

Because in dermal toxicity studies only limited burn area could be inflicted, most single and repeated toxicity studies were conducted with the intravenous application to achieve higher exposures compared to the dermal application. Based on the results obtained, the NOEL (i.v.) for a single dose of NexoBrid

powder was determined to 12 mg/kg (achieving plasma levels 2.5fold of the human plasma level after application of the clinical proposed dosage to 15% TBSA). A 2-week intravenous dose toxicity study in minipigs no NOEL could be determined, mainly due to the findings of haemorrhages in multiple tissues, including in the thymus with cortical lymphoid depletion and pancreatic acinar cell degeneration even in the lowest dosage group (4 mg/kg three times weekly for 2 weeks followed by 2 weeks recovery period). If observed necropsy results in rapids were immune related cannot be fully excluded. Based on the observation in the preclinical studies the CHMP requested to restrict the clinical use of the product to max. 15% TBSA and to implement warnings reflecting the possible impact of the product on coagulopathy parameters 4.4 of the SmPC.

NexoBrid was tested in a standard battery for genotoxicity. It is concluded that NexoBrid is devoid of a clinically relevant genotoxic potential. For the intended use carcinogenicity studies are not considered applicable.

No studies on possible effects of bromelain on male and female fertility as well as on prenatal and postnatal development were submitted. It is acknowledged that the product is administered as a single topical application to hospitalised trauma patients and that NexoBrid is relatively rapidly eliminated from the body (plasma elimination half-life in the range of 10-15 hours) and there should hence be no risk for a delayed effect on male and female fertility. This is reflected in 4.6 of the SmPC.

The pivotal developmental studies were conducted in rats and rabbits. Standard embryo-foetal developmental studies conducted in the rabbit and rat showed that rabbits are particularly sensitive to systemically delivered NexoBrid/NexoBrid. No embryo-foetal effects were observed in rabbits but one unexplained maternal death in each of the two highest dose groups resulted in a maternal no-observed-adverse-effect-level (NOAEL) of 0.01 mg/kg. The rat study did also not reveal any embryo-foetal toxicity but maternal toxicity in the form of transient reductions in body weight gain and feed consumption, increased clinical signs and injection site reactions were seen at an i.v. dose from 4 mg/kg. The reproduction toxicity data has thus demonstrated that there is no embryo-foetal toxicity in the absence of clear maternal toxicity. It should be noted, however, that maternal exposure levels at the end of dosing at the highest doses investigated in both the rat and rabbit embryo-foetal development study were considerably lower than those maximally reported in the clinical setting. Based on standard nonclinical studies, it is therefore not possible to fully ascertain the true potential for NexoBrid to interfere with embryo-foetal development in humans. Appropriate warning statements have therefore been included in the SmPC.

The data on local tolerability suggest that there is a potential for reversible local reactions when the gel is applied on intact skin and that contact with abraded skin could be irritating and painful. Within the SmPC it is clearly labelled, that the treatment area should be encircled with a sterile paraffin ointment adhesive barrier from surrounding area to protect intact skin. NexoBrid induced pain would be mitigated by the preventive analgesia medication as commonly practiced for an extensive dressing change.

A sensitization study (maximization method) in guinea pigs was conducted and had to be terminated after the induction phase due to the extensive adverse response exhibited by animals (after treatment with sodium lauryl sulphate - SLS). The potential to cause sensitization in the clinical setting needs to be determined from the clinical use of the product. In the SmPC it is therefore clearly labelled that the potential of NexoBrid to cause sensitisation should be taken into account when re-exposing patients to bromelain-containing products at a later point in time and that in case of skin exposure, NexoBrid should be rinsed off with water to reduce the likelihood of skin sensitisation.

2.3.7. Conclusion on the non-clinical aspects

A single intravenous infusion of a solution prepared from NexoBrid powder in the mini-pig was well tolerated at dose levels of up to 12 mg/kg (achieving plasma levels 2.5fold of the human plasma level after application of the clinical proposed dosage to 15% TBSA) but higher doses were overtly toxic, causing haemorrhage in several tissues.

After repeated intravenous injections of doses up to 12 mg/kg every third day in the mini-pig severe clinical signs of toxicity (e.g. haemorrhages in several organs) were observed. Such effects could still be seen after the recovery period of 2 weeks.

Following these results (and the results from the clinical pharmacology studies as described in the chapter below) the CHMP requested to restrict the clinical use of the product to a single application to max. 15% TBSA furthermore warnings reflecting the possible impact of the product on coagulopathy parameters were added in chapter 4.4 of the SmPC.

The data on local tolerability suggest that there is a potential for reversible local reactions when the gel is applied on intact mini-pig skin and that contact with abraded skin could be irritating and painful. Within the SmPC it is clearly labelled, that the treatment area should be encircled with a sterile paraffin ointment adhesive barrier from surrounding area to protect intact skin and that NexoBrid induced pain should be mitigated by the preventive analgesia medication as commonly practiced for an extensive dressing change.

Overall the applicant showed to an acceptable degree that in animal studies NexoBrid does not remove healthy tissue and fully removes eschar from wounds. However the selectivity of NexoBrid for dead eschar and not viable dermis was not sufficiently evidenced to support the use of the term 'selective' in Section 4.1 of the SmPC.

Overall, the SmPC and the risk management plan adequate reflect the findings for the nonclinical development programme.

2.4. Clinical aspects

2.4.1. Introduction

The main study in support of the present application was a confirmatory Phase 3 study (MW 2004-11-02) evaluating the efficacy and safety of NexoBrid for removal of eschar from burn wounds.

These findings were supported through

- a Phase 2 study (MW 2002-04-01) evaluating the safety and enzymatic debriding efficacy of NexoBrid as compared to SOC and vehicle, and
- a retrospective data collection (35-98-910) using data from 154 subjects in a single centre.

Additional supportive studies included:

- a dose-ranging study (MW 2001-10-03) evaluating the efficacy and safety of three doses of NEXOBRID.
- study MW 2005-10-05 evaluating the safety and exploratory efficacy of NEXOBRID in comparison to Vehicle, and SOC in subjects with DPT and/or full thickness burns ranging from 1-5% TBSA.
- study MW 2008-09-03 evaluating the safety and exploratory efficacy of NEXOBRID, as well as the systemic absorption of NexoBrid when applied topically on thermal burns, through

pharmacokinetic (PK) assessments in hospitalize male and female adult subjects aged 18 to 55 years with partial thickness burns of 4-30% TBSA.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Overview of Clinical Studies

Study Number	Study Phase	Design and Primary Objective	Study Population N = Total Adults/Pediatric Pts (n/n)	Location Number of Sites (n)
Controlled Clinical Studies				
MW 2002-04-01	2	Randomized, observer-blind, three-arms, multi-centre, safety and efficacy study	140 (140/0)	International, Multicenter (18 centres)
MW 2005-10-05	2	Randomized, open-label, three-arms, single-centre safety study	30 (30/0)	USA, (Single-centre)
MW 2004-11-02	3	Randomized, open-label, two-arms, multi-centre efficacy and safety study	181 (148/33)	International, Multicentre (26 centres)
DRF/Single Arm Clinical Studies				
MW 2001-10-03	2	Randomized, open-label, observer-blind, multi-centre, dose-ranging, safety and efficacy study	20 (20/0)	Israel, Multicentre (2 centres)
MW 2008-09-03	2	Single-arm, open-label, multi-centre, safety, efficacy (exploratory) and systemic absorption PK) study	10 subject planned[6]	Israel, India (2 centres)
Retrospective Data Collection Study				
35-98-910	1/2	Retrospective data collection study to demonstrate safety and efficacy	154 (77/77[7])	Israel, Single-centre
Total:			533 (423/110)	

2.4.2. Pharmacokinetics

The pharmacokinetics of NexoBrid following topical application was investigated in the efficacy and safety study MW 2008-09-03, where one objective was to to explore NexoBrid absorption as measured by PK testing. The bio-analytical method was validated and has adequate accuracy for detecting and following the time course of compounds in a complex biological matrix. Specificity, sensitivity, and range of quantification were shown.

No PK studies in healthy volunteers have been conducted with NexoBrid, as applying NexoBrid to intact healthy skin will not result in meaningful PK information, due to the protein-mixture inability to be absorbed through intact skin.

[6] Interim data after the enrolment of 8 subjects is presented in this report. Study is ongoing.
[7] The data for this study were analyzed and prepared for a clinical report in 2004. At that time the age for children was considered as <16 years and for adults as ≥16 years (n = 75 children); Data presented in this module are based on a cut-off age of 18 years (n = 77 children).

Absorption

Study MW-2008-09-03 was is a Phase II open-label, single-arm, two centre (Israel, India) study designed to evaluate the safety and efficacy of NexoBrid in hospitalised subjects with partial thickness (mid and deep dermal) thermal burns of 4-30% TBSA, and to explore systemic absorption as measured by pharmacokinetic testing.

At the time of submission of the dossier study MW 2008-09-03 was ongoing; hence complete results were not yet available. An interim look was conducted following enrolment of the first eight subjects.

Eligible subjects were male and female patients aged 18-55 years, with burn wounds defined as (a) partial thickness (mid & deep dermal) thermal burn wound of ≥ 4% and ≤30% TBSA and/or (b) full thickness burns of ≤5% TBSA, requiring hospitalisation. NexoBrid was applied once to the burn wound at a dose of 2 g NexoBrid Powder/20 g gel/100 cm2 of skin, and kept under occlusive wound dressing for 4 hours before debridement.

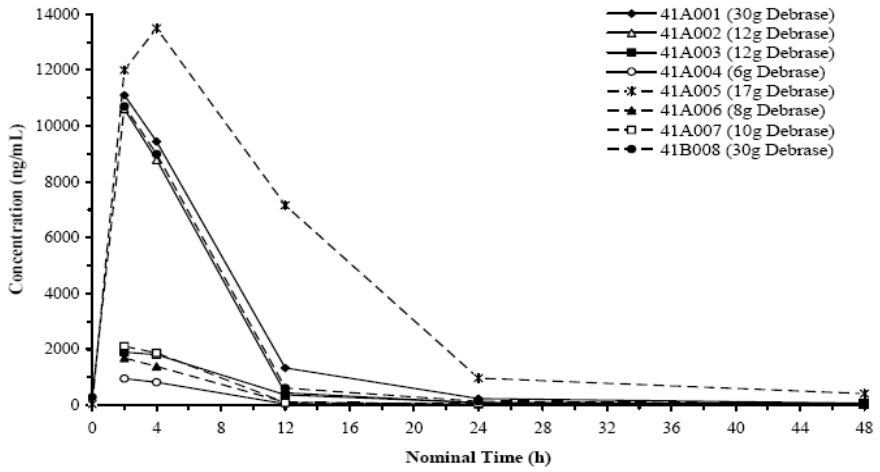
Blood samples were collected from all patients prior to treatment and at nominal times of 2, 4, 12, 24, and 48 hours following treatment. The range of doses applied was 6 to 30 g partially purified bromelain from NexoBrid. Serum was prepared from blood and was analyzed for concentrations of NexoBrid. Serum NexoBrid concentration-time data for each patient was analyzed by non-compartmental pharmacokinetic methods using WinNonlin, with actual sampling times and doses, and the results are summarized in the figure below. Cmax and AUClast were reported both as observed and as dose-normalized results, because the treated skin area differed for each patient.

Following topical administration of NEXOBRID at concentration of 0.02 g/cm2 (the application of Bromelain is estimated to be approximately 20 mg/cm^2) serum NexoBrid concentration-time profiles were qualitatively similar for all subjects. There was a rapid uptake of NexoBrid post-administration of topical NEXOBRID, at doses of 6-30 g. Concentrations increased relatively rapidly, attaining C_{max} (dose-normalized mean 383 ng/ml/g) by 2 h post-dose, with a mean half-life of 12.8 h. Total blood exposure through 48 h post-administration (AUC_{last}) averaged 49300 ng•h/ml/g (dose-normalized 2930 ng•h/ml/g due to the influence of results for 2 subjects). Individual C_{max} estimates ranged from 951 to 13500 ng/ml, with a mean of 6570 ng/ml. Dose-normalized C_{max} values for 6 of the 8 patients ranged from 158 to 370 ng/ml/g NexoBrid, but the mean for all patients was somewhat higher (393 ng/ml/g NexoBrid), due to the influence of results for 2 patients with individual values of 883 and 794 ng/ml/g NexoBrid, respectively.

Individual AUC_{last} estimates ranged from 5650 to 167 000 ng·h/ml, with a mean of 49 300 ng·h/ml. Dose-normalized AUC_{last} values for 6 of the 8 patients ranged from 942 to 2530 ng·h/ml/g NexoBrid, but the mean for all patients was somewhat higher (2930 ng·h/ml/g NexoBrid), due to the influence of results for 2 patients with individual values of 4500 and 9820 ng·h/ml/g NexoBrid, respectively.

The variability (CV%) of dose-normalized C_{max} (73.3%) and AUC_{last} (103%) was somewhat lower than for observed C_{max} (81.1%) and AUC_{last} (110%).

Figure 2
Individual Serum Debrase Concentrations after Dermal Administration of Debrase Gel Dressing to Burn Patients (Linear-Linear)



For all but one patient, Tmax was 2 hours from the start of debridement. However, this was also the first time point post-treatment start that serum NexoBrid concentration was evaluated.

PK data from a further 8 patients in study MW 2008-09-03 were available during the assessment. This includes data from 1 patient who received 2 applications of NexoBrid. The PK profile for this patient exhibited a broad peak from 8 to 16h post-dose, as a consequence of the dose having been administered in two portions over a period of 4 hours. The following updated summary data were presented. Overall, the summarised data did not change significantly with the inclusion of data from the 8 additional patients.

Table 132.1- Summary of Pharmacokinetic Parameters for Serum NexoBrid after Dermal Administration of NexoBrid to Burn Patients

Patient	Observed Data						Dose-Normalized Data	
	Dose (g)[a]	C_{max} (ng/mL)	t_{max} (h)[b]	AUC_{last} (ng·h/mL)[c]	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	C_{max} (ng/mL)/ Dose (g)	AUC_{last} (ng·h/mL)/ Dose (g)
Mean[d] Data								
NA	14	6020	2	43400	51000[e]	11.7[e]	435	2990

The AUC from time zero to 48 hours after administration (AUClast) was 43,400 ± 46,100 ngh/ml (mean ± SD) for the entire group of 16 patients, with a range of 4560 to 193,000 ngh/ml. These results for Cmax and AUClast indicate that systemic absorption may depend both on the applied NexoBrid dose (proportional to the covered wound area) and other, patient-specific factors.

No studies have been conducted investigating the bioavailability or bioequivalence of NEXOBRID (NexoBrid Gel Dressing), since it is used for acute topical therapy, applied once, or at most twice to the same burn wound. The absence of such studies is considered justified, as no major changes were made with the formulation during drug development, and the same formulation of the NexoBrid drug product (lyophilized powder) was used during the entire clinical program of NexoBrid (conducted by MediWound). The formulations of the Gel Vehicle that were used during the NexoBrid clinical program

differ only in component that was used during the Phase 2 studies and not during the Phase 3 study. This difference is not considered to have an effect on the performance of the product in terms of safety and efficacy.

Distribution and Biotransformation

Once absorbed, NexoBrid should undergo proteolytic digestion to its amino acid constituents which are further metabolised by usual biochemical pathways. As the administration of NexoBrid is local and applying NexoBrid to intact healthy skin will not result in meaningful PK information, due to the protein-mixture's inability to be absorbed through intact skin, specific human studies of bioavailability, distribution and metabolism were not performed.

Elimination

There are no data that specifically address the excretion of absorbed NexoBrid. However, it is not expected that any significant amount of absorbed NexoBrid will be excreted as the intact protein molecule. As indicated above, once absorbed, NexoBrid should undergo proteolytic digestions to its amino acid constituents and subsequently to carbon dioxide and water when fully metabolised. Formed amino acids may be reused for the synthesis of endogenous proteins. Since NexoBrid is only applied once, or at most twice; in view of its known use as food and as a food supplement; and considering its fast clearance (t1/2 = 12.8 hours), the issue of accumulation is irrelevant.

Dose proportionality and time dependencies

See above

Special populations

No specific studies in special populations have been conducted. This is considered acceptable.

Pharmacokinetic interaction studies

During a literature search for Bromelain a possible interaction with sedatives is noted; for sedatives and orally administered Bromelain as food supplement. Several possible interactions were found with orally administered Bromelain. Interactions of topically applied antibiotics and disinfectants were investigated with the forerunner product. Non-clinical studies showed that silver sulfadiazine and povidone-iodine had an inhibitory effect on the debriding activity of the forerunner product. According to the instructions for use prior to NexoBrid treatment, all local medications are removed and the wound bed is soaked for a minimum of 2 hours.

Effects of Intrinsic and Extrinsic Factors on Pharmacokinetics

No studies have been conducted investigating effects of intrinsic or extrinsic factor on the PK of NexoBrid as its intended use involves a single topical application of short duration on burn wounds. The absence of such studies is considered justified based on the composition, the mechanism of action, the single topical application and the short duration of application. Systemic absorption is followed by rapid

decomposition of the Bromelain enzymes due to lysis by plasma proteases to peptides and the individual amino acids that are re-used for protein synthesis within the body. In addition, a large and long-established database exists on Bromelain use [Maurer H. et al, 2001][8].

Pharmacokinetics using human biomaterials

A single in vitro study in the literature using human microsomes demonstrated potent inhibition of CYP2C9 activity (Hidaka et al 2008)[9]. The Applicant investigated CYP enzyme inhibition in human hepatocytes and showed IC_{50} values of 30 µg/ml and 129 µg/ml, after an incubation period of 30 minutes, for CYP2C8 and CYP2C9 isoenzymes respectively. It was concluded that as the highest reported C_{max} and AUC in the clinical setting approximated C_{max} 13.5 µg/mL and AUC 167 µg.h/mL, it was unlikely for NexoBrid to cause clinically significant inhibition of any CYP enzyme. However, this potential for cytochrome CYP2C8 and CYP2C9 inhibition should be considered in patients treated with substrates of CYP2C8 and CYP2C9 (see SPC 4.5).

2.4.3. Pharmacodynamics

Mechanism of action

Concentrate of proteolytic enzymes enriched in bromelain is a debriding agent, applied topically for removal of eschar in deep partial- and full-thickness burns. The mixture of enzymes in NexoBrid dissolves burn wound eschar. The specific components responsible for this effect have not been identified (see non clinical part of the report).

Primary and Secondary pharmacology

Pharmacodynamic effects of NexoBrid were assessed in non-clinical studies that investigated the concentration-response relationship in in vivo debridement dose-ranging studies. The debriding activity was investigated in piglets using a burn wound model and a visual score. In part of the studies, a histological score was used as well, and in one study the rate of epithelialisation after debridement was also assessed. These studies showed that a dose smaller than 2 g/100 cm2 was slightly less effective than a 2 g/100 cm2 dose. A double dose of 4 g/100 cm2 did not result in any significant improvement of the final debridement efficacy.

The Applicant has summarised the main pharmacodynamic effects of Bromelain from the literature and provided the cited publications. The provided evidence suggests that the main pharmacodynamic effects could be defined as anti-inflammatory, antithrombotic and fibrinolytic.

No special clinical immunogenicity studies were conducted. However, the Applicant has committed to develop an assay to detect and measure anti-NexoBrid antibodies in patients enrolled into a paediatric study (MW2012-01-01) and in a phase IIIb study in adults and children, MW2010-03-02 to be initiated in 2012 (Annex II condition).

[8] Maurer H. Review: Bromelain: biochemistry, pharmacology and medical use. CMLS, Cell Mol Life Sci. 2001;58 1234–45
[9] Hidaka M, Nagata M, Kawano Y, Sekiya H, Kai H, Yamasaki K, et al. Inhibitory effects of fruit juices on cytochrome P450 2C9 activity in vitro. Biosci Biotechnol Biochem. 2008 Feb;72(2):406-11

2.4.4. Discussion on clinical pharmacology

The Applicant has developed an assay for quantifying the extent of NexoBrid absorption into the systemic circulation. Sufficient evidence was provided for the validation of the assay and the nature of the measured substances was considered sufficiently clarified.

Due to the protein-mixture's inability to be absorbed through intact skin, specific human studies of bioavailability, distribution and metabolism were not performed which is considered acceptable.

The human pharmacokinetic study MW 2008-09-03 is currently ongoing. Data from 16 patients (including 1 patient who received two applications of NexoBrid) were made available and show a high variability in Cmax and AUC. From the applied schedule and frequency of the blood sampling, especially for subjects undergoing a second administration of NexoBrid it cannot be excluded that earlier sampling post-treatment start would have lead to higher Cmax and AUC values and earlier Tmax values. Further, the severity of the burn wounds in this study are not as severe or as large as those in the pivotal study and there is a potential that there would be increased absorption of NexoBrid from wounds that were predominantly DPT and/or FT.

A number of publications submitted by the Applicant indicate potential interactions of oral bromelain with anticoagulants. Also, in the pre-clinical studies of minipigs, trends of clotting interference and subsequently haemorrhages were apparent at doses of 40µg/ml. It is noted by the Applicant that this dose range is approximately 2.5 times the highest Cmax noted in humans. However, it should be pointed out that a Cmax of 40µg/ml may be possible in humans administered NexoBrid according to the posology indicated in the initially proposed SmPC, when it is considered that PK has only been evaluated in patients with largely superficial burns, receiving half the maximum dose and in a single administration.

Therefore, the CHMP requested that the maximum wound surface area on which NexoBrid can be applied is limited to 15% TBSA, towards the upper limit of the wound sizes evaluated in study MW 2008-09-03. In addition the use of NexoBrid should be limited to one application only. The SmPC contains adequate guidance. Possible off lable use will be monitored within the planned retrospective drug utilisation study MW2013-06-01. Furthermore, to further characterise the PK profile of NexoBrid, the Applicant has been requested by the CHMP to undertake a full evaluation of NexoBrid PKs in a planned phase IIIb study, MW 2010-03-02.

No drug interaction studies with NexoBrid have been performed. During a literature search for Bromelain a possible interaction with sedatives is noted. A discussion on the breadth of available literature on PD effects of bromelain was provided; the most important of which were deemed to be its fibrinolytic and antithrombotic effects and its inhibition of various CYP isoenzymes. There is both literature evidence and in vitro data from the Applicant which suggest that these effects are dose dependent (i.e. extent of transcutaneous absorption). The relevant information is reflected in the SmPC.

Immunogenicity studies have not been performed. The available clinical data from the pivotal trial do not indicate severe immune related reactions. According to the SmPC the use of NexoBrid is restricted to a single application per wound and to a maximum wound surface area of 15% TBSA. According to the CHMP, these measures adequate reflect the current knowledge. Nevertheless, there is a possibility of treatment with NexoBrid after longer intervals or on other occasions, especially in groups at higher risk of burns (occupational hazards etc...), even if off-label. Therefore, the CHMP requested the Applicant to provide further data post-authorisation by evaluating the presence of anti-drug antibodies in subjects administered NexoBrid in the upcoming phase III studies (MW 2010-03-02 and MW 2012-01-01), as documented in the risk management plan.

CYP enzyme inhibition testing in human hepatocytes was performed and showed IC50 values of 30 g/ml and 129 µg/ml, after an incubation period of 30 minutes, for CYP2C8 and CYP2C9 isoenzymes respectively. Considering the provided PK data, the results suggest that when used on wounds it may be possible to selectively inhibit these enzymes, with resulting drug-drug interactions between NexoBrid and medicinal products metabolized by these isoenzymes. SmPC and RMP are taking this potential for drug interactions appropriately into account.

2.4.5. Conclusions on clinical pharmacology

Sufficient data on clinical pharmacology were presented.

Based on the available pharmacokinetic data and considering that with the current proposed posology blood concentrations may be reached, which in preclinical studies have shown clotting interference and subsequently haemorrhages, the maximum wound surface area on which NexoBrid can be applied has been limited to 15% TBSA. Furthermore, to take also into account the potential for immunological reactions, even if no severe immune related reactions have been observed in the clinical studies, the use of NexoBrid has been limited to one application only.

Appropriate warnings have been implemented in the SmPC and an educational programme to healthcare professionals will be performed to assure the safe application of the product.

The CHMP requested that the applicant provides further data to better characterise the pharmacokinetic profile of NexoBrid and the potential immunogenicity of the product. This will be addressed through the planned phase IIIB study (MW2010-03-02) and the planned paediatric study (MW 2012-01-01), as described in the risk management plan.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

Description	Due date
The MAH shall conducts a study on enzymatic debridement in burns patients (children and adults): A comparison to standard of care (protocol MW2010-03-02), based on a CHMP approved protocol.	31/03/2017

2.5. Clinical efficacy

Description of Clinical Efficacy Studies

Type of Study	**Stud y ID**	**Study Design and Type of Control**	**Test Product(s); Route of Administration; Dosage Regimen**	**Objective(s) of the Study**	**Subjects (N)**	**Dura-tion of Treat-ment**	**Healthy Subjects or diagnosis of patients**	**Study Status; Type of Report**
Dose-ranging study	MW 2001 -10-03	Phase II Open-label, observer blinded, randomised, Non-controlled, three-arm.	NEXOBRID at a dose of 1g, 2g, 4g. Topical	Debriding efficacy and safety of 3 different NexoBrid doses	20 rando-mised: NexoBrid 1 g (6) NexoBrid 2 g (7) NexoBrid 4 g (7)	4 h	Hospitalised patients with partial deep dermal and/or full thickness burns of 1-15% TBSA.	Comple-ted. Final report
Safety, efficacy	MW 2002 -04-01	Phase II Open-label, randomised, parallel, three-arm.	NEXOBRID (2g) Vehicle SOC Topical	Debriding efficacy and safety of NEXOBRID in comparison to Vehicle and SOC	148 rando-mised: NexoBrid 2 g (70) vehicle (35) SOC (35)	4 h	Hospitalised patients with deep partial thickness and full thickness thermal burns of 2-15% TBSA.	Comple-ted. Final report.

Type of Study	Study ID	Study Design and Type of Control	Test Product(s); Route of Administration; Dosage Regimen	Objective(s) of the Study	Subjects (N)	Dura-tion of Treat-ment	Healthy Subjects or diagnosis of patients	Study Status; Type of Report
Safety, explo-ratory efficacy	MW 2005 -10-05	Phase II Open-label, randomised, parallel, three-arm.	NEXOBRID (2g) Vehicle, SOC Topical	Safety, exploratory efficacy of NEXOBRID in comparison to Vehicle and SOC.	31 rando-mised: NexoBrid 2 g (10) vehicle (9) SOC (11)	4 h	Hospitalised patients with deep partial thickness and/or full thickness thermal burns of 1-10% TBSA.	Comple-ted. Final report
Safety, efficacy PIVO-TAL	MW 2004 -11-02	Phase III Open-label, randomised, parallel, two-arm	NEXOBRID (2 g) SOC Topical	Safety and debriding efficacy of NEXOBRID in comparison to SOC.	156 rando-mised NEXOBRID (2 g) (75) SOC (81) Non-rando-mised NEXOBRID training subjects (26)	4 h	Hospitalised patients with deep partial thickness and full thickness thermal burns of 5-30% TBSA.	Comple-ted. Final report
Safety and efficacy	35-98-910	Phase II Retrospective data collection study. Single-arm, non-controlled	NEXOBRID (2 g Debridase)	Safety and efficacy of NEXOBRID (2g Debridase)	154 analysed	4 h	Hospitalised patients with partial deep dermal or full thickness burns caused by fire/flame, scald or contact.	Comple-ted. Final report
Safety and efficacy	MW 2012 -01-02	Phase III Open-label, single-arm (long term follow up study from patients enrolled previously enrolled in MW2004-11-02)	NEXOBRID (2 g NexoBrid)	Safety and exploratory efficacy	Analyzed: 72 adults and 17 children.	4 h	Hospitalised patients with deep partial thickness and full thickness thermal burns of 5-30% TBSA..	Comple-ted. Final report

2.5.1. Dose response study

MW 2001-10-03

Study MW 2001-10-03 was an open label, observer blinded, randomized, multicenter, dose ranging study. The study was designed to evaluate the efficacy and safety of three NexoBrid doses in the treatment of patients with partial deep dermal and/or full thickness burns. Twenty hospitalized adult, male and female subjects, with DPT and/or full thickness burns of 1-15% TSBA were randomized to a 1 g (6/20 subjects), 2 g (7/20 subjects) or 4 g (7/20 subjects) dose of NexoBrid powder per 20 g of Gel Vehicle. The investigator performing the debridement efficacy and re-epithelialisation assessments was blinded for this study. The primary endpoint was time to wound closure following debridement as measured by 95% epithelialization (spontaneous healing or graft take), aiming to evaluate whether NEXOBRID impairs wound healing.

Of the 20 treated patients, 18 (1g, 5; 2g, 6; 4g, 7) achieved >95% epithelialization for wound closure during the weekly follow-up visits. One of the two patients who did not comply with the weekly visit

appointments had wound closure at the 3 month follow up visit. The mean time to >95% epithelialization from last debridement was 21.2 ± 2.4 days, 13.0 ± 6.7 days and 19.0 ± 8.5 days, for the 1g, 2g and 4g NexoBrid treatment groups, respectively. The median of time to >95% epithelialization from last debridement was 20.0, 11.5 and 16.0 days for the 1g, 2g and 4g NexoBrid treatment groups, respectively.

The average treated wound area (2.0 – 2.5% TBSA) was similar among the three treatment groups. NexoBrid at 1g, 2g and 4g removed 98.9%, 100% and 99.1% of the eschar, respectively. None of the patients required repeat debridement or additional eschar removal by excision during the study and only one patient required an autograft.

The 2g NexoBrid dose was considered effective in the debridement of partial deep dermal and full thickness burns. In this study the 1g dose showed results in the removal of eschar similar to those observed for the 2g and 4g doses. However, the 2g dose provided a safety margin in comparison to the 1g dose, for achieving efficacious treatment in more severe or difficult to treat burns than those of the patients in this study.

There was no difference observed in safety measurements among the three treatment groups and it was concluded, by the Applicant that NexoBrid is safe for the treatment of 1-15 % TBSA partial deep dermal and/or full thickness burns.

2.5.2. Main study

MW 2004-11-02

This was an open-label, randomised, parallel group, multicenter study, to evaluate the efficacy and safety of NexoBrid used for debridement treatment in patients hospitalised with partial deep dermal and/or full thickness burns.

Methods

Study Participants

Main Inclusion Criteria

1. 4 to 55 years of age
2. Thermal burns caused by fire/flame, scalds or contact
3. DPT (mixed deep dermal) and/or full thickness (3°) burn wounds≥ 5 % and ≤30% TBSA; all these wounds must receive study treatment. Total burn wounds ≤ 30% TBSA.
4. At least one wound of ≥2% TBSA DPT and/or full thickness burn
5. At least 50% of the DPT and/or full thickness burn wound area of the patient is intended for surgical debridement as judged at hospital admission

Main Exclusion Criteria

1. Other severe cutaneous trauma at the same sites as the burns (i.e. blunt, avulsion or deep abrasion) or previous burn(s) at the same treatment site(s) or one or more burn wounds that do not meet study criteria
2. DPT and/or full thickness facial burn wounds, >0.5% TBSA; study treatment of facial burns

3. Study treatment of perineal and/or genital burns (A patient with these wounds may be enrolled but the wounds may not be designated as TWs.)
4. Use of the following pre-enrolment dressings: a). Flammacerium, b). Silver Nitrate (AgNO3) Pre-enrolment wounds which are covered by eschar heavily saturated with iodine or by pseudoeschar (e.g. pseudoeschar as a result of SSD treatment)
5. Pre-enrolment escharotomy
6. Heavily contaminated burns or pre-existing infections (Adults: WBC ≥20.0 x 103 cells/μL; Children aged 4-16: WBC ≥25.0 x 103 cells/μL)
7. Signs that may indicate smoke inhalation
8. General condition of patient would contraindicate surgery
11. Poorly controlled diabetes mellitus (HbA1c>9%), Cardiopulmonary disease, peripheral circulatory disease
15. Chronic systemic steroid intake
16. History of allergy and/or known sensitivity to pineapples or papain

Treatments

2 g or 5 g of NexoBrid powder were mixed in 20 g or 50 g of Vehicle (ratio of 1:10) to obtain NexoBrid. NexoBrid was applied to the burn wound at a dose of 2 g NexoBrid powder per 100 cm2 of skin (approximately 1% TBSA in the average adult) for four hours. A total wound area of ≤15% TBSA was allowed NexoBrid treatment in one session; if the wound area to be treated was >15% TBSA, NexoBrid was applied in two separate sessions. In cases of partial debridement, a second topical NexoBrid treatment was applied, per investigator's discretion but no later than 48 hours after the start time of the first debridement. NexoBrid and Vehicle were mixed at the bedside ≤15 minutes prior to use.

It was required to apply study treatment to all DPT and/or FT burns of each subject. Cleansing, removal of blisters (burned keratin) and dressing with antibacterial solutions were performed for all wounds. Prior to debridement with, NexoBrid the subject received analgesic medication, as commonly practiced in dressing change of extensive burns, to ensure proper pain-free treatment (as mandated by the protocol). Interstitial/compartment pressure was also measured in circumferential extremity wounds prior to NexoBrid or SOC treatments. In addition, the wound was surrounded with a sterile paraffin ointment adhesive barrier by applying it on healthy skin a few millimetres from the wound's edges.

DEBRASE Treatment: Freshly prepared NexoBrid was applied topically to the burn wound at a thickness of 1.5 to 3 mm to all wounds designated to receive study treatment (target wounds [TW]) in a given subject. Each wound was covered with occlusive dressing for four hours. The occlusive dressing was then removed using aseptic techniques and additional analgesia. The adhesive barrier was removed using a sterile blunt-edged instrument such as a sterile tongue depressor. The dissolved eschar was removed from the wound using a similar sterile blunt edged instrument. The wound was then wiped and rubbed first with a large sterile dry gauze or napkin, followed by sterile saline-soaked gauze or napkin. If treatment had been ineffective, there was undigested eschar that strongly adhered to the underlying tissue and could not be removed. A dressing soaked with an antibacterial solution, e.g. 3-5% sulfamylon or 0.05-0.5% chlorhexidine was applied for an additional 2 hours. Appropriate preventive analgesia medication was implemented.

SOC Treatment: SOC included surgical and/or non-surgical procedures, depending on wound characterisation (e.g. burn depth) and each site's clinical practice. Surgical debriding procedures included tangential excision, minor excision, fascial avulsion, scraping, dermabrasion, brushing, or

Versajet Non-surgical procedures included covers and/or topical medication to induce maceration and autolysis of eschar.

Subsequent to debridement (NexoBrid or SOC), all wounds were visually assessed for debridement efficacy and treated in accordance with the post-debridement wound care routine. FT burns were usually autografted. Mixed dermal wounds were usually treated with protective biological covers, temporary skin substitutes, or topical medications. In some cases, burn management involved application of various treatments to different wound sites in a given subject or even to the same wound site, depending on wound assessment.

Objectives

The objective of this study was to evaluate the safety and enzymatic debriding efficacy of NexoBrid in hospitalized subjects 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.

Outcomes/endpoints

Primary Endpoint

- The % treated wound excised (by tangential/minor/Versajet excision) or dermabraded, in first surgery. Wounds which were entirely full thickness or have full thickness areas are excluded from this analysis. Surgical excision/dermabrasion performed in first surgery was defined as tangential/minor/Versajetexcision or dermabrasion, performed (a) as the initial eschar removal (debridement) procedure in the surgical SOC group or (b) as the first surgical debridement performed after initial eschar removal (debridement), in the DEBRASE or non-surgical debridement (NSD) SOC groups.

- The % treated wound autografted of deep partial wounds where the potential tissue-sparing effect may be seen. Wounds which are entirely full thickness or have full thickness areas are excluded from this analysis. The sum of all post-debridement autografts performed was taken.

Secondary Endpoints

- The % treated wound excised (by tangential/minor/Versajetexcision) or dermabraded, in first surgery (as described above), for all wounds
- Time to complete wound closure
- Timely eschar removal (debridement)
- Blood loss

Exploratory Endpoints

- Interstitial/compartment pressure in circumferential extremity wounds
- Time to hospital discharge

Safety

- General parameters: systemic adverse events, vital signs, pain assessments, laboratory tests, volume of blood transfusions (if required) and general functional disability assessments
- Local parameters: wound infection, local adverse events, graft loss and scarring assessment

The limit of ≥90% eschar removed (calculated as a weighted average of % eschar removed off all wounds per patient with respect to wound size) was used as the practical lowest success/failure threshold for this study, based on data from study MW2002-04-01where the calculated average percent of eschar removed with SOC was 92.7%, (95% CI 86.1%-99.3%).

Sample size

The sample size justification is based on the consideration of two co-primary endpoints for this study. To protect the experiment-wise type I error rate (falsely concluding treatment differences) at the alpha level of 0.05, a hierarchy testing procedure for two primary endpoints were used in which the % treated wound excised was tested first at the significance level of 0.05 and then only if the effect measured by the first primary end point was statistically significant, the % treated wound autografted was tested at the significance level of 0.05. The overall significance level for this scheme remained at or below 5%. Therefore, sample size calculation for both primary endpoints were based on α=0.05.

For the first primary endpoint, % treated wound excised (by tangential/minor/Versajet excision) or dermabraded, a sample size of 68 completed subjects per treatment group would have at least 80% statistical power to detect a difference of 22% in the endpoint at the significance level of 0.05, assuming a pooled standard deviation of 45%.

For the second co-primary endpoint, % treated wound autografted, the sample size estimation was based on wounds and not subjects since the clinical decision to graft a wound is taken per wound based on the unique characteristics of each wound. Assuming a target treatment difference of 11% in the % treated wound autografted between NexoBrid and SOC and a pooled standard deviation of 40%, a sample size of 210 wounds per group would be required to have at least 80% power to detect the treatment difference at significance level 0.05. Assuming an average of two wounds per subject, a total of 105 subjects per group would be required to contribute to the total number of wounds (210).

The study sample size was to be increased to account for dropouts, potential correlation among the wounds within the same subject and complete randomisation block size. Therefore, 240 subjects were to be randomised into NexoBrid or SOC treatment arms (120 subjects per arm).

In addition, one subject per site (≤ 30 subjects in total) was enrolled and designated as a NexoBrid subject as part of a training protocol.

Randomisation

The first subject at each site was designated as a DEBRASE subject as part of the training protocol. Subsequent subjects were stratified into two subgroups based on %TBSA of burn wounds, as assessed at Screening:
A. ≥ 5%, ≤15% TBSA of burn area
B. >15%, ≤30% TBSA of burn area

Within each stratification level, eligible subjects were randomized, per site, in a 1:1 ratio to receive DEBRASE or SOC treatment.

Blinding (masking)

It was not feasible to implement blinding for treatment procedures (topical DEBRASE vs. surgical/non-surgical SOC) since there is a great difference in the administration of these two modalities and thus

obvious to the caregiver as well as the patient. Moreover, it was not possible to implement post-treatment blinding procedures between the DEBRASE and the SOC groups, since the post-treatment physical appearance of burn wounds differs greatly between DEBRASE and SOC treated wounds.

Statistical methods

Unless otherwise specified, all statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05. Appropriate summary statistics are presented, depending on the variable. For continuous variables, the observed sample size, mean, median, and standard deviation are presented; the minimum and maximum values are also presented. For categorical variables, the Chi-squared test was used for treatment comparison and when the data were inadequate, Fisher's exact test was used. All statistical analyses were performed using SAS Version 9.1. An interim analysis was pre-planned when the study reached 152 randomized completed subjects.

Study Populations

- *Enrolled population* - all subjects who passed through the screening processes (training subjects and randomised subjects).

- *Intention-to-Treat (ITT) population* - all subjects who were randomised into the trial.

- *Modified Intention-to-Treat (MITT) population* - all randomised subjects with at least one wound that was entirely DPT, as evaluated in the pre-debridement assessment.

- *Complete case population (CC)* - all randomised subjects who provided efficacy data for wound closure (achieve 100% epithelialisation at weekly visit or > 95% epithelialisation at weekly visit and confirmed at a monthly follow-up assessment).

- *Evaluable (per protocol) population* - consisted of two subsets:

    - *Subset A* - ITT subjects who fulfilled all inclusion/exclusion criteria and were not excluded due to major protocol violations
    - *Subset B* - MITT subjects who fulfilled all inclusion/exclusion criteria and were not excluded due to major protocol violations

- *Safety population* - all enrolled subjects who received study treatment (training subjects and randomised subjects).

The training subjects were included only in safety evaluations and not in any efficacy analyses.

Efficacy Analysis

Primary endpoints:

- % treated wound excised: MITT and Evaluable Subset B
- % treated wound autografted: MITT and Evaluable Subset B

The analysis for these endpoints is per wound.

To control the type 1 error from the multiple comparisons, a sequential testing procedure was used. Both primary endpoints (the % treated wound excised and the % treated wound autografted) were tested at a significance level of 0.05. Testing for the % treated wound excised was performed first. If the test for the % treated wound excised had not been significant, then the test for the % treated wound autografted would not have been eligible for testing the significance.

Interim Analysis

An interim analysis was conducted when the study reached 152 randomised completed subjects as had been planned. An early stopping rule was used to terminate accrual to the trial at an interim point in the event that the results would appear to be very promising or indicate a futility result. The following stopping rule was used:

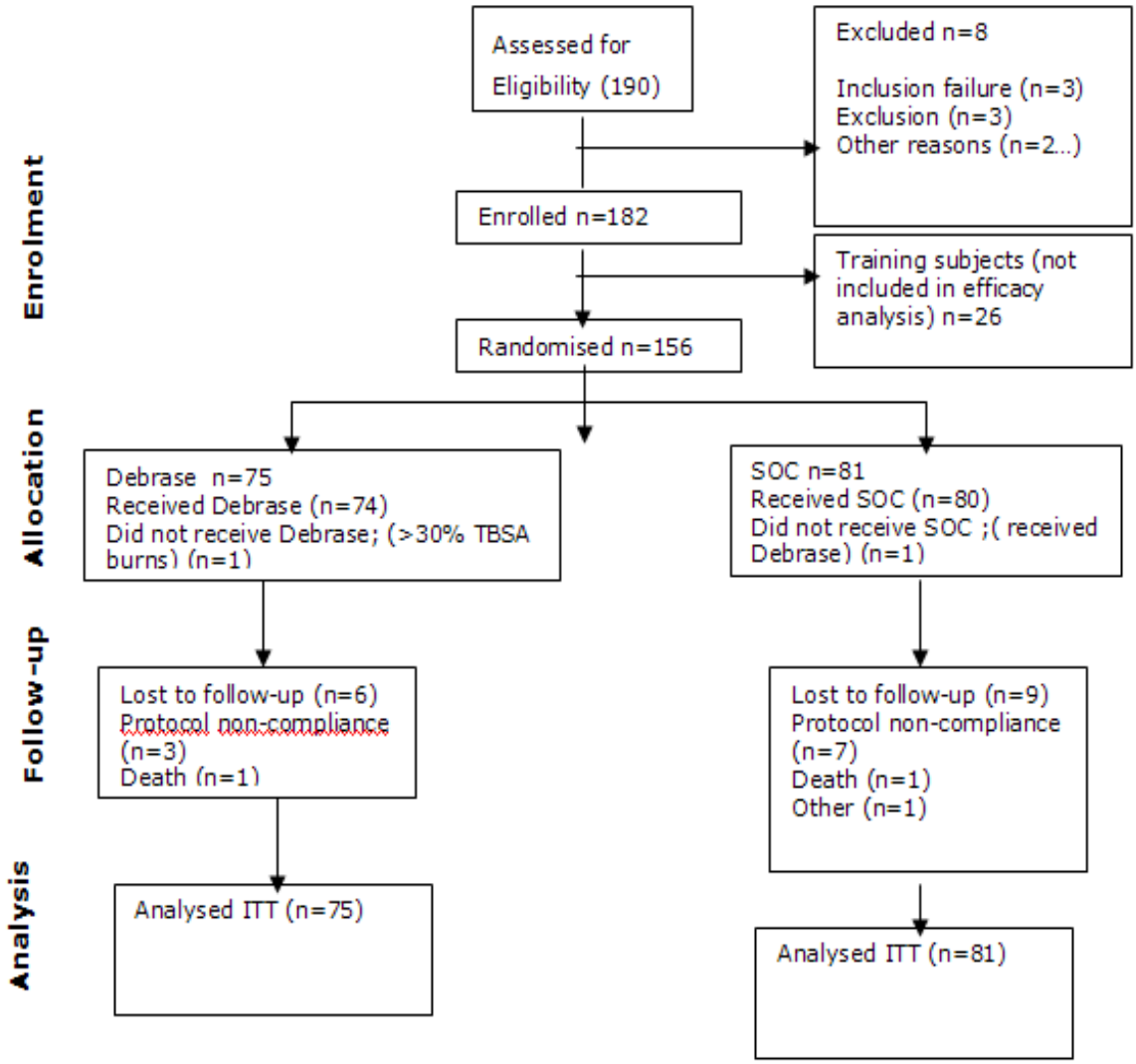
- Stop the study for efficacy if p value for %wound excised <0.02 and the p value for %wound autografted <0.02
- Stop the study for futility if both p values for %wound excised and for %wound autografted >0.5

Otherwise the study would be continued. To control the overall alpha level, pre-defined critical values were used, which were calculated in accordance with the Fleming, Harrington and O'Brien boundary.

As stopping rule number 1 was achieved, recruitment was stopped on October 15, 2009. Complete statistical analyses were performed as described in the SAP.

Results

Participant flow



Recruitment

32 centres from Europe, Israel, Brazil Australia and India underwent study initiation procedures; 26 centres enrolled subjects.

Conduct of the study

Protocol MW 2004-11-02, protocol amendments, and informed consent forms (ICF) were submitted for review and approval to the competent authorities (CA), and ethics committees (EC)/site institutional review boards (IRB) before initiation of the study and enrolment of any subjects.

Baseline data

Demographic Data and Baseline Characteristics (Enrolled Population)

				Randomized				
		NEXOBRID Training N=26		NEXOBRID (N=75)		SOC (N=81)		P-Value
Age (years)	N	26		75		81		
	Mean± SD	34.7±14.0		31.6±15.3		29.3±14.0		0.2301
	Median	35.5		32.6		26.6		
	Min	11.7		4.4		5.1		
	Max	54.7		55.7		55.7		
Weight (Kg)	N	26		75		81		
	Mean± SD	70.4±15.7		68.9±24.5		72.0±22.4		0.6866
	Median	73.0		69.1		75.1		
	Min	33.0		16.0		16.0		
	Max	97.0		116.0		119.0		
		N	**%**	**N**	**%**	**N**	**%**	
Gender	N	26		75		81		0.2375
	Male	23	88.5	54	72.0	61	75.3	
	Female	3	11.5	21	28.0	20	24.7	
Race	N	26		75		81		0.7969
	Caucasian	21	80.8	58	77.3	61	75.3	
	Middle Eastern	2	7.7	5	6.7	4	4.9	
	Black	0	0	4	5.3	5	6.2	
	Asian	1	3.8	5	6.7	3	3.7	
	Other	2	7.7	3	4.0	8	9.9	

Source: CSR MW 2004-11-02

In both study groups, circumstances of injury were mainly accidents not related to work. The great majority of subjects (>90.0%) in both groups did not have associated injuries or complications upon study enrolment.

Pre-Treatment Burn Description per Wound (ITT Population)

		NEXOBRID (N=75) 163 wounds			SOC (N=81) 170 wounds	
		N	**%**		**N**	**%**
Treated TW burn depth	N (wounds)	163			170	
	Second degree	1	0.6		3	1.8
	DPT	49	30.1		34	20.0
	Third degree	7	4.3		17	10.0
	First degree/second degree	1	0.6		1	0.6
	First degree/third degree	0	0		1	0.6
	Second degree/DPT	53	32.5		51	30.0
	DPT/Third degree	31	19.0		42	24.7
	First degree/second degree/DPT	4	2.5		3	1.8
	Second degree/DPT/third degree	16	9.8		18	10.6
	First degree/second degree/DPT/third degree	1	0.6		0	0
Wounds with no FT component (DPT wounds)	N (wounds)	163			170	
	Yes	106	65.0		88	51.8
	No	57	35.0		82	48.2
Wounds with any FT component	N (wounds)	163			170	
	Yes	55	33.7		78	45.9
	No	108	66.3		92	54.1
Treated TW total body surface area (%TBSA)	N (wounds)	163			170	
	Mean± SD	5.1±3.5			5.2±3.4	
	Median	5.0			5.0	
	Min	0.3			0.5	
	Max	16.0			15.0	
Treated TW %TBSA of wounds with no FT component (DPT wounds)	N (wounds)	106			88	
	Mean± SD	4.3±3.0			4.7±2.9	
	Median	4.0			4.5	
	Min	0.4			0.5	
	Max	15.0			13.0	

Source: CSR MW 2004-11-02,

There was a higher percentage of DPT wounds (wounds with no full thickness component) in the NexoBrid as compared to the SOC group (65.0%, and 51.8%, in the NexoBrid and SOC groups, respectively) with statistically significant difference between groups (p=0.0141). On the other hand, there was significantly higher percentage of wounds with any full thickness component in the SOC group (33.7%, and 45.9%, in the NexoBrid and SOC groups, respectively, p=0.0238).

Numbers analysed

Panel 10.3-1 Summary of Analysis Populations

Analysis Population	Training* DGD N=26		Randomized DGD N=75‡		SOC† N=81‡		Total N=156‡	
	n	%	n	%	n	%	n	%
ITT	-	0.0	75	100.0	81	100.0	156	100.0
MITT	-	0.0	49	65.3	48	59.3	97	62.2
Complete Case	-	0.0	70	93.3	78	96.3	148	94.9
Evaluable A	-	0.0	63	84.0	67	84.0	130	83.3
Evaluable B	-	0.0	41	54.7	41	50.6	82	52.6

	DGD N=101§		SOC N=81		Total N=182§	
	n	%	n	%	n	%
Safety	100	99.0	81	100.0	181	99.5

*According to the protocol, training DGD subjects were excluded from the efficacy analyses. (MITT/ITT/Complete Case/Evaluable A/Evaluable B populations); they were included in safety analyses

† One subject (no. 27B014), who received DGD treatment despite being randomized to SOC group, is analyzed in the latter group.

‡ Percentage of number of subjects in each data set are calculated based on N; for DGD and Total number does not include training DGD.

§ N includes randomized + training; one subject (no. 25B014) was excluded from safety data since he was randomized but did not receive treatment.

Outcomes and estimation

The trial was stopped at the first interim analysis for efficacy in accordance with the pre-specified analysis plan. The results are shown below:

Primary endpoints

Percent treated wound excised

The percent (number) of treated wounds excised (by tangential/minor/Versajet excision) or dermabraded in randomized subjects with at least one wound that was entirely DPT (MITT population) was significantly lower in the DEBRASE group, (15.1%, 16/106 wounds) as compared to the SOC group (62.5%, 55/88 wounds; p<0.0001).

Percent Treated Wound Excised (MITT Population)

		NEXOBRID (N=49) 106 wounds		SOC (N=48) 88 wounds		
		N (wounds)	%	N (wounds)	%	p-value
Excision (by tangential/minor/Versajet excision or dermabrasion) performed	N (wounds)	106		88		
	Yes	16	15.1	55	62.5	<.0001
	No	90	84.9	33	37.5	
Percent wound <u>area</u> excised (by tangential/minor/Versajet excision or dermabraded)	N (wounds)	106		88		
	Mean ± SD	5.5±14.6		52.0±44.5		<.0001 *
	Median	0.0		65.0		
	Min	0.0		0.0		
	Max	70.0		100.0		

* p-value using parameter square root.
Source: CSR MW 2004-11-02,

The results were sustained in the Evaluable B subset population. The effect was also demonstrated across age groups. In accordance with the SAP, no statistical tests were performed for subgroup analyses.

Post hoc analyses of treated wound area excised by TW area (TBSA) and baseline burn area in DPT wounds (mITT population) support the findings of the primary analysis and show that surgical debridement of DPT wounds can be reduced by NexoBrid regardless of TW or burn area size (0-30% TBSA).

Percent treated wound autografted

The percent (number) of wound autografts performed was significantly lower in the DEBRASE group (17.9%, 19/106 wounds) vs. the SOC group (34.1%, 30/88 wounds) (p=0.0099, MITT population)

Percent treated Wound Autografted (MITT Population)

		NEXOBRID (N=49) 106 wounds		**SOC (N=48) 88 wounds**		
		N (wounds)	**%**	**N (wounds)**	**%**	**p-value**
Wound autografts performed	N (wounds)	106		88		
	Yes	19	17.9	30	34.1	0.0099
	No	87	82.1	58	65.9	
Percent treated wound <u>area</u> autografted	N (wounds)	106		88		
	Mean ± SD	8.4 ± 21.3		21.5 ± 34.8		0.0054 *
	Median	0.0		0.0		
	Min	0.0		0.0		
	Max	100.0		100.0		

* p-value using parameter square root.
Source: CSR MW 2004-11-02, module 5.3.5.1.3, Panel 11.1-3.

Analysis of Evaluable B subset population also indicated lower percent of wound autografts performed in the NexoBrid group (21.9%) compared with the SOC group (31.9%); however, the difference did not achieve statistical significance due to smaller sample size in this subset population (p=0.16). Mean percent treated wound area autografted was 9.2%, and 20.6% in the NexoBrid and SOC groups, respectively, with no statistical difference between groups using two-way ANOVA model or repeated measurement ANOVA model.

Additional data revealed that some wounds underwent additional wound excision procedures (including those for reasons other than eschar removal) and, autografting procedures, as wounds may have been grafted in multiple stages. There was an excess of additional autografting procedures in the NexoBrid arm. Data on differences in number of autograft procedures undertaken or in the wound area autografted did not form part of the primary endpoint.

Data presented showed statistically and clinically significant differences between NexoBrid and SOC arms for the analysis of number of wound excision procedures undertaken for any reason and mean % wound area excised in all excisions, across different wound subgroups.

Post hoc analyses showed that for mixed wounds '% wound autografted' and '% wound area autografted' was greater for NexoBrid debrided wounds than for SOC wounds

Autografted wounds and procedures per depths in autografted DPT and Mixed wounds

NexoBrid	Number of Autografted wounds	Total number of Autografting procedures
Total DPT Mixed	52 19 33	67 24 43

SOC	Number of Autografted wounds	Total number of Autografting procedures
Total DPT Mixed	66 29* 37	70 29 41

* In the SOC group, 37 wounds were autografted in the mixed depth wounds and 30 in the DPT wounds however, for only 29/30 DPT wounds, TTCWC data was available.

NexoBrid:
Numerator = 2664% (same methodology as described above).
Denominator = 48 = the number of Mixed target wounds.
Result: NexoBrid % of Mixed wound area autografted = 2664% / 48 = 55.5%

SOC:
Numerator = 2747% (same methodology as described above).
Denominator = 60 = the number of Mixed target wounds.
Result: SOC % of Mixed wound area autografted = 2747% / 60 = 45.8%.

Secondary endpoints

Percent treated wound excised of all wounds

Patients with wounds that are entirely full thickness or have full thickness areas, the non-MITT population, were not included in the co-primary endpoints analyses.

The ability of NexoBrid to remove the eschar from all burn wound depths (ITT population) was supported in the secondary endpoint when the percent treated wound excised was analyzed for all treated wounds, including those with FT components. In the NexoBrid group the incidence of wounds that were excised was 24.5% (40/163 wounds) as compared to 70.0% (119/170 wounds) in the SOC. Significantly less treated wound area was excised in NexoBrid-treated all wounds (13.1%) as compared to the SOC group (56.7%); $p<0.001$.

Percent Treated Wound Excised (ITT Population)

		NEXOBRID (N=75*) 163 Wounds		SOC (N=81) 170 Wounds		
		N of (Wounds)	%	N of (Wounds)	%	p-value
Excision (by tangential/minor/Versajet excision) or dermabrasion performed	N (wounds)	163		170		
	Yes	40	24.5	119	70.0	<.0001
	No	123	75.5	51	30.0	
Percent wound <u>area</u> excised (by tangential/minor/Versajet excision) or dermabraded	N (wounds)	163		170		
	Mean± SD	13.1±26.9		56.7±43.3		<.0001**
	Median	0.0		80.0		
	Min	0.0		0.0		
	Max	100.0		100.0		

* One NEXOBRID subject (no. 25B014) was included in the ITT population but did not receive study treatment. This subject was excluded from this analysis since no information was recorded for his wounds. Therefore, the 163 wounds in this analysis belong to 74 ITT subjects.
** P-value using parameter square root.
Source: CSR MW 2004-11-02,

These results were sustained in the Evaluable A subset population.

Post hoc analyses for the non-MITT population (i.e. full thickness and mixed wounds) were performed showing also statistically significant differences in percent treated wound excised (table below).

Table 125.4 Percent treated wound excised per wound (full thickness and mixed wounds, MW 2004-11-02)

		NexoBrid 55 WOUNDS		SOC 78 WOUNDS		p-value
		N	%	N	%	
EXCISION (TANGENTIAL/MINOR/VERSAJET) OR DERMABRASION PERFORMED	N (wounds)	55		78		
	YES	24	43.6	64	82.1	<.0001
	NO	31	56.4	14	17.9	
% WOUND EXCISED VIA EXCISION (TANGENTIAL/MINOR/VERSAJET) OR DERMABRASION	N (wounds)	55		78		
	MEAN	28.1		64.9		<.0001
	SD	37.5		40.2		
	MEDIAN	0.0		90.0		
	MIN	0.0		0.0		
	MAX	100.0		100.0		

Post hoc analyses requested by the CHMP showed that number excision procedures for any cause exceeded the number of excisions for debridement in both study arms but more so in the NexoBrid arm than the SOC arm. Nevertheless, significant differences were still seen between the study arms in favour of NexoBrid treatment, where excision per wound rates were lower. Total number of 'all-cause' surgical excision procedures (including preparation of wounds for autograft placement which did not include eschar removal) for the ITT, MITT and non-MITT populations are presented below.

Table 3- Total number of excisions procedures, all excisions (MW2004-11-02)

	NexoBrid	SOC	p-value
Number of excision procedures, all excisions, ITT (wounds)	65 (163)	145 (170)	<0.0001
Number of excision procedures, all excisions, MITT (wounds)	22 (106)	61 (88)	<0.0001
Number of excision procedures, all excisions, non-MITT (wounds)	43 (57)	84 (82)	<0.0001

Table 4- % area wound excised, all excisions (MW2004-11-02)

	NexoBrid	SOC	p-value
ITT (wounds)	21.1 ± 35.7%	62.5 ± 48.9%	<0.0001
MITT (wounds)	7.6 ± 19.4%	54.2 ± 46.4%	<0.0001
Non-MITT (wounds)	46.2 ± 44.7%	71.5 ± 50.3%	0.0026

Time to complete wound closure

The last wound closed per subject was taken as the wound closure date, representing the maximum wound-healing time per subject.

Time to Complete Wound Closure* from informed consent form (ICF) Date (CC Population

		NEXOBRID (N=70)	SOC (N=78)	P-Value** Log-rank	Hazard Ratio *** 95% CI
Time to complete wound closure from ICF date (Days)	N	70	78		
	Mean ± SD	36.2 ± 18.5	28.8 ± 15.6	0.0185	1.46
	Median	32.5	23.0		(1.05, 2.03)
	Min	8.0	6.0		
	Max	98.0	74.0		

*Wound closure date per subject is the time of last wound closed per subject.
† P-value is based on the Log-rank rest of Kaplan-Meier survival analysis (ITT population).
‡ Hazard ratio is based on Cox regression model (ITT population).
Source: CSR MW 2004-11-02, module 5.3.5.1.3, Panel 11.2-3

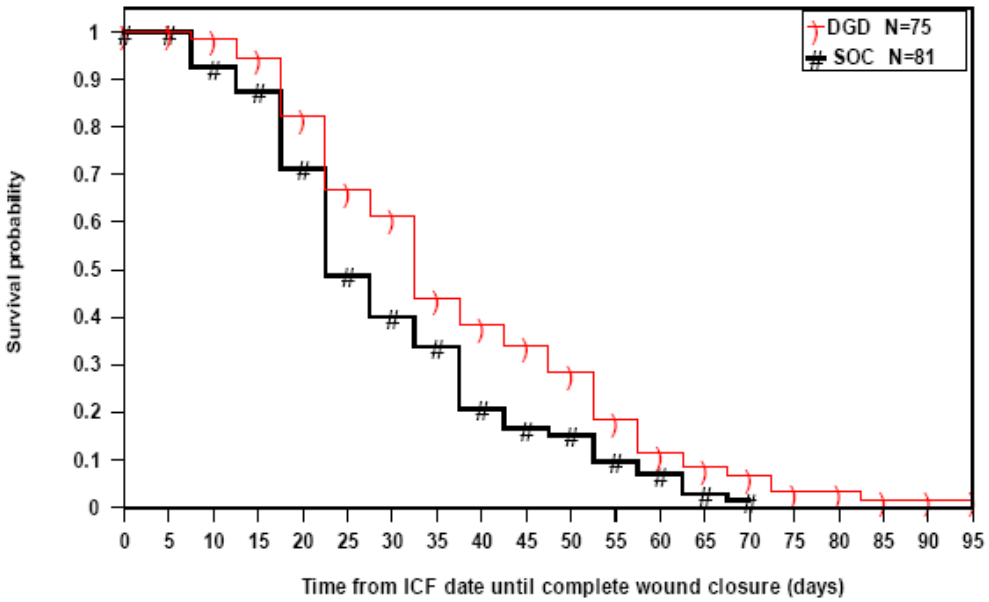


Figure 11.2-1 Kaplan-Meier Plot of Time to Complete Wound Closure from ICF Date (ITT Population, per Subject)

The hazard ratio (HR) based on Cox regression model and the Kaplan-Meier plot of time to complete wound closure per subject from ICF date (ITT population) show similar findings (HR=1.46; 95% CI: 1.05- 2.03; p=0.0185); the Kaplan-Meier plot is presented in Figure 11.2-1 above. The Kaplan- Meier curve shows that 100% of the SOC subjects and approximately 97% of the NexoBrid subjects achieved wound closure within 75 days; only 3% of the NexoBrid subjects had at least one wound which took longer to heal. Results were similar in the Evaluable A subset population.

Autografting is a surgical procedure which has a direct impact on the time to complete wound closure in NexoBrid debrided wounds.

Since a positive correlation was found between autografts performed and time to wound closure only in the NexoBrid group (Spearman Correlation Coefficients test), the results were adjusted as well as the interaction between the groups as per the SAP. In the NexoBrid group, less autograft procedures were performed vs. SOC.

When wound closure results were adjusted for % wound area autografted as well as the interaction between the groups, it was found that there was no significant difference in time to wound closure per subject from ICF between the NexoBrid and SOC groups (ITT population); HR based on Cox regression model was 0.925 (95% CI: 0.595-1.436; p=0.73 (Table 14.3-41). Per wound results from ICF date showed similar results.

Time to Complete Wound Closure (Per Wound)* from ICF Date (ITT Population, Per Wound)

		NEXOBRID (N=70)	SOC (N=78)	P-Value** Log-rank	Hazard Ratio *** 95% CI
Time to complete wound closure from ICF date (Days)	N	154	164		
	Mean ± SD	31.3 ± 16.9	27.4 ± 15.9	0.0738	1.21
	Median	28.5	22.0		(0.97, 1.52)
	Min	8.0	6.0		
	Max	98.0	74.0		

*Wound closure date per wound, all wounds that had closure data were included even if they belonged to subjects not included in the complete case population.
** P-value is based on the Log-rank rest of Kaplan-Meier survival analysis (ITT population).
*** Hazard ratio is based on Cox regression model (ITT population).
Source: CSR MW 2004-11-02,

The differences are larger (than seen in the mITT or ITT groups) when the subgroup of full thickness and mixed wounds are evaluated.

Table 125.5- Time to complete wound closure (Days) per wound (Full thickness and mixed wounds, MW2004-11-02)

ANALYSIS PER WOUND		NexoBrid (55 WOUNDS)	SOC (78 WOUNDS)	p-value
TIME TO COMPLETE WOUND CLOSURE FROM INJURY DATE (DAYS)	N (Wounds)	55	77	
	MEAN	40.6	32.4	0.076
	SD	17.2	17.8	
	MEDIAN	37.0	29.0	
	MIN	12.0	6.0	
	MAX	102.0	76.0	
TIME TO COMPLETE WOUND CLOSURE FROM ICF DATE (DAYS)	N (Wounds)	55	78	
	MEAN	39.1	30.5	0.0723
	SD	16.8	17.8	
	MEDIAN	35.0	27.5	
	MIN	12.0	6.0	
	MAX	98.0	74.0	

A post hoc analysis of time to wound closure from end of debridement from the pivotal study highlights the extent of the differences in time to wound closure between the study arms.

Whilst a useful sensitivity analysis, the Applicant has highlighted that for the wounds treated with non-surgical SOC debridement, the majority of the wound healing process may occur during debridement, thus giving a very low TTCWC once debridement is complete, as it takes only for few days for wound closure post-completion of debridement. Ultimately, it is considered that analyses of TTCWC from the start of debridement are equally clinically relevant to TTCWC from injury as they take into account the benefit of earlier eschar removal with NexoBrid and minimise the possible bias associated with the decision to start debridement.

Table 1- Time to complete wound closure from start of debridement date (ITT, MW2004-11-02)

	NexoBrid	SOC	P Value
N (Wounds)	154	164	
Mean	30.5	26.1	0.0404
SD	16.9	16.0	HR (CI 95%)
Median	28.0	21.5	1.25
Min	7.0	6.0	(1.0,1.56)
Max	97.0	74.0	

Table 4: Time to complete wound closure from start of debridement date (Non-MITT, Mixed wounds, MW2004-11-02)

	NexoBrid	SOC	P Value
N (Wounds)	44	59	
Mean	40.2	27.7	0.0015
SD	17.1	15.8	HR (CI 95%)
Median	40.5	23.0	1.85
Min	11.0	6.0	(1.24,2.76)
Max	97.0	64.0	

Table 2- Time to complete wound closure from start of debridement date (MITT, MW2004-11-02)

	NexoBrid	SOC	P Value
N (Wounds)	101	87	
Mean	26.6	23.7	0.1359
SD	15.4	13.6	HR (CI 95%)
Median	21.0	20.0	1.24
Min	7.0	6.0	(0.93,1.65)
Max	78.0	64.0	

The Applicant has noted that in subgroup comparisons where the wound closure modalities were similar, time to wound closure results did not significantly differ. These analyses provide some useful supportive information, though they are somewhat difficult to interpret since they are not based on fully randomised groups. Instead the comparisons are made as defined by wound closure modality, where the choice of modality may differ between NexoBrid treated patients and patients receiving SOC.

Table 5- Time to complete wound closure by wound depth- ITT, injury date

Wound Type	NexoBrid	SOC	Comments
All wounds	32.8 (154)	29.2 (164)	p= 0.1197
FT wounds	34.1 (7)	39.2 (14)	p= 0.2804
DPT wounds	29.0 (101)	26.9 (87)	p= 0.3563
DPT Non-autografted	26.1 (82)	25.9 (58)	p= 0.8552
DPT autografted	41.6 (19)	28.7 (29)	p= 0.0134
Mixed wounds	42.5 (44)	31.0 (59)	p= 0.0032
Mixed Non-autografted	30.4 (11)	31.4 (22)	p= 0.5039
Mixed autografted	44.5 (33)	28.1 (37)	p= 0.0007
Superficial wounds	9.0 (2)	17.8 (4)	-

Further analyses presented by the Applicant during the assessment demonstrated that there were significant delays in autografting NexoBrid debrided DPT and mixed wounds and that these delays were the principal cause of the delays in TTCWC in NexoBrid debrided autografted wounds.

Table 2- Time to 1st Autograft (TTAg) and use of multiple-stage grafting by wound depth (MW2004-11-02)

Wound type		NexoBrid	SOC	p-value
DPT autografted wounds (wounds)	TTAg from end of debridement (days)	15.0 (19)	1.7 (23[2])	0.0002
	Number of multiple-stage/autograft procedures	5	0	
Mixed autografted wounds (wounds)	TTAg from end of debridement (days)	13.4 (34)	2.2 (30[2])	<.0001
	Number of multiple-stage/autograft procedures	10	4	
FT autografted wounds (wounds)	TTAg from end of debridement (days)	4.6 (7)	3.3* (8[2])	NA
	Number of multiple-stage/autograft procedures	2	3	

* Without one SOC outlier patient

[2] For wounds which were treated with a combination of surgical and non-surgical eschar removal techniques, there were several wounds for which an autograft was performed on the surgically debrided area (the deep parts) while the rest of the wound area was continued to be debrided using non-surgical techniques. As these wounds (20 wounds) result in a negative time to autograft from end of debridement (as the debridement of the wound was completed after the autografting), the data is presented in Table 2 after omitting such wounds in order not to totally skew the data.

Similar TTCWC from end of autografting procedure data were noted for both arms. Therefore, the delays occurred before (or during) the autografting procedures. The relatively fast time to NexoBrid debridement therefore suggests that the delay in TTCWC results from delays in autografting wounds post-debridement.

Figure 1- TTCWC from end of Autograft procedure

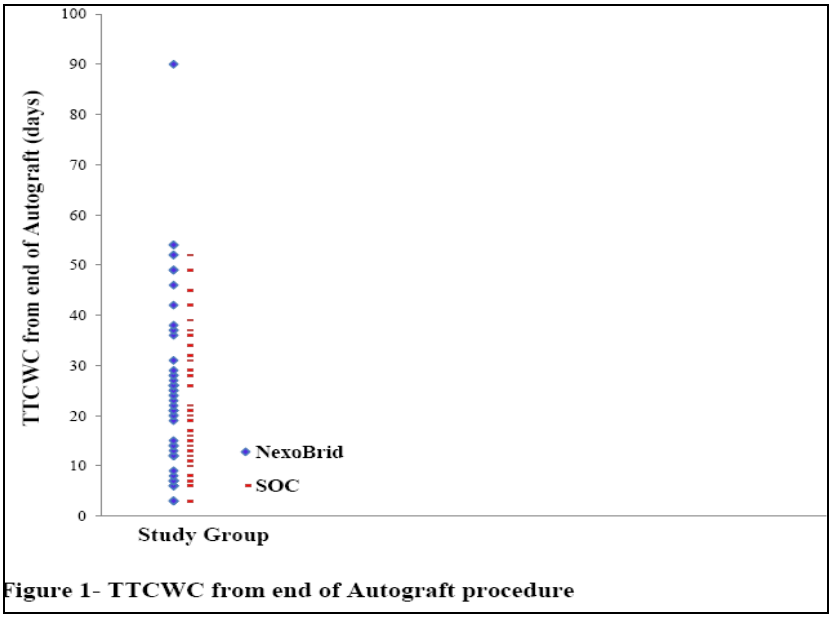


Figure 1- TTCWC from end of Autograft procedure

The analyses above are partially supported by those comparing TTCWC in NexoBrid and SOC debrided FT wounds, early (within 7 days on injury date) autografted wounds and non-autografted DPT wounds which showed only small, non-significant differences, suggesting that NexoBrid has a minimal or no effect on wound healing.

Timely eschar removal

Percent (number) of subjects in the ITT population with successful eschar removal (defined as ≥90% eschar removal per subject), was very similar in both study groups, 90.5% (67/74 subjects) and 90.1% (73/81 subjects) in the NexoBrid and SOC group, respectively (Panel 11.2-6), demonstrating that NexoBrid is as effective as SOC in eschar removal. Time to achieve successful eschar removal from ICF was significantly shorter in the NexoBrid group (mean 0.8 days) compared to the SOC group (mean 6.7 days; p<0.0001). The robustness of the effect was also demonstrated across age. In accordance with the SAP, no statistical tests were performed for subgroup analyses.

Second applications

12 wounds on 8 patients required a second application of NexoBrid. The patients usually completed the second application within 24 hours of the first. The percentage increase in eschar removal as a result of the second application, whilst sizeable in some patients, did not lead to avoidance of surgical excision or wound autografting, which were on the whole delayed (whether delayed or not by the 2nd application is uncertain) and required surgical treatment of a wider area than seen with SOC in the mITT and ITT populations. The Applicant however states that the majority of the excisions were to prepare the wounds for grafting and that successful eschar removal had already been achieved by the time of surgical excision in the majority. Time to wound closure was delayed even more compared to the delays already seen in the NexoBrid ITT population.

Blood Loss

Blood loss was measured by mean changes in haemoglobin and haematocrit from screening visit to 24 hours post-treatment. A statistically significant smaller reduction in mean haemoglobin values occurred in the NexoBrid group compared with the SOC group as indicated by mean haemoglobin and haematocrit reduction. Similar results were obtained in the Evaluable A population.

Blood Loss (ITT Population)

Change from screening to 24 hours post-treatment		**NEXOBRID (N=75)**	**SOC (N=81)**	**p-value**
Haemoglobin (mmol/L)	N	61	55	
Mean at screening		8.86	8.94	
Mean after 24 h		8.34	7.91	
Mean of change	Mean± SD	-0.52±0.96	-1.04±1.03	0.0061
	Median	-0.50	-1.00	
	Min	-3.30	-4.30	
	Max	1.70	0.68	
Haematocrit (L/L)	N	61	55	
Mean at screening		0.42	0.42	
Mean after 24 h		0.40	0.37	
Mean of change	Mean± SD	-0.03±0.06	-0.05±0.05	0.0374
	Median	-0.02	-0.03	
	Min	-0.20	-0.22	
	Max	0.10	0.05	

Source: CSR MW 2004-11-02

Ancillary analyses

Exploratory endpoints

Interstitial/Compartment Pressure

Elevated (above >25 mmHg threshold) interstitial/compartment pressure especially in extremities is considered an emergency. For diagnosis in this study direct measurement of the pressure was required. Results for interstitial/compartment pressure are based on a limited sample size, since the protocol required that this measurement be done only for circumferential extremity wounds; this occurred in a small proportion of the study subjects.

Interstitial/Compartment Pressure in Circumferential Extremity Wounds (ITT Population)

Interstitial/Compartment Pressure		**NEXOBRID (N=75) 163 wounds**	**SOC (N=81) 170 wounds**	**p-value**
Prior to debridement or escharotomy (mmHg)	N (wounds)	13	9	
	Mean± SD	17.8±11.1	16.2±12.6	0.7520
	Median	15.0	9.0	
	Min	5.0	6.0	
	Max	47.0	40.0	
Post debridement or escharotomy (mmHg)	N (wounds)	12	7	
	Mean± SD	12.5±6.2	10.9±4.4	0.5558
	Median	13.3	8.5	
	Min	3.0	7.0	
	Max	22.0	18.5	
Change (mmHg)	N (wounds)	12	7	
	Mean± SD	-5.7±12.8	-2.9±6.0	0.5975
	Median	-2.3	-0.8	
	Min	-44.0	-16.0	
	Max	5.0	1.0	

Source: CSR MW 2004-11-02

A post-hoc analysis of hand wounds treated with NexoBrid and SOC demonstrated that only 4/31 (12.9%) hand wounds required excision in the NexoBrid as compared to 29/41 (70.7%) in the SOC (ITT population). The number of DPT hand wounds autografted in the NexoBrid was only 1/24 (4.2%) vs. the SOC 10/20 (50%). The area autografted in the NexoBrid was 2.1% as compared to 30.5% in the SOC. None of the NexoBrid treated hands required escharotomy as compared to 4/41 (9.7%) in the SOC.

Time to Hospital Discharge

Time to Hospital Discharge (ITT Population)

		NEXOBRID (N=75)	**SOC (N=81)**	**P-value**
Time to hospital discharge from ICF date (Days)	N	72	81	
	Mean± SD	20.9±14.3	17.9±13.2	0.1775
	Median	16.0	15.0	
	Min	2.0	3.0	
	Max	62.0	75.0	

Source: CSR MW 2004-11-02

Among the ITT population, mean time to hospital discharge from ICF date was 20.9 days in the NEXOBRID group, compared with 17.9 days in the SOC group, with no statistical difference between groups.

Among adult subjects (>18 years) mean time to hospital discharge was longer in the NEXOBRID group (mean 23.0 days from injury, range 2-62 days) compared with the SOC group (mean 17.2 days from ICF, range 3-75 days).

Conversely, among children (≤18 years), the NEXOBRID group had much shorter time to hospital discharge (mean 12.2 days from ICF Date, range 4-22) vs. the SOC group (mean 21.0 days, range 4-54).

In the ITT population of the pivotal study MW2004-11-02, mean time to hospital discharge from injury date was 22.5 days in the NexoBrid group, compared with 20.2 days in the surgical SOC group and 18.9 days in the NSD SOC group (dominated by more superficial wounds), with no statistical difference between groups (Table 16).

The results per the sub-groups of autografted and non-autografted wounds revealed similar time to HD in the non autografted wounds that were allowed to epithelialise spontaneously. Time to HD from injury was comparable in the NexoBrid group (16.3 days) vs. the SOC group (16.8 days). In autografted wounds, time to HD from injury was longer in NexoBrid (28.6 days) vs. (21.6 days) in surgical SOC due to autografting at a later stage, further illustrated by the time to HD of the NSD wounds (38.0 days).

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial: Enzymatic Debridement in Burns Patients (Children & Adults): A Comparison to Standard of Care (MW2004-11-02)

Title: Enzymatic Debridement in Burns Patients (Children & Adults): A Comparison to Standard of Care		
Study identifier	MW2004-11-02	
Design	This was a multi-center, open label, randomized, two-arm study aimed at evaluating the clinical benefit of enzymatic debridement in thermal burn patients. Adults and children, hospitalized in burn units, with deep partial thickness and/or full thickness burns ranging from 5%-30% TBSA and who met the entrance criteria were enrolled and randomized to receive NexoBrid or the Standard of Care (SOC) treatment.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Average duration was 4 months including a 3 months follow-up. Not applicable Not applicable
Hypothesis	Superiority of NexoBrid over SOC	
Treatments groups	NexoBrid	4 hour treatment. 75 randomized patients and additional of 26 training patients (first patient at each site was treated with NexoBrid as part of the training protocol and were included as part of the safety population)

	Standard of Care		Included surgical or non surgical standard of care treatments. Treatment duration was few hours to several weeks and included 81 randomized patients.
Endpoints and definitions	Co-Primary	% area wound excised	The % treated wound excised (by tangential/minor/Versajet excision) or dermabraded, in first surgery. Wounds which are entirely full thickness or have full thickness areas are excluded from this analysis.
	Co-Primary	% area wound autografted	The % treated wound autografted of deep partial wounds where the potential tissue-sparing effect may be seen. Wounds which are entirely full thickness or have full thickness areas are excluded from this analysis.
	Secondary	% area wound excised	The % treated wound excised (by tangential/minor/Versajet excision) or dermabraded, in first surgery (as described above), for all wounds.
	Secondary	Time to complete wound closure	Time to complete wound closure from ICF date
	Secondary	Time to achieve successful eschar removal	Timely eschar removal (debridement) from ICF date
Database lock	16 February 2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Co-Primary: Modified Intent to Treat (MITT)[10] Co-Primary analysis was per wound. The analysis was performed on the Debridement and wound management phase.		
Descriptive statistics and estimate variability	Treatment group	NexoBrid	SOC
	Number of wounds	106	88
	Co-Primary- % area wound excised (ANOVA)	5.5%	52.0%
	STD	14.6%	44.5%
	Co-Primary- % area wound autografted (ANOVA)	8.4%	21.5%
	STD	21.3%	34.8%
Analysis population and time point description	Secondary: Intent to Treat Analysis was per wound. The analysis was performed on the Debridement and wound management phase.		
Descriptive	Number of wounds	163	170

[10] Modified Intention-to-Treat (MITT) population consists of all randomized subjects with at least one wound that was entirely DPT, as evaluated in the pre-debridement assessment.

statistics and estimate variability	Secondary- % area wound excised (ANOVA)	13.1%	56.7%
	STD	26.9%	43.3%
Analysis population and time point description	Secondary: Complete Case Analysis was per patient. The analysis was performed on the wound management phase, during follow-up.		
Descriptive statistics and estimate variability	Number of subjects	70	78
	Secondary- Time to complete wound closure from Inform Consent Form (ICF) (Log-rank test of Kaplan-Meier survival analysis)	36.2 days	28.8 days
	STD	18.5 days	15.6 days
Analysis population and time point description	Secondary: Intent to Treat Analysis was per patient. The analysis was performed on the Debridement phase.		
Descriptive statistics and estimate variability	Number of subjects	67	73
	Secondary- Time to achieve successful eschar removal from ICF (Log-rank test of Kaplan-Meier survival analysis)	0.8 days	6.7 days
	STD	0.8 days	5.8 days

Effect estimate per comparison	Co-Primary- % area wound excised (MITT, Per wound)	Comparison groups	NexoBrid (106) vs. SOC (88)
		Effect	46.5%
		Weighted SD	28.2%
		P-value	<0.0001
	Co-Primary- % area wound autografted (MITT, Per wound)	Comparison groups	NexoBrid (106) vs. SOC (88)
		Effect	13.1%
		Weighted STD	27.4%
		P-value	0.0054
	Secondary- % area wound excised (ITT, Per wound)	Comparison groups	NexoBrid (163) vs. SOC (170)
		Effect	43.6%
		Weighted STD	35.3%
		P-value	<0.0001
	Secondary- Time to complete wound closure from ICF date (CC, Per patient)	Comparison groups	NexoBrid (70) vs. SOC (78)
		Effect	(-) 7.4 days
		Weighted STD	17.0 days
		P-value	0.0185
		HR (95% CI)	1.46 (1.05, 2.03)
	Secondary- Time to achieve successful eschar removal from ICF date (ITT, Per patient)	Comparison groups	NexoBrid (67) vs. SOC (73)
		Effect	5.9 days
		Weighted STD	3.4 days
		P-value	<0.0001
		HR (95% CI)	0.25 (0.16, 0.40)

Analysis description	An interim analysis was planned when the study reached 152 randomized completed subjects. An early stopping rule was used to terminate accrual to the trial at an interim point in the event that (1) the results would appear to be very promising or (2) indicate a futility result. Otherwise the study would be continued. As stopping rule number (1) was achieved, study recruitment stopped on October 15, 2009.

Analysis performed across trials (pooled analyses and meta-analysis)

The CHMP during the assessment requested re-assurance regarding the quality of debridement, which was also particularly raised by the ad-hoc expert group. To substantiate the quality of debridement with clinical data, analyses were conduchted investigating the success rate of grafting since grafts will take only on completely clean wound bed. Data from studies MW2004-11-02 and MW2002-04-01 were used for these analyses.

Skin grafting

A comparison of baseline demographic and wound-related characteristics in wounds autografted shortly after debridement (1-2 days post debridement) (studies MW2004-11-02 and MW2002-04-01) is presented in Table 4 below.

Table 4: A comparison of baseline demographic and wound-related characteristics in wounds autografted shortly after debridement

		NexoBrid	SOC
Number of wounds (# of patients)		19 (16)	75 (47)
Mean % of Graft take		91.3 ±14.8%	94.9 ± 7.6%
% wound area autografted		82 ± 32%	77 ± 30%
Age (years)		42.0 ± 10.5	29.8 ± 15.9
Gender - Female /Male		4 (25%)/12 (75%)	6 (12.5%)/42 (87.5%)
Mean TBSA of TW		6.1 ± 3.7%	6.0 ± 3.2%
Wounds Depth	DPT- number of wounds (%)	9 (47.4%)	25 (33.3%)
	Mixed- number of wounds (%)	6 (31.6%)	37 (49.3%)
	FT- number of wounds (%)	4 (21.1%)	13 (17.3%)
Anatomical Areas	Arms & hands	6 (31.6%)	29 (38.7%)
	Trunk	2 (10.5%)	9 (12%)
	Legs, Thighs and feet	7 (36.8%)	28 (37.3%)
	Neck	0 (0.0%)	1 (1.3%)
	Buttock	0 (0.0%)	2 (2.7%)
	Mixed locations	4 (21.0%)	6 (8.0%)

A graft take success rate of 91.3% was recorded in 16 patients participating in studies MW2002-04-01 and MW2004-11-02, having 19 wounds that were debrided with NexoBrid and autografted shortly after use of NexoBrid (e.g. Day 1 and Day 2).

Other types of grafts

Biological temporary primary coverage (e.g. Allograft, Xenograft) and synthetic dressings (e.g. SuprathelTM) will take only, as autograft, on completely clean bed. In the pivotal (MW2004-11-02) and Phase II (MW2002-04-01) studies, unsuccessful "graft take" resulting in lack of adherence would have been more commonly termed as wound re-opening or decomposition in temporary primary coverage.

As presented in Table 5 below, 74 wounds in NexoBrid and 27 wounds in SOC have been covered with such dressings shortly after debridement in the pivotal (MW2004-11-02) and Phase II (MW2002-04-01) studies. None of the wounds in both arms reported any wound re-opening or decomposition following coverage with temporary primary coverage, during the period of 7 days post complete debridement (as for assessments of autografts which are being performed 2-7 days after application).

Table 5: Success rate of other type of grafts

		NexoBrid			SOC		
		wounds		Reported wound re-opening/ decomposition, graft failure/complication*	wounds		Reported wound re-opening/ decomposition*
		N= 74	%		N= 27	%	
MW2004-11-02	Xenograft	17	23	None	4	14.8	None
	Allograft	3	4	None	3	11.1	None
	Suprathel	49	66.3	None	20	74.1	None
MW2002-04-01 **	Xenograft	3	4	None	-	-	-
	Allograft	2	2.7	None	-	-	-
	Suprathel				-	-	-

* Graft loss is reported in temporary primary covers as wound re-opening/decomposition/graft failure/complication

** One target wound per patient

In addition, in the retrospective data collection study 35-98-910, graft take was recorded as incidence in a range rather than as a single value. For the purpose of this analysis, the mid value of the range was taken. The success rate of graft take in 35 wounds grafted shortly after enzymatic debridement was 95%.

Clinical studies in special populations

Special studies in children, the elderly and in patients with renal and hepatic impairment were not performed.

Supportive studies

MW 2002-04-01: Enzymatic Debridement in Burn Subjects: A Comparison to Standard of Care

This was a Phase II, randomised, multi-centre, parallel, observer-blind, three-arm, prospective study to evaluate the safety and efficacy of NexoBrid in comparison with its vehicle and standard of care (SOC) in subjects with thermal burns hospitalised in burn units. Another objective of the study was the evaluation of possible deleterious effects of the vehicle on wound healing. The study was conducted at a total of 18 centres located in the following countries: 1 centre in Czech Republic, 2 centres in France, 1 centre in Germany, 4 centres in India, 1 centre in Italy, 2 centres in Slovak Republic, 2 centres in the UK, 5 centres in the US.

Main Inclusion Criteria

- male and female subjects of 18-70 years of age

- DPT and/or FT burns, ranging from 2%-15% total body surface area (TBSA) per wound treated but not more than 30% TBSA burns in total. The wound with the largest continuous area of DPT and/or FT burns was selected as the TW to be treated with NexoBrid or SOC. NexoBrid was only placed on TWs. All other wounds of the same subject were treated with SOC.

Main Exclusion Criteria

- other cutaneous trauma
- previous burn at the same treatment site
- study treatment of facial burns
- study treatment of hand burns and other burn sites potentially complicated by compartment syndrome
- wounds that cannot be excised
- pregnancy and nursing mothers
- poorly controlled diabetes mellitus
- evidence of significant haematological, cardiovascular, liver or neoplastic disease; (13) other immediately life-threatening conditions (e.g. severe inhalation injury, immunocompromised, or pre-existing oxygen-dependent pulmonary diseases)
- chronic steroid intake
- heavily contaminated burns
- burn wounds >30% TBSA.

<u>Methods</u>

Subjects were stratified into 3 groups based on the %TBSA of the DPT (mixed deep dermal) and/or full thickness burns of the TW: (Group A: ≥2% to ≤6% TBSA; Group B: >6% to ≤10% TBSA; and Group C: >10% to ≤15% TBSA.). Subjects were then randomized at a ratio of 2:1:1 to receive NexoBrid, Vehicle or SOC, respectively. Since NexoBrid and the vehicle were not similar in appearance, the individual who applied and removed the NexoBrid and Vehicle gels was different from the person who did the safety/efficacy assessments to maintain observer blinding.

Prior to each treatment and after each important wound treatment procedural step, photographs of the TWs were taken in the three treatment groups. The wound was characterized by assessing the location, %TBSA, degree of burn's depth, % of dry eschar and condition of the wound.

DEBRASE debridement: After wound cleaning, freshly mixed NexoBridGel Dressing (NexoBrid powder was mixed 1:10 in Gel Vehicle and was applied in a dose of 0.02 g NexoBrid for cm2 of skin) was then administered topically to the TW at a thickness of between 1.5 and 3 mm. Likewise, Gel Vehicle (0.2 g gel for cm2 of skin) was administered to the TW of subjects randomized to the Vehicle group at a thickness of between 1.5-3 millimetres. Both treatments were then left in place for 4 hours under occlusive dressing. After four hours of NexoBrid or Vehicle treatment, the occlusive dressing was removed. The amount of eschar removed was visually estimated by the investigator and recorded as percentage of the intended treatment area of the wound. Following failure of the Vehicle treatment the

subjects were debrided by SOC methods. One repeat treatment with NexoBrid could be applied but no more than two debridement procedures were permitted.

SOC treatment included two modalities: surgical and non-surgical procedures. Surgical procedures that included tangential excision, minor excision, or excision/avulsion to fascia. Non-surgical methods included application of covers and/or topical medications to induce maceration or autolysis of eschar.

Blood transfusions, if required, were documented. After surgical or non-surgical debridement the wound was visually assessed for debridement efficacy. Subjects in the NexoBrid group were therefore treated by a combination of NexoBrid as well as SOC.

Following debridement, wound management was in accordance with the centre's normal practice and included: autografts, allografts, skin substitutes, xenografts, synthetic dressings, or medications.

Following debridement, weekly follow-up assessments were performed and continued following hospital discharge until complete wound closure of all treated wounds. Subsequently, monthly follow-up visits were conducted for three months after complete wound closure for all wounds during which maintenance of wound closure, scarring and functional disability were assessed.

Efficacy Variables

The primary efficacy variable was:

- The time to complete wound closure following debridement (spontaneous healing or graft take).

The secondary efficacy variables were:

- Time to >95% wound closure (epithelialisation),
- % of the burn wound that was excised,
- % TBSA that was grafted (any grafts: autograft, allograft & xenograft).

Additional measurements were

- % eschar removed from the TW by debridement,
- Time to start of debridement from time of injury,
- Time to complete debridement,
- Number of debridement procedures,
- Blood loss (as measured by blood transfused),
- Pain during and after debridement procedures (using a numerical pain-scale ruler)
- Concomitant medication (narcotics, anesthetics).

Analysis of the primary efficacy variable was based on the Intention-to-treat (ITT) population (all randomised subjects), the Complete Case (CC) population (all randomized subjects and treated subjects with complete wound closure), and the Per Protocol (PP) population, which consisted of all subjects in the CC population without major protocol violations.

Objective

The objective of the study was to explore whether NexoBrid impairs wound healing vs. SOC treatment as measured by time to complete wound closure (non-inferiority), and whether the gel vehicle had any deleterious effect on wound healing.

Statistical Analysis Plan

Data were initially analyzed using one-way ANOVA to compare differences among the three treatment groups and between pairs of treatment groups, i.e. NexoBrid vs. SOC, and NexoBrid vs. Vehicle. An exploratory non-inferiority analysis was performed for the primary efficacy endpoint. A two-sided 95% confidence interval (CI) was calculated to determine whether the time to complete wound closure following debridement with NexoBrid was within 25% of the time to complete wound closure with SOC or Vehicle. If the lower bound of the CI of the difference between NexoBrid and SOC fell above -25% of the time to complete wound closure in the SOC group, NexoBrid was to be declared no worse than SOC. Similarly, if the lower bound of the CI of the difference between NexoBrid and Vehicle fell above -25% of the time to complete wound closure in the Vehicle group, NexoBrid was to be declared no worse than Vehicle. For analysis of the secondary variables, differences among the three treatment groups and between pairs of treatment groups were assessed using one-way ANOVA.

Results

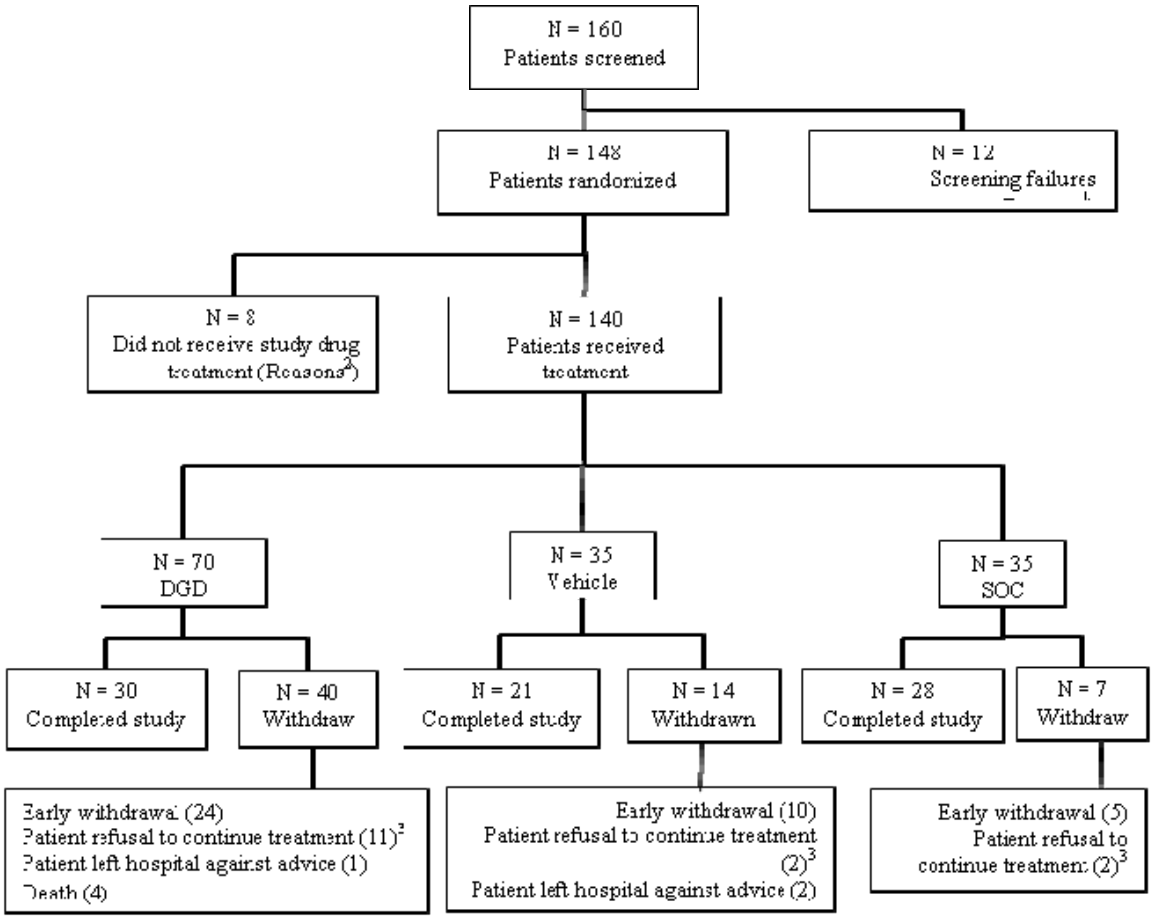
Study Subjects

A total of 160 subjects were screened, 148 of whom were randomised (ITT population); of the 148 subjects, 140 subjects received treatment. These subjects were randomized in a 2:1:1 ratio to NEXOBRID (n=70), Vehicle (n=35), and SOC (n=35).

- Of the 140 randomised subjects that received study treatment, 79 subjects completed the study including all follow-up visits (NEXOBRID, n=30; Vehicle, n=21; SOC, n=28). Of the 61 subjects who withdrew from the study, 38 reached wound closure and were included in the CC data set (117 in total). Of the 23 subjects excluded from the CC data set, 22 had no wound closure data (early withdrawal 4, missed visits 3, incomplete wound closure 5, death 4, lost to follow-up 6, and one subject withdrew early from study treatment).

Complete Case (CC) Population: all randomized and treated subjects with complete wound closure. Complete wound closure was defined as 100% epithelialisation achieved at a weekly visit or > 95% epithelialisation achieved at weekly visit and confirmed at a monthly visit.

Subjects Disposition Flow Chart



[1]Reasons for screening failures
Non-compliance with entrance criteria (6)
Withdrawal of consent (2)
Investigator judgment – patient not suitable (1)
No randomization due to computer failure (1)
Unknown (2)

[2]Reasons for non-receipt of study treatment (after randomization)
Non-compliance with entrance criteria (3 DGD, 1 Vehicle)
Withdrawal of consent (2 SOC)
Withdrawal due to AE (1 SOC)
MW halted study enrollment (1 Vehicle)

[3]Only two patients (12C002, DGD; 23A059, SOC) withdrew from study treatment as described in the text above. The remaining 13 patients were either lost to follow-up or unable / unwilling to attend clinic follow-up visits.

Baseline Demographics

Table 25. Demographic Data (ITT Population)

Parameter		NexoBrid (N=73)	Vehicle (N=37)	SOC (N=38)
Age (year) at signed informed consent	**N**	**73**	**36**	**38**
	Mean	35.4	36.6	37.3
	SD	14.3	10.9	12.9
	Median	33.0	36.5	37.0
	Range	18-69	18-63	18-63
	p-Value	Among Group: 0. 745 NexoBrid vs. Vehicle: 0. 666 NexoBrid vs. SOC: 0.481		
Gender	**N**	**73**	**36**	**38**
	Male	54 (74.0%)	25 (69.4%)	28 (73.7%)
	Female	19 (26.0%)	11 (30.6%)	10 (26.3%)
		Among Group: 0. 886 NexoBrid vs. Vehicle: 0. 653 NexoBrid vs. SOC: 1.000		
Race	**N**	**73**	**36**	**38**
	Caucasian	40 (54.8%)	18 (50.0%)	22 (57.9%)
	Middle Eastern	1 (1.4%)	0 (0.0%)	0 (0.0%)
	Black	8 (11.0%)	5 (13.9%)	0 (0.0%)
	Asian	23 (31.5%)	13 (36.1%)	15 (39.5%)
	Other	1 (1.4%)	0 (0.0%)	1 (2.6%)
	p-Value	Among Group: 0. 294 NexoBrid vs. Vehicle: 0.912 NexoBrid vs. SOC: 0.155		
Weight (kg) at screening	**N**	**73**	**36**	**38**
	Mean	69.1	73.1	71.0
	SD	17.0	20.5	21.0
	Median	70.0	70.0	67.2
	Range	28-104	42-127	42-140
	p-Value	Among Group: 0. 570 NexoBrid vs. Vehicle: 0.278 NexoBrid vs. SOC: 0.599		

P-values for age and weight are from one-way ANOVA. P-values for gender and race are from Fisher's Exact test.
Source: CSR MW 2002-04-01

Table 26. .Pre-Treatment Burn Description (ITT Population)

Parameter		NexoBrid (N=73)	Vehicle (N=37)	SOC (N=38)
Burn Depth	**N**	**71**	**35**	**35**
	Second degree	1 (1.4%)	0 (0.0%)	0 (0.0%)
	Mixed deep dermal	23 (32.4%)	9 (25.7%)	5. (14.3%)
	Third degree	6 (8.5%)	3 (8.6%)	2 (5.7%)
	Second degree/mixed deep dermal	24 (33.8%)	10 (28.6%)	14 (40.0%)
	Second degree/third degree	1 (1.4%)	1 (2.9%)	0 (0.0%)
	Mixed deep dermal/third degree	11 (15.5%)	10 (28.6%)	8 (22.9%)
	Second degree/mixed deep dermal/third degree	4 (5.6)	2 (5.7%)	4 (11.4%)
	First degree/second degree/mixed deep dermal/third degree	1 (1.4%)	0 (0.0%)	2 (5.7%)
	p-Value	Among Group: 0. 590 NexoBrid vs. Vehicle: 0.800 NexoBrid vs. SOC: 0.363		
TW Total Burned Surface Area (%TBSA)	**N**	**71**	**35**	**35**
	Mean	6.4	6.3	6.7
	SD	3.4	3.3	3.3
	Median	5.0	6.0	6.0
	Range	2-16	2-15	3-14
	p-Value	Among Group: 0. 885 NexoBrid vs. Vehicle: 0. 922 NexoBrid vs. SOC: 0.674		
Distribution	**N**	**71**	**35**	**35**
	< 2%	0 (0.0%)	0 (0.0%)	0 (0.0%)
	≥ 2% to ≤ 6%	41 (57.7%)	19 (54.3%)	20 (57.1%)
	> 6% to ≤ 10%	18 (25.4%)	13 (37.1%)	11 (31.4%)
	>10% to ≤ 15%	11 (15.5%)	3 (8.6%)	4 (11.4%)
	> 15%	1 (1.4%)	0 (0.0%)	0 (0.0%)
	p-Value	Among Group: 0. 794 NexoBrid vs. Vehicle: 0.474 NexoBrid vs. SOC: 0.781		
%TBSA of Mixed Deep Dermal/Third Degree TW	**N**	**71**	**35**	**35**
	Mean	4.8	5.3	5.2
	SD	2.7	3.1	3.0
	Median	4.0	5.0	4.0
	Range	0-14	2-15	3-14
	p-Value	Among Group: 0. 720 NexoBrid vs. Vehicle: 0.457 NexoBrid vs. SOC: 0.563		
Distribution	**N**	**71**	**35**	**35**
	< 2%	1 (1.4%)	0 (0.0%)	0 (0.0%)
	≥ 2% to ≤ 6%	52 (73.2%)	25 (71.4%)	26 (74.3%)
	> 6% to ≤ 10%	14 (19.7%)	8 (22.9%)	6 (17.1%)
	>10% to ≤ 15%	4 (5.6%)	2 (5.7%)	3 (8.6%)
	> 15%	0 (0.0%)	0 (0.0%)	0 (0.0%)
	p-Value	Among Group: 0. 949 NexoBrid vs. Vehicle: 0.893 NexoBrid vs. SOC: 0.829		

P-values are from one-way ANOVA.
Source: CSR MW 2002-04-01

There were no statistically significant differences in total burn surface area among the three treatment groups (TWs and non-TWs) for the ITT population (p=0.246). The mean total burn surface area ranged

from 12.8 to 15.5% of TBSA. However, there was a statistically significant difference in the severity of non-TWs among the three treatment groups for the ITT population (p=0.005). Both the NEXOBRID and Vehicle groups had significantly more subjects (67.1% and 73.0%, respectively) with mixed deep dermal (MDD) and/or 3rd degree burns than the SOC treatment group (39.5%).

Efficacy Results

Primary efficacy variable: Time to complete wound closure following debridement (spontaneous healing or graft take)

Table 27. Time to Complete Wound Closure from Injury (CC and PP Populations)

Parameter		**NexoBrid**	**Vehicle**	**SOC**
CC Population				
Time to complete wound closure from injury (days)	**N**	**57**	**27**	**33**
	Mean	34.7	37.0	32.4
	SD	17.8	22.6	21.4
	Median	32.0	31.0	29.0
	Range	9-90	14-106	9-114
	p-Value	Among Group: 0.675 NexoBrid vs. Vehicle: 0.604 NexoBrid vs. SOC: 0.595		
	95% CI of Mean	29.9-39.4	28.1-46.0	24.9-40.0
	(Two-Tailed) Lower Bound		-5.4*	-9.5**
PP Population				
Time to complete wound closure from injury (days)	**N**	**52**	**26**	**31**
	Mean	34.8	37.6	31.7
	SD	18.6	22.9	21.1
	Median	30.0	32.0	29.0
	Range	9-90	14-106	9-114
	p-Value	Among Group: 0.556 NexoBrid vs. Vehicle: 0.565 NexoBrid vs. SOC: 0.490		
	95% CI of Mean	29.6-40.0	28.3-46.8	24.0-39.5
	(Two-Tailed) Lower Bound		-5.3*	-10.8**

P-values are from one-way ANOVA.
* Lower bound of one-tailed 95% CI of the mean difference between Vehicle and NexoBrid.
** Lower bound of one-tailed 95% CI of the mean difference between SOC and NexoBrid.
Source: CSR MW 2002-04-01

Study results demonstrated non-inferiority in wound closure time between NexoBrid treatment and the SOC treatment.

The primary efficacy variable was also analysed by pre-specified stratification levels of %TBSA for the following subgroups: 2%-6%, >6%-10%, and >10%-15% of TBSA, and by skin grafting, i.e. TW autografted vs. TW not autografted.

Table 28. Time to Complete Wound Closure from Injury by Wound Size (CC Population)

Parameter	%TBSA Mixed/3rd Degree		NexoBrid	Vehicle	SOC
CC Population		**N**	**57**	**27**	**33**
Time to complete wound closure from injury (days)	≥2% to ≤6%	n	43	21	24
		Mean	34.2	35.6	26.3
		SD	18.3	23.2	13.9
		Median	32.0	31.0	23.0
		Range	9-90	14-106	9-59
		p-Value	Among Group: 0.172 NexoBrid vs. Vehicle: 0.785 NexoBrid vs. SOC: 0.073		
	>6% to ≤10%	n	12	5	6
		Mean	37.0	40.8	47.2
		SD	18.1	23.9	34.9
		Median	31.0	35.0	34.0
		Range	19-76	21-81	18-114
		p-Value	Among Group: 0.712 NexoBrid vs. Vehicle: 0.723 NexoBrid vs. SOC: 0.421		
	>10% to ≤15%	n	2	1	3
		Mean	31.5	48.0	51.7
		SD	12.0	0.0	19.7
		Median	31.5	48.0	61.0
		Range	23-40	48-48	29-65
		p-Value	Among Group: 0.520 NexoBrid vs. Vehicle: 0.464 NexoBrid vs. SOC: 0.297		

P-values are from one-way ANOVA.
Source: CSR MW 2002-04-01

Table 29. Time to Complete Wound Closure from Injury by Autograft (CC Population)

Parameter			NexoBrid	Vehicle	SOC
CC Population		**N**	**57**	**27**	**33**
Time to complete wound closure from injury (days)	Autografted	n	39	16	21
		Mean	38.5	39.6	38.0
		SD	18.6	25.0	22.7
		Median	34.0	34.0	33.0
		Range	13-90	14-106	16-114
		p-Value	Among Group: 0.975 NexoBrid vs. Vehicle: 0.861 NexoBrid vs. SOC: 0.929		
	Not autografted	n	18	11	12
		Mean	26.4	33.4	22.7
		SD	13.0	19.2	15.1
		Median	21.5	25.0	16.5
		Range	9-58	16-81	9-56
		p-Value	Among Group: 0.256 NexoBrid vs. Vehicle: 0.253 NexoBrid vs. SOC: 0.478		

P-values are from one-way ANOVA
Source: CSR MW 2002-04-01

There was no statistically significant difference in time to complete wound closure from injury in both the CC and PP populations among the three treatment groups for autografted wounds (p=0.975 and 0.895, respectively) or for wounds which were allowed to heal spontaneously (not autografted; p=0.256 and 0.237, respectively)

Secondary Efficacy Variables

Time to >95% wound closure (epithelialisation)

Both the CC and PP populations showed no statistically significant differences between treatment groups in time to >95% wound closure from injury among all wound sizes in MDD and/or third degree burns. Results for time to >95% wound closure from injury were also similar for autografted wounds in both the CC and PP populations (p=0.707 and 0.567, respectively) and in not autografted wounds which healed spontaneously (p=0.101 and 0.104 for the CC and PP populations, respectively).

Percent of the burn wound that was excised

For all three treatment groups, the percentage of the burn wound requiring excision was assessed in the ITT and PP populations. First surgery for each treatment was defined in the NexoBrid treatment group as an additional procedure after enzymatic debridement process; in the Vehicle group as an additional procedure after Vehicle application; and in the SOC group as primary removal of eschar or an additional procedure after non-surgical debridement. The % wound area excised was the % eschar removed vs. the intended wound treatment area (TW) when the type of surgery was specified as tangential excision or minor excision.

Table 33. Extent of Surgery: Subjects that Required Surgery (ITT Population)

Parameter		**NexoBrid (N=73)**	**Vehicle (N=37)**	**SOC (N=38)**
ITT Population				
Need for surgery	**N**	**70**	**35**	**35**
	Yes	50 (71.4%)	21 (60.0%)	24 (68.6%)
	No	20 (28.6%)	14 (40.0%)	11 (31.4%)
	p-Value	Among Group: 0.512 NexoBrid vs. Vehicle: 0.273 NexoBrid vs. SOC: 0.822		
Tangential excision (in first surgery)	**N**	**70**	**35**	**35**
	Yes	14 (20.0%)	8 (22.9%)	13 (37.1%)
	No	56 (80.0%)	27 (77.1%)	22 (62.9%)
	p-Value	Among Group: 0.165 NexoBrid vs. Vehicle: 0.801 NexoBrid vs. SOC: 0.096		
Minor excision (in first surgery)	**N**	**70**	**35**	**35**
	Yes	8 (11.4%)	1 (2.9%)	1 (2.9%)
	No	62 (88.6%)	34 (97.1%)	34 (97.1%)
	p-Value	Among Group: 0.252 NexoBrid vs. Vehicle: 0.266 NexoBrid vs. SOC: 0.266		

Parameter		NexoBrid (N=73)	Vehicle (N=37)	SOC (N=38)
% Wound Area Excised				
First Surgery	**N**	**49**	**21**	**24**
	Mean	22.9	73.2	50.5
	SD	34.2	39.6	47.4
	Median	5.0	100	60.0
	Range	0-100	0-100	0-100
	p-Value	Among Group: <0.001 NexoBrid vs. Vehicle: <0.001 NexoBrid vs. SOC: <0.006		

P-values are from one-way ANOVA.
Source: CSR MW 2002-04-01

Similar results were observed in the PP population.

Percent of TBSA of the wound that was grafted

In this study, skin grafting included autografts, flaps, homografts, xenografts or skin substitutes.

The area of wound grafted was higher in the Nexobrid arm compared to SOC (mean 80.4 vs 69.9) however the difference did not reach statistical significance. Similar results were also observed in the PP population. With regard to percentage of graft take, there were no significant differences amongst the groups in the outcome of operations in subjects following first, second or third surgery (ITT population; p=0.182, 0.657, and 0.583, respectively). Similar results were also observed in the PP population. Similar numbers of wounds administered NexoBrid and SOC received grafts or skin substitutes.

Additional Measurements

- Percentage eschar removed vs. intended wound area
- Time to start debridement from time of injury
- Time to complete debridement

There was no statistically significant difference in the percentage of eschar removed from the intended wound treatment area between the NexoBrid and SOC treatment groups (88.5% vs. 92.7%, p=0.261). The Vehicle removed only 2.8% of eschar (NexoBrid vs. Vehicle, p<0.001). There was a statistically significant difference between the NexoBrid and the SOC treatment group in the time to start of debridement procedure (mean days 1.6 vs. 3.4, p<0.001). Moreover, the NexoBrid treatment group also demonstrated significantly less time (1.6 days) to completion of the initial debridement procedure compared to the SOC (14.3 days, p<0.001).

In the ITT population, 14.3% of subjects in the NexoBrid treatment group required repeat debridement. The Vehicle did not demonstrate debriding activity (2.8%) and was re-applied for only one subject; all subjects in the Vehicle group required further SOC treatment to achieve debridement (surgical and/or non-surgical).

Blood loss (as measured by blood transfused)

There was no statistically significant difference in the number of subjects who had blood transfusions during their initial hospital stay or at readmission to the hospital among the three treatment groups;

28.8% in the NexoBrid, 29.4% in the Vehicle and 23.5% in the SOC treatment groups (p=0.877). The recorded amounts of blood transfused were similar for all three study groups.

MW 2005-10-05: Safety Study on Enzymatic Debridement in Burn Subjects: A Comparison between NexoBrid Gel Dressing (NEXOBRID), NEXOBRID Vehicle and Standard of Care

This was a Phase II, randomised, open-label, three-arm, single-centre study primarily designed to evaluate the safety of enzymatic debridement by NexoBrid in comparison with Vehicle and SOC in subjects with DPT and/or full thickness thermal burns.

Objective

The main objective was to establish that NexoBrid is safe in the treatment of burn wounds following corrective actions aimed to address common adverse events (AEs) observed in earlier stages of the previous Phase II study, MW 2002-04-01. The study was conducted at one centre in the US. Efficacy was evaluated as exploratory endpoints.

Main Inclusion Criteria

- male and female subjects of 18-65 years of age
- DPT and/or FT thermal burns of 1-10% TBSA. As part of the safety measures the study treatment area was limited to ≥1% and ≤5% TBSA DPT and/or full thickness thermal burns.

Main Exclusion Criteria

- Other severe cutaneous trauma at the same sites as the burns, or previous burn(s) at the same treatment site(s) or one or more burn wound that did not meet study criteria
- DPT and/or FT facial burn wounds, >0.5% TBSA
- circumferential burns necessitating escharotomy
- heavily contaminated burns of pre-existing infections
- general condition of subjects that would contraindicate surgery
- poorly controlled diabetes mellitus
- cardio-pulmonary disease
- chronic systemic steroid intake

Methods

Study MW 2005-10-05 was similar in design to the Phase II study MW 2002-04-01 (see above) and similar study procedures were applied, except that prior to wound treatment steps, preventive analgesic medication was administered as commonly practiced pain-free dressing changes as a corrective measure for the procedural pain. In addition, soaking with antimicrobial solution was performed for a minimum period of 2 hours before and after NEXOBRID application as a corrective measurement to reduce wound infections and pyrexia. Subjects were randomised at a ratio of 1:1:1 to receive NexoBrid, Vehicle or SOC.

Efficacy Variables

Due to the small sample size, all efficacy endpoints were of exploratory nature. The following efficacy endpoints were assessed:

- Time to start of debridement from injury/randomization
- Percent eschar removed by debridement procedures
- Time to complete debridement
- Percent treated wound autografted
- Time to complete wound closure
- Time to hospital discharge

Study Subjects

31 subjects were screened and enrolled in the study; 10 subjects each were randomised to the NEXOBRID and Vehicle groups and 11 were randomised to the SOC group. One subject in the Vehicle group did not receive treatment; this subject was replaced with a subject who was randomised to the SOC group. Therefore, 31 subjects were randomised and 30 were treated. Twenty-one subjects completed the study.

Table 36. Demographic Data

Parameter		**NexoBrid (N = 10)**	**Vehicle (N = 10)**	**SOC (N = 11)**
Age (year)	**N**	**10**	**10**	**11**
	Mean	52.5	34.8	38.8
	SD	8.9	12.4	11.2
	Median	54.5	35.5	37.0
	Range	(36-63)	(18-60)	(24-62)
Gender	**N**	**10**	**10**	**11**
	Male	9 (90.0%)	9 (90.0%)	8 (72.7%)
	Female	1 (10.0%)	1 (10.0%)	3 (27.3%)
Race	**N**	**10**	**10**	**11**
	Caucasian	7 (70.0%)	4 (40.0%)	6 (54.5%)
	Middle Eastern	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black	3 (30.0%)	5 (50.0%)	4 (36.4%)
	Asian	0 (0.0%)	0 (0.0%)	1 (9.1%)
	Other	0 (0.0%)	1 (10.0%)	0 (0.0%)

p-values are from one-way ANOVA.

Baseline characteristics of the burn wound were as follows: The total burn surface areas (TWs and non-TWs) were similar among the three treatment groups (NexoBrid, 6.1%; Vehicle, 5.5%; SOC, 5.6%). The groups' average DPT/third degree burn was 2.3-2.5% TBSA. In all three treatment groups, virtually all of the deep partial thickness / 3rd degree burn areas were specified as TWs.

Exploratory Efficacy Results

Table 37. Summary of Debridement Procedures

Parameter		NEXOBRID (N=10)	SOC (N=11)	Vehicle (N=9)
Treated TW area (% TBSA) (per wound)	**N***	**14**	**13**	**10**
	Mean	2.2	2.6	2.9
	SD	1.5	1.1	2.8
	Median	2.0	3.0	2.0
	Range	1-6	1-4	1-10
Time to start of debridement from injury (days)	**N**	**10**	**11**	**9**
	Mean	0.6	1.4	0.7
	SD	0.5	0.7	0.5
	Median	1.0	1.0	1.0
	Range	0-1	1-3	0-1
Time to start of debridement from randomisation (days)	N	10	11	9
	Mean	0.0	0.4	0.1
	SD	0.0	0.7	0.3
	Median	0.0	0.0	0.0
	Range	0-0	0-2	0-1
% Eschar removed by debridement procedures (per wound)	**N***	**14**	**13**	**10**
	Mean	88.4	100	0.0
	SD	12.8	0.0	0.0
	Median	92.5	100	0.0
	Range	65-100	100-100	0-0
Time to complete debridement from randomization (days)	N	**10**	**11**	**9**
	Mean	0.2	0.4	1.1
	SD	0.4	0.7	0.6
	Median	0.0	0.0	1.0
	Range	0-1	(0-2)	0-2
Initial Debridement done by tangential excision	**N**	**10**	**11**	**9**
	Yes	0 (0.0%)	11 (100.0%)	0 (0.0%)
	No	10 (100.0%)	0 (0.0%)	9 (100.0%)

A "0" value indicates that debridement was performed on the same day as injury or randomization.
*Number of wounds: Two subjects had two TW that were one continuous wound and treated in one session as one wound. However, these were designated as two TWs in error. These wounds were combined in the analyses for the statistical table.
Source: CSR MW 2005-10-05

The NexoBrid enzymatic debridement and Vehicle control procedures both took ~4 hours.

The NexoBrid enzymatic debridement procedure removed on average 88.5% of the eschar per wound. Eight of 10 subjects had complete eschar removal and two subjects (the first two NEXOBRID subjects in the study) had incomplete debridement due to technical difficulties (incomplete keratin removal) during the cleansing procedure prior to debridement. In the SOC group there was 100% eschar removal with tangential excision. The Vehicle did not demonstrate any debriding activity and no eschar was removed during the control procedures.

Time to complete debridement from randomisation was 0.2, 1.1 and 0.4 days for the NexoBrid, Vehicle and SOC treatment groups, respectively. For the two subjects in the NexoBrid treatment group who had incomplete debridement, tangential excision was performed the next day in order to complete the

debridement. NexoBrid debridement was not repeated for cases of incomplete debridement due to the burn management routines of the burn unit. Two of the SOC subjects required additional tangential excision post-debridement. All 9 subjects in the Vehicle group required tangential excision to remove the eschar post-Vehicle application. Tangential excision was performed on the same day of Vehicle application for one subject, the day after application for 7 subjects and 2 days after application for one subject.

The mean areas of the treated wounds that underwent autografting were 61.1%, 76.0% and 60.0% of the total treated wound areas, for the NexoBrid, Vehicle and SOC groups, respectively.

The mean time to observed complete wound closure from randomisation was 42.5 (SD= 6.9) days for the NexoBrid, 30.6 (SD= 10.8) days for the Vehicle and 30.4 (SD= 10.2) days for the SOC treatment group. One subject in the NexoBrid group had complete wound closure 56 days post-randomisation and three subjects in the SOC group had wound closure 16-20 days post-randomisation. Due to the small size of the groups these outlying data have influenced the mean values.

Time to hospital discharge from injury/randomisation was similar among the three study arms and ranged between 5.0 to 5.6 days from injury and 4.0 to 5.0 days from randomisation.

Study 35-98-910: Retrospective Data Collection

A retrospective clinical data collection and study efficacy assessment was performed from files of hospitalised burn subjects with burn wounds treated by Debridase. Only for subjects who had signed consent forms and had full photographic documentation of their wounds, pre- and post- eschar removal, in their medical files were included. Data from a total of 154 patients was available for the analuysis.

All Wounds: Analysis of Efficacy

Dates of complete wound closure were recorded per wound for all subjects, if known. Therefore, complete wound closure was analyzed per subject (all wounds) as "yes" or "unknown". Data were available for 135 subjects (87.7%) for whom date of complete closure were known; however, there was no reliable comprehensive information for 19 subjects (12.3 %).

Time to Complete Wound Closure – Primary Efficacy Parameter

The mean time to wound closure was 25.7 days. In addition, the mean time to complete wound closure for all wounds was very similar for both age groups; 25 days for children and 26.4 for adults.

Percent Wound Area Grafted

A total of 171/397 wounds (43.1%) that were treated with Debridase and required skin grafting, were assessed for %TBSA grafted; all of these wounds were mixed dermal or third degree burns. 35/397 wounds (8.8%) underwent excision prior to grafting. The mean area of all the wounds was 2.7 + 1.9 % TBSA pre-debridement; 0.8 + 1.5 %TBSA was grafted. Thus 30% of the original wound area debrided required grafting. This difference was statistically significant ($p<0.001$).

Percentage Take of Skin Graft

The surgical outcome results following skin graft showed that 94.7% (161/170) of the wounds had a graft take of more than 90%

Debridement

Debridement was evaluated visually by the treating investigator during the study and was reassessed as part of the data collection using photographs of the wounds. Percent debridement achieved was calculated in relation to intended debridement area and to the actual area treated. For various technical reasons, e.g. incomplete keratin removal or difficult wound locations, Debridase was not always in complete contact with the wound; thus inadvertently leaving some small areas undebrided. The actual area treated was assessed after taking these untreated areas into account. Debridement data were obtained for 388/400 wounds (97%). Debridement was achieved in 86.5% of the total TW mean area intended for treatment, with actual area treated being 94.1% of the original TW area. Therefore, debridement was achieved over 91.8% of the area that was in contact with Debridase.

Examination of Subgroups

Age: Analysis of Efficacy by TW

Similar numbers of children (n=75, 0.6-15.9 years) and adults (n=79, 16.8-82.1 years) were included in this retrospective data collection.

Time to Complete Wound Closure

Mean time to complete TW closure was 21.4 + 16.5 days and 22.9 + 16.2 days, respectively in children (67) and adults (71). For wounds ranging from ≥2% to <15% TBSA, closure was quicker for children in comparison to adults, mean time approximately 18 vs. 23 days, respectively.

Percent Wound Area Grafted

In children and adults treated with Debridase, 33 and 32 TWs, respectively, required skin grafting and were assessed for % TBSA grafted; all of these wounds were mixed dermal or third degree burns.

2 TW in children and 12 TW in adults underwent excision prior to grafting, with mean pre-debridement areas of 4.4±3.4 and 3.6±2.9% TBSA, respectively, and total mean TW area requiring grafting of 1.5±2.5 and 1.0±1.6% TBSA. Thus, out of the original TW area, only 34% in children and 28% in adults needed grafting. This difference between the original debrided area and the area requiring grafting was statistically significant ($p<0.001$).

Debridement

In children, debridement was achieved in 87.8% of the total TW mean area intended for treatment and the actual treated area was 95.2 % of the original TW area. Therefore, debridement was achieved over 92.0% of the area that was in contact with the Debridase. In adult, debridement was achieved in 82.9% of the total mean area TW intended for treatment. The actual treated area was 91.2 % of the original TW area. Therefore, debridement was achieved over 90.3% of the area that was in contact with the Debridase.

Hand Wounds: Analysis of Efficacy

Time to Complete Wound Closure

Dates of complete wound closure were recorded per hand wound. Complete wound closure of the hands was analysed as 'yes' or 'unknown'. Closure data were available for 74/81 hands (91.4%) in 65 subjects, with no information for 7 hands (8.6%). The mean time to complete wound closure was 21.1 days. Hand wounds which underwent surgical grafting had a mean closure time of 17.6 days.

Percentage Wound Area Grafted

Thirty out of 80 hand wounds (37.5%) for which these data were available, underwent surgical treatment. The majority of the 30 hand wounds (63.3%) which were grafted were third degree and the remaining 36.7% were mixed deep dermal. Only two hands underwent excision prior to the grafting. 27% of the original hand wound area needed grafting. The difference between the original debrided area and the area requiring grafting was statistically significant ($p<0.001$).

The surgical outcome for 26 out of 27 hand wounds was graft take of more than 90%.

Debridement

Debridement was achieved in 80.3% of the total mean area intended for treatment, with actual treated area being 89.7% of the original intended hand wound area. Therefore, debridement was achieved in over 90.1% of the area that was in contact with Debridase.

Escharotomy

None of the subjects and none of the hands had to undergo surgical Escharotomy.

MW2012-01-02

Study MW2012-01-02 was a multi-center, non-interventional, assessor-blinded study designed to evaluate long-term scar formation (using MVSS model) and Quality of Life in adults (using SF-36 model) and children (Burn Outcome Questionnaire1), who had their DPT and FT thermal burn eschar removed by NexoBrid or SOC in study MW2004-11-02.

The study assessments were performed al least 2-4 years post-wound closure within study MW2004-11-02 (i.e., at a time-point when scar maturation, convalescence and rehabilitation processes would have ended).

Eighty-nine (89) patients, who previously participated in study MW2004-11-02, were enrolled into this study, evaluating 191 wounds (113 in NexoBrid vs. 78 in SOC initially treated in MW2004-11-02).

To support the adequate representation of MW2004-11-02 randomized population by MW2012-01-02 enrolled population the applicant submitted the following analyses on demographics, wound characteristics and outcome measures:

Table 1- Comparison of demographic data between enrolled population in MW2012-01-02 and safety population in MW2004-11-02

Demographic Data	*MW2012-01-02 enrolled population*						*MW2004-11-02 safety population*					
	NexoBrid (N=54)			SOC (N=35)			NexoBrid (N=101)			SOC (N=81)		
	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI
Gender												
Male	39	72.2	58.4-83.5	29	82.9	66.4-93.4	77	76.2	66.7-84.1	61	75.3	64.5-84.2
Female	15	27.8		6	17.1		24	23.8		20	24.7	
Race												
Caucasian	38	70.4	56.4-82.0	26	74.3	56.7-87.5	79	78.2	68.9-85.8	61	75.3	64.5-84.2
Middle Eastern	6	11.1		2	5.7		7	6.9		4	4.9	
Black	2	3.7		2	5.7		4	4.0		5	6.2	
Asian	4	7.4		1	2.9		6	5.9		3	3.7	
Other	4	7.4		4	11.4		5	5.0		8	9.9	
Age Group (years)												
Under 18	9	16.7	7.9-29.3	8	22.9	10.4-40.1	18	17.8	10.9-26.7	16	19.8	11.7-30.1
Over 18	45	83.3		27	77.1		83	82.2		65	80.2	
Age at start of MW2004 study												
Mean	31.5		27.3-35.8	27.7		22.3-33.0	32.4		29.5-35.4	29.3		26.2-32.4

Table 2- Pre-treatment burn description data, MW2012-01-02 enrolled population and MW2004-11-02 safety population

	MW2012-01-02 enrolled population						*MW2004-11-02 safety population*					
	NexoBrid (N=113)			**SOC (N=78)**			**NexoBrid (N=224)***			**SOC (N=170)***		
	N	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**	**N**	**%**	**95% CI**
DPT	70	61.9	52.3-70.9	35	44.9	33.6-56.6	136	60.7	54-67.2	88	51.8	44-59.5
Mixed Burns	38	33.6	25-43.1	30	38.5	27.7-50.2	77	34.4	28.2-41	60	35.3	28.1-43
Full Thickness	5	4.4	1.5-10	13	16.7	9.2-26.8	9	4.0	1.9-7.5	18	10.6	6.4-16.2

The demographic data show an imbalance in the proportion of DPT wounds in each arm (61.9 vs. 44.9 NexoBrid vs. SOC). A greater proportion of SOC enrolled patients are males (72.2 vs. 82.9 NexoBrid vs. SOC).

A comparison of co-primary and secondary efficacy outcome measures within MW2004-11-02 between patients enrolled in MW2012-01-02 and the MW2004-11-02 randomized population did not show relevant differences regarding outcome measures within MW2004-11-02 between MW2012-01-02 enrolled population and MW2004-11-02 randomized population. The 95% CIs were overlapping for all efficacy outcome measures categories between the two enrolled populations.

Overall and sub-group analysis of Scar assessment per wound – MVSS overall Score is described in the table below:

Table 9- Overall and sub-group Analysis of Scar Assessment per Wound - Modified Vancouver Scar Scale Overall Score

	Debrase 113 wounds						SOC 78 wounds					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Overall Score	113	3.12	2.55	3.00	0.00	13.00	78	3.38	2.59	3.00	0.00	9.00
Age												
<18 Years	18	3.39	1.82	4.00	0.00	6.00	19	4.37	2.43	4.00	1.00	9.00
>18 Years	95	3.07	2.67	3.00	0.00	13.00	59	3.07	2.58	3.00	0.00	9.00
Gender												
Male	84	2.63	2.26	2.00	0.00	10.00	66	3.18	2.64	3.00	0.00	9.00
Female	29	4.55	2.84	4.00	0.00	13.00	12	4.50	2.07	5.00	1.00	9.00
Autograft												
Yes	44	4.07	2.48	4.00	0.00	10.00	49	3.98	2.30	4.00	0.00	9.00
No	69	2.52	2.43	2.00	0.00	13.00	29	2.38	2.77	2.00	0.00	9.00
Location												
Hands	22	3.14	2.59	2.00	1.00	10.00	21	4.05	2.82	5.00	0.00	9.00
Arms	36	2.83	2.59	2.00	0.00	10.00	27	4.00	2.65	4.00	0.00	9.00
Thighs	27	3.22	1.97	4.00	0.00	8.00	17	2.71	2.39	2.00	0.00	9.00
Legs	36	2.75	2.18	3.00	0.00	9.00	24	2.58	2.22	2.50	0.00	9.00
Trunk	29	4.34	3.21	4.00	0.00	13.00	14	3.86	3.03	4.00	0.00	9.00
Feet	10	2.30	1.89	2.00	0.00	5.00	6	2.83	1.47	2.50	1.00	5.00
% TBSA												
≥5%, ≤15%	67	2.96	2.16	3.00	0.00	9.00	42	3.81	2.60	3.00	0.00	9.00
>15%, ≤30%	46	3.37	3.04	3.00	0.00	13.00	36	2.89	2.53	2.00	0.00	9.00
Depth												
DPT	70	2.50	2.36	2.00	0.00	13.00	35	2.77	2.74	2.00	0.00	9.00
Mixed Burns	38	4.11	2.69	4.00	0.00	10.00	30	4.10	2.54	5.00	0.00	9.00
Full Thickness	5	4.40	1.14	4.00	3.00	6.00	13	3.38	1.94	4.00	0.00	6.00

The overall long-term MVSS scores were comparable for both treatment groups, NexoBrid and SOC (3.12 and 3.38 respectively, p=0.88) (MVSS range 0-13).

The mean MVSS score of autografted wounds, regardless of the treated arm, was higher (worse) than for non-grafted wounds and comparable between treatment arms. The MVSS was noticeably better in DPT wounds regardless of initial burns treatment.

A positive trend in cosmesis and function in hand burns (MVSS score 3.14 in NexoBrid vs. 4.05 in SOC) can be seen. In contrast to this for a number of scar locations; thighs, legs and trunk, NexoBrid shows higher (worse) MVSS score than SOC treatment.

The MVSS results are comparable for NexoBrid and the SOC sub-groups with slightly lower (favourable) result in the Non-surgical SOC sub-group (3.12 and 2.16, respectively) and slightly worse in the Surgical SOC sub-group (3.12 and 3.78, respectively) (see table below)*.

Table 33- MVSS scores for split SOC per surgical and NSD patients study MW2012-01-02, ITT population

MW2012-01-02		NexoBrid	Surgical SOC	NSD SOC
MVSS-ITT	N	113	59	19
	Mean	3.12	3.78	2.16
	SD	2.55	2.53	2.43
	Median	3.00	2.00	2.00
	Min	0.00	0.00	0.00
	Max	13.00	9.00	9.00

Scar Modulation Therapy

The number of wounds requiring scar modulation therapy (e.g. compression garments) was roughly equal in NexoBrid patients compared to SOC (27.8% vs. 34.3%, respectively).

Table 20- Scar Modulation Therapy, study MW2012-01-02

Patients having undergone any Scar modulation Procedures	NexoBrid (N=54)		SOC (N=35)	
	N	%	N	%
NO	39	72.2	23	65.7
YES	15	27.8	12	34.3

Quality of life assessment

In QoL assessments, the overall results in adults (SF-36 questionnaire) appeared to be comparable between NexoBrid and SOC groups as indicated by the physical component score (51.1 and 51.3, respectively) and the mental component score (52.3 vs. 49.1, respectively).

In paediatric and adolescent patients, the total overall score (BOQ) was similar, 118.7 in the NexoBrid arms compared with 121.6 in the SOC arm.

Table 15- Quality of life Adults: SF-36 Questionnaire - Score, study MW2012-01-02

	NexoBrid							SOC						
	N= Subjects	Mean	SD	Median	Min	Max	95% CI	N= Subjects	Mean	SD	Median	Min	Max	95% CI
PCS- Physical Component Score	45	51.1	9.1	54.4	29.3	61.7	48.36-53.86	27	51.3	8.6	52.9	21.1	61.1	47.88-54.73
MCS- Mental Component Score	45	52.3	11.5	56.7	15.5	68.8	48.83-55.73	27	49.1	10.4	51.9	20.4	67.1	44.96-53.16

Table 16- Quality of Life Pediatrics: Burn Outcomes Questionnaire (BOQ) - Score

	NexoBrid							SOC						
	N= Subjects	Mean	SD	Median	Min	Max	95% CI	N= Subjects	Mean	SD	Median	Min	Max	95% CI
Total Overall Score	7	118.7	7.6	117	107	132	111.7-125.7	8	121.6	13	128	100	134	114.4-126.1

Long-term cosmesis sequelae resulting from donor site scarring

The overall results by MVSS of donor sites were comparable for both treatment groups and within the expected MVSS range for donor sites, which is < 1[1] (NexoBrid and SOC 0.75 vs. 0.97, respectively).

Table 19- MVSS of Donor Sites, study MW2012-01-02

	NexoBrid						SOC					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Total Overall Score	32	0.75	1.14	0.00	0.00	4.00	35	0.97	1.25	0.00	0.00	4.00

NexoBrid-treated patient had fewer donor sites scars; the area of the donor sites in the NexoBrid arm was smaller vs. SOC (5.8% TBSA vs. 8.3% TBSA, respectively).

Table 17- Incidence of Donor Sites, study MW2012-01-02

Incidence of patients with Donor Sites	NexoBrid (N=54)		SOC (N=35)	
	N	%	N	%
Total	22	40	24	68

Table 18- Area of Donor Site in% TBSA per patient, study MW2012-01-02

	NexoBrid (N=22)						SOC (N=24)					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
% TBSA of donor site per patient	22	5.8	3.8	5.8	1.0	15.0	24	8.3	6.2	7.0	2.0	30.0

Additional expert consultation

The CHMP convened during the assessment an ad-hoc expert group to address specific questions. The deliberations from this meeting are provided below. It should be noted that subsequent to this input further data was provided by the applicant in response to questions from the Committee, which were not yet available at time of the expert consitation (e.g. additional data to substantiate the quality of debridement).

1) **What is the relative importance to the patient and the burns specialist of the following measures of efficacy/ clinical outcome:**
   - **Removal of eschar**
   - **Avoidance of surgical (tangential/ minor/ Versajet) excision**
   - **Reduction in use of autografts**
   - **Time to complete wound healing**
   - **Cosmetic outcome**

The complete removal of eschar is the prerequisite for most burns treatment and for any good outcome after a deep burn. In terms of relative importance there was broad agreement amongst the

clinicians and patient representatives that cosmetic and functional outcome is the most relevant clinical outcome.

The clinicians agreed that the second most important outcomes are the reduction in use of autografts as well as the time to complete wound healing as this is correlated to the risk of wound related complications.

The patient representatives stressed that minimising the amount of scaring as much as possible is of particular relevance. Also the reduction of donor sites is important given the pain and discomfort felt at these sites. Time to complete wound healing is of less interest compared to the overall outcome.

In general, the experts were in agreement that the use of NexoBrid could be an effective debridement tool and may be considered as an alternative to surgical excision. However, this would require the demonstration of adequate quality of the debridement in terms of completeness and optimal depth. The clinical study was not designed to generate these data hence the experts stressed the need for further data on quality of the debridement with NexoBrid (e.g. histology of tissue removed, wound biopsies after debridement, number of failed auto grafts after NexoBrid treatment).

Whilst considering the potential use of NexoBrid for debridement, the experts stressed that this alternative procedure itself is not expected to impact the outcome of the overall burn treatment hence it will not introduce a new treatment concept. The experts were in agreement that the avoidance of surgical excision is only to be seen as of relative importance as prompt surgical excision in DPT and FT burns and subsequent autografting, when performed by an experienced surgeon preserving all undamaged tissue, was considered as the fastest and most effective treatment.

With regard to the main clinical study, the experts noted that the post-debridement care was not standardized, which may have affected time to complete wound closure. Also, the study was performed in many countries and regions introducing a very heterogeneous SOC treatment. This study design might have had an impact on some of the differences seen between treatment arms.

2) Based on clinical experience, is there a (sub) group of patients for whom the use of NexoBrid might be of particular interest considering any limitations of surgical or other non-surgical interventions?

The use of NexoBrid might be of particular interest in debriding areas of special functional interest (e.g. hands or face, if the eyes can be effectively protected) where it is of major importance to preserve all undamaged tissue, e.g. dermis. However it should not be used to avoid grafting as grafting is of particular importance for the functional outcome in these areas. The experts noted that data on functional outcome in the dossier is sparse and that functionality should be measured with the appropriate tools.

Debridement with NexoBrid might also be an alternative to the surgical excision when treatment needs to be initiated or performed in situations without immediate availability of qualified burns surgeons and in cases of mass causalities.

Treatment of very large burns (over 60 % TBSA) could be of particular interest for use of NexoBrid to ensure optimal use of the limited number of donor sites. The experts noted however that the present proposal only allows the use of the product for up to 15% TBSA in one session, which is based on the lack of data on systemic exposure and safety considerations.

The experts noted that there are some patients where surgical excision may not be possible due to the general condition and co-morbidities (e.g. shock, acute respiratory failure). For such cases a non-surgical alternative would be of interest.

3) Considering that there have been patients included in the clinical trials with co-morbidities which could have led to increased morbidity / mortality is there a subgroup for which NexoBrid treatment cannot be applied?

The experts advised that considering the fibrinolytic and antithrombotic activity NexoBrid should not be applied in patients with bleeding conditions such as bleeding ulcers, coagulation disorders including sepsis and patients with low platelet counts. Furthermore the experts considered that NexoBrid should be avoided in chemical burns, wounds contaminated with radioactive and other hazardous substances to avoid unforeseeable reactions with the product and an increased risk of spreading the noxious agent. Finally, the product should not be used in penetrating wounds, wounds in which foreign material (e.g. implants, joint replacements, pacemakers, shunts) and/or vital structures (e.g. larger vessels, eyes) are or could become exposed during debridement.

4) How do you consider the plausibility and / or relevance of the trend to increased mortality in the clinical trial dataset taking into account other data, e.g. on blood transfusion, infections and systemic exposure to bromelain?

According to the experts the available data does not suggest an increased mortality related to treatment with NexoBrid. It was noted that in general the population included in studies investigating burn patients is very heterogeneous. It was also noted that the exclusion criteria for the clinical NexoBrid studies excluded all patients with increased risk of mortality after burns and that the rate of mortality probably was affected by this patient selection. The data from the studies with NexoBrid do not appear to be out of the bounds concerning the occurrence of deaths in this population.

The experts also noted that any treatment that will increase time to complete wound healing will also increase the risk for complications during healing. Theoretically, this could indirectly increase mortality.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The studies were designed as unblinded comparison to standard of care. In the pivotal study MW2004-11-02 patienst were not older than 55 years and important exclusion criteria were probale smoke inhalation, cardiopulmonary disease, peripheral circulatory disease, a general condition of patient that would contraindicate surgery and poorly controlled diabetes mellitus (HbA1c>9%). These criteria select patients with an overall better prognosis (excluding some multimorbid patients) which is in line with the generally good outcome (e.g. low mortality) in both arms of the study. As recommended by the scientific advice received study endpoints were the % treated wound excised, the % treated wound autografted of deep partial wounds, time to complete wound closure timely eschar removal (debridement) and blood loss.

Efficacy data and additional analyses

Primary endpoints

The pivotal study data show that compared to standard of care, NexoBrid reduced the need for excisional surgery in FT, mixed and DPT wounds (excised: 25% NexoBrid vs. 70% SOC) and the need for autografting of DPT wounds (autografted: 18% Nex vs. 34% SOC). Efficacy of eschar removal and reduction in excisional surgery was also demonstrated across wound depth and wound area subgroups (DPT wounds; Mixed and FT wounds and wounds of TBSA >5%-≤15%; >15%-≤30% respectively) with similar magnitudes of effect seen within the subgroups as for the entire population.

Exploratory analyses also revealed similar benefits for subgroups according to site of wounds, including the hand areas. The hands are often affected in patients with severe or extensive burns and they are particularly difficult to debride with surgical excision due to the proximity of the skin to underlying structures which are vital for effective hand function. During the clinical development programme, NexoBrid was used to treat 130 DPT and FT burns of the hands.

None of the hands treated with NexoBrid required escharotomy whereas 9.7% (4 of 41 hands) in the SOC cohorts were escharotomised. It was later claimed by the Applicant that these results were accompanied by improved cosmetic results compared to SOC treated hand wounds, (MVSS score 3.14 in NexoBrid vs. 4.05 in SOC). Whilst these results are encouraging it should be noted that the analyses were exploratory in nature, the number of hand wounds small (representing only 14% of treated wounds at a maximum) and that there were some concerns with the robustness of the long-term cosmetic data (see safety discussion).

The primary endpoint data were supported by some data from the phase II study MW 2002-04-01 and the retrospective study, 35-98-910 which showed quick and clinically complete debridement of burn wounds (according to the definitions employed in the study). However there were some conflicting efficacy data from study MW 2002-04-01 where similar numbers of wounds administered NexoBrid and SOC received grafts or skin substitutes and wound grafts of larger area were placed on NexoBrid treated wounds compared to those placed on SOC treated wounds, although the difference was not statistically significant.

Whilst the pivotal study endpoints were successfully achieved the additional benefits of minimising autografting remained uncertain. The real magnitude of the difference for DPT wounds between NexoBrid and SOC arms and its clinical significance was questioned due to the unblinded design of the pivotal study, the differences between study arms in post-debridement wound management and the small reduction in absolute terms in the number of wounds and patients undergoing autografting. However, it was clear that for a study of this nature an open trial could not be avoided. The investigator's knowledge of treatment allocation and potentially a change in the characteristics of the wound as a result of the debridement procedure resulted in the adoption of differing wound closure strategies post-debridement in the two study arms.

In agreement with the outcome of the Scientific Advice procedure, the co-primary endpoint of '% wounds autografted' was investigated. However, the data submitted by the Applicant showed that a higher number of autografting procedures took place than the number of wounds autografted. There is a 15 vs. 4 imbalance in the number of repeat autografts that occurred in DPT & mixed wounds, almost causing the number of autograft procedures in both treatment arms to be equal, with 67 autograft procedures in the NexoBrid arm versus 70 autograft procedures in the SOC arm. A maximum of 29% of such wounds debrided with NexoBrid would have undergone repeat procedures but only 6% in the SOC group. The Applicant has argued that autografting procedures can be performed in a single stage or in multiple stages and that the 'multiple stages' approach is well established in burn care practice. In a single stage, the eschar is removed from the burn wound and the wound is entirely grafted,

whereas with the multiple stages wound closure strategy each of the burned areas is grafted according to the progression of the healing process. Therefore, the multiple grafting procedures in the NexoBrid or SOC wounds were not due to graft failures but rather were part of the established multiple stage grafting approach. From the Applicant's response and from data submitted, the CHMP considers that this is plausible. The 'multiple stages' strategy is essentially trialing wound closure by spontaneous epithelialisation for wounds or areas of wound with likely potential for healing (e.g. where area of remaining dermis persist) - when wounds partially covered with autograft developed non healing areas within the uncovered areas, these areas of the wound were also subsequently autografted.

It can be argued that number of autograft procedures performed is more clinically relevant than number of wounds autografted, as each procedure is accompanied by preparation of the wound bed for the graft, harvesting of the graft from a donor site, known risks of surgery and a challenging post operative recovery phase. For this outcome, for the mITT population (DPT wounds), it is likely that there is no statistically significant difference between study arms (24 vs. 29 procedures).

The CHMP notes that only limited information on the use in the paediatric population is available. These data are insufficient to ascertain the efficacy of NexoBrid in this population. A dedicated phase III study including paediatric patients has alrady been planned by the applicant. The CHMP concurs that at present time the indication of NexoBrid should be limited to the use in adults only.

Mixed wounds subgroup

For the mixed wounds subgroup (making up 32% of the treatment wounds in the enrolled population) the efficacy or clinical benefit of NexoBrid debridement is less clear. Data for the '% wound autografted' endpoint for mixed wounds was provided and showed a higher percentage of NexoBrid-debrided mixed wounds autografted than SOC-debrided mixed wounds (71% vs. 63%) and a larger mean wound area autografted (55.5 vs. 45.8%). Further, the data show the autograft procedure per wound rate to be higher for NexoBrid debrided mixed wounds (NexoBrid 0.90 vs. SOC 0.68). These data are in line with data provided for the non-mITT (mixed and FT wounds) population during the procedure and the phase II study data which showed larger areas of wound receiving autografts in the NexoBrid arm. Also, the data show the autograft procedure per wound rate to be higher for NexoBrid debrided mixed wounds (NexoBrid; 43 procedures/48 mixed wounds) (SOC; 41 procedures/ 60 mixed wounds). Whilst some caution is required in interpreting these data, as they result from post hoc analyses of non-randomised groups, the CHMP questioned the observed trend. In response, the Applicant argued that the adverse autografting data were due to baseline differences between study arms for the mixed wounds subgroup. NexoBrid debrided mixed wounds were approximately 17% larger and had approximately 23% more DPT area and 27% more FT area than SOC debrided wounds. However, whilst proportional differences of FT and DPT areas between study arms appear significant, the absolute differences suggest that they are less clinically significant. The Applicant's justification for the detrimental autografting data for mixed NexoBrid debrided wounds to address the larger number of autografting procedures that NexoBrid debrided mixed wounds underwent compared to SOC was questioned. Therefore, the applicant provided additional subgroup analyses to show, that mixed wounds in the NexoBrid treatment arm with a comparable %-age of FT wound area did not have an inferior outcome regarding autografting compared to the SOC-treatment arm. The importance of balanced baseline characteristics was hereby corroborated. Overall, the CHMP concurred that it appears not plausible that a negative effect of the NexoBrid debridement can have a detrimental effect on autografting solely in the mixed wounds. If NexoBrid had a negative effect, this should be present in all wound subgroups. Taking into account the diagnostic limitations to correctly determine the wound depth in mixed wounds before debridement, the baseline imbalance and subsequent inferior outcome is considered sufficiently explained. CHMP also acknowledges that this unexpected outcome may be related to a lack in experience with NexoBrid which in some instances induced wrong decisions regarding the timing and extent of autografting.

Whereas the results of the first primary endpoint focus on the direct debriding effect of Nexobrid which was readily assessable (leading to unambigously interpretable data), the autografting results of the 2. endpoint - and even more the additional subgroup analyses (on non.randomised mixed wound-subgroups) – might be confounded by other factors that influenced the post debridement management of the patients (some as a consequence of the debriding tool, others related to local wound management policies or perhaps patient preference). The non-standardised post debridement wound management significantly hamper interpretation of the 2. efficacy endpoint results.

To avoid any negative impact of NexoBrid treatment on TTCWC – as a risk minimisation measure – on the other hand, warnings have been implemented into the SmPC to ensure direct autografting of all wounds / wound areas with full thickness areas.

Secondary endpoints

Further support was lent to the primary endpoints by the secondary endpoint results, the time to successful eschar removal, percentage of all treated wound excised and blood loss, which appeared largely in line with the primary results. The speed of debridement of NexoBrid was clearly superior to SOC. On average NexoBrid debridement was started within 0.77 days and was completed by 0.8 days after ICF date compared to 1.26 days and 6.7 days respectively for SOC.

Time to complete wound closure

The results obtained for the time to complete wound closure (TTCWC) analyses, which showed statistically significant differences in favour of SOC, were concerning in the beginning. Multiple post hoc analyses of TTCWC from different start points (e.g. start of debridement, end of debridement etc...) and of different wound subgroups (non-mITT, mixed wounds, FT wounds) confirmed that NexoBrid debridement was associated with an increased TTCWC. The effect was especially clear for late autografted DPT and mixed wounds, with mean delays of approximately two weeks. It has become clear that throughout this procedure interpretation of the efficacy and safety outcome data, especially TTCWC, has been complicated by the heterogeneity of SOC treatments and post-debridement wound care.

The Applicant initially reasoned that the delay in wound closure was due to the greater number of wounds being left to heal by epithelialisation (which takes longer but is less invasive) in the NexoBrid arm rather than being autografted. After further analysis it became clear that in the pivotal study there were large delays in autografting NexoBrid debrided wounds (time to autograft from end of debridement in DPT wounds 15.0 vs. 1.7 days Nex vs. SOC). It is accepted that the differences in post-debridement wound management between the two study arms led to delays in TTCWC in NexoBrid debrided wounds which were autografted late.

Supportive data were provided by the Applicant which showed there to be only a small difference in TTCWC between study arms in the DPT subgroup where autografting had not occurred but significant differences between treatment arms (approx 2-3 weeks) in DPT wounds where it had.The lack of a difference in TTCWC in non-autografted wounds indicates that NexoBrid has no detrimental effect on the wound. Further supportive data on TTCWC of autografted wounds from the end of the autograft procedure, wounds autografted early (i.e. within 7 days of injury), FT wounds and non-autografted DPT wounds from the end of debridement also showing only small differences between NexoBrid and SOC groups were also submitted. The results from these post hoc analyses from non-randomised groups had to be interpreted with caution as some of the estimated differences between groups were based on relatively small numbers in subgroups. However, the totality of the data demonstrated that the principal cause of the delay in TTCWC in NexoBrid debrided wounds was the delay in placing autografts on such wounds. The small differences seen in the above analyses may suggest a small as yet

uncharacterised direct effect of NexoBrid on wound healing and the possibility should be investigated further in the randomised controlled study MW2010-03-02.

Based on the available data, the CHMP considers of utmost importance to provide healthcare professionals with the adequate guidance and training to avoid potential delays in TTCWC. Appropriate warnings and a discussion of TTCWC have been incorporated into the SmPC and delay in TTCWC has been included in the RMP as identified risk with associated risk minimisation measures including a suitable educational material has been generated for circulation to health care professionals.

Quality of debridement

With regard to time to complete eschar removal, the quality of NexoBrid debridement was considered by the CHMP to have been adequately demonstrated by the Applicant based on presentation of non-clinical data on quality of debridement and clinical data suggesting the completeness of NexoBrid debridement (surrogate data of similar graft failure rates of wounds which were autografted soon after debridement in NexoBrid and SOC arms). The study reports for the additional non-clinical data presented were submitted. The reports regard two animal studies using the pig burn wound model, where histology results were provided by a blinded dermatohistopathologist. Visual and histological results from Study A suggested that post-NexoBrid treatment no eschar could be detected, intact skin was unharmed and that remaining dermis was similar in thickness and structure to that seen in wounds treated with a control agent. Results from Study B appeared to corroborate these findings. However, very little quantitative data (in comparison to study A) were provided with regard to depth of remaining dermis and comparison to controls for this study. Overall, the Applicant showed to an acceptable degree that in animal studies NexoBrid does not remove healthy tissue and fully removes eschar from wounds. Ultimately, it is expected for the clinical sequelae of incomplete and unselective debridement e.g. graft failure and possibly other wound related complications (especially in patients receiving autografts or temporary covers shortly after NexoBrid debridement) to be apparent in the clinical data.

Blood loss

As regards blood loss, change in Hb and haematocrit (HCT) alone were not considered sufficiently sensitive or specific surrogates for blood loss in the pivotal study, due to the large changes in intravascular volumes in patients with severe burns secondary to aggressive fluid replacement (or in some cases restriction), occurring at vastly different times, usually in a treatment dependent manner. The difficulty in evaluating blood loss related to burns surgery was acknowledged by the CHMP. However, other methods are more commonly used in practice for example estimating blood loss in terms of millilitres of blood replaced per centimetre squared of wound excised and grafted or estimating the blood volume exchanges used at the time of burn surgery. It was considered that in the pivotal study the frequency and volume of blood transfusions may provide a better measure of debridement related blood loss (see safety discussion).

2.5.4. Conclusions on the clinical efficacy

The pivotal study data show that NexoBrid significantly reduces the amount of surgical excision of eschar required by burn wounds in adult patients in a significantly shorter period of time compared to SOC treatment. The primary endpoint data are supported by secondary efficacy outcome data from the pivotal study (including timely eschar removal), results of efficacy analyses across subgroups and by data from the dose-response, phase II and retrospective studies. Another positive trend was noted regarding the exploratory endpoint of compartment pressure in circumferential burns of the extremities. There is also preliminary evidence of benefit particularly for hand wounds.

Nexobrid reduces autografting vs. SOC (approximately 18% of the DPT wounds in NexoBrid were autografted vs. 34% in the SOC arm). Whilst efficacy has been shown, some uncertainties remain regarding TTCWC (especially for autografted DPT and mixed wounds) and the amount of autografting in mixed wounds.

It is important that NexoBrid should only be applied by trained healthcare professionals in specialist burn centres. The SmPC provides appropriate guidance to address findics from the clinical development, and a dedicated training programme will be required as part of the risk minimisation activities.

The CHMP considers the following measures necessary to address issues related to efficacy:

Description	Due date
The MAH shall conducts a study on enzymatic debridement in burns patients (children and adults): A comparison to standard of care (protocol MW2010-03-02), based on a CHMP approved protocol.	31/03/2017

2.6. Clinical safety

The safety and efficacy of NexoBrid were evaluated in Phase II and Phase III randomised studies, as well as a retrospective data collection.

Table 40. Clinical Studies Assessing the Safety and Efficacy of NexoBrid

Study No.	Development Phase	Primary Objective	No. of treated Subjects	No. of Paediatric Subjects	Range of treated %TBSA
Controlled Clinical Studies					
MW 2002-04-01	Phase 2	Safety and efficacy (0.02g NexoBrid/cm²)	(total 140): NexoBrid 70, Vehicle: 35, SOC: 35	-	≥2% and ≤30% yet treatment was restricted to one TW of up to 15% TBSA
MW 2005-10-05	Phase 2	Safety, efficacy (explorative) (0.02g NexoBrid/cm²)	(total 30): NexoBrid 10, Vehicle: 9, SOC: 11	-	≥1% and ≤10%, yet treatment was restricted to 5% TBSA
MW 2004-11-02	Phase 3	Safety and efficacy (0.02g NexoBrid/cm²)	(total 181): NexoBrid 100*, SOC: 81	33	≥5% and ≤ 30%
Dose-Ranging /Single Arm Studies					
MW 2001-10-03	Phase 2	Safety and efficacy, Dose ranging study.	(Total 20): NexoBrid 1g: 6, NexoBrid 2g: 7, NexoBrid 4g: 7	-	≥1% and ≤15%
MW 2008-09-03	Phase 2	Safety and	10 Planned, 8	-	≥ 4% and ≤

Study No.	Development Phase	Primary Objective	No. of treated Subjects	No. of Paediatric Subjects	Range of treated %TBSA
		efficacy (exploratory), systemic absorption (PK)	enrolled and analysed in interim analysis for PK and safety		30%
Retrospective Data Collection Study					
35-98-910	Phase 1&2	Retrospective data collection to demonstrate the safety and efficacy of (0.02g Debridase/cm²)	Total 154 (all Debridase)	77[11]	≥1% and ≤67%%

* Includes 26 training subjects who were not included in any efficacy analyses, but only in safety analyses.

Adverse events (AEs) were recorded post-enrolment from the date of signing the informed consent form (ICF), throughout the study, and at early termination in the phase II and III studies.

In all five studies, safety assessments were based on the following:

- General parameters: Systemic AEs, vital signs, pain assessments, laboratory tests, volume of blood transfusions (if required), as well as general functional disability assessments.
- Local parameters: Wound infection, local AEs graft loss, and short-term scarring assessments.

AEs were reported and rated by the investigator for severity, seriousness and relationship to treatment throughout the hospital stay and during follow-up visits.

Patient exposure

Exposure by Number of Applications

A total of 208 subjects were exposed to NexoBrid (safety population), 44 to Gel Vehicle alone, and 127 to SOC treatment. In addition, safety data is available from 154 subjects from a retrospective data collection study.

	5 Prospective Studies (NexoBrid)		**Retrospective Study (Debridase)**	
	N = 208		**N = 154**	
NexoBrid	**N (%)**	**Person-hours**	**N (%)**	**Person-hours**
1 application	187 (89.9%)	757	104 (67.5%)	416
2 applications	21 (10.1%)	169	42 (27.3%)	336
3 applications	0 (0.0%)	0	6 (3.9%)	72
4 applications	0 (0.0%)	0	2 (1.3%)	32

Adverse events

More subjects in the NEXOBRID treatment group experienced at least one AE compared to the SOC group. During the development programme, the following precautionary measures have been implemented to mitigate safety findings.

Provision of a pre-treatment pain management protocol as commonly practiced during routine dressing change in standard of care of burns in order to prevent NEXOBRID related pain

Use of approved topical antibacterial solutions during the soaking stages prior to and post-treatment in order to minimise the potential for infection and associated fever

Treatment of a subject's entire burn wound which allowed more accurate assessment of systemic safety issues

All AEs and SAEs were reviewed by an independent medical monitor during the studies.

This is addressed in the below data presentations. The majority of AEs were of mild or moderate intensity irrespective of treatment. More subjects in the NEXOBRID treatment group compared to the SOC treatment group experienced an AE of severe intensity.

In most studies, the majority of subjects experienced unrelated or only remotely related AEs, although more subjects in the NEXOBRID treatment group experienced AEs that were considered treatment-related compared to the SOC group.

With regard to the NexoBrid training group, which was assessed as a distinct subgroup for safety outcomes, overall, a similar safety profile were observed when compared to the NexoBrid randomised group.

Common adverse events

Summary of Adverse Events in Descending Order of Frequency Whether or Not Treatment-Related and Occurring in ≥3.0% of Subjects (Safety Population)

Adverse Event*	**NEXOBRID**	**SOC**
	N=208(%)	**N=127 (%)**
Pruritus	32 (15.4%)	24 (18.9%)
Anaemia	13 (6.3%)	8 (6.3%)
Nausea	13 (6.3%)	6 (4.7%)
Insomnia	6 (2.9%)	5 (3.9%)
Headache	6 (2.9%)	5 (3.9%)
Skin graft failure	6 (2.9%)	2 (1.6%)
Diarrhoea	6 (2.9%)	1 (0.8%)
Vomiting	5 (2.4%)	7 (5.5%)

* Pain, pyrexia and wound infection are presented in the table below, before and after the implementation of corrective measurements.

Comparison of the Incidence of Adverse Events Pain, Pyrexia/ Hyperthermia, Wound Infection before and after corrective measures

Adverse Event	Group 1*		Group 2**	
	NEXOBRID N=90	SOC/Vehicle N=70	NEXOBRID N=118	SOC/Vehicle N=101
	N (%)	N (%)	N (%)	N (%)
Pain	21 (23.3)	8 (11.4)	4 (3.4)	4 (4.0)
Pyrexia/ hyperthermia	32 (35.6)	13(18.6)	20 (17.0)	16 (15.8)
Wound infection	6 (6.7)	4 (5.7)	7 (5.9)	7 (6.9)

* Group 1: data combined from MW 2001-10-03, and MW 2002-04-01, **Group 2: data combined from MW 2005-10-05, MW 2004-11-02, and MW 2008-09-03,

It should be emphasized that basic wound management in the NexoBrid arm changed between the 'Group 1' studies and the 'Group 2' studies and were brought in line with standard of care during this period. The incidence of pain in the NEXOBRID group was reduced from 23.3% to 3.4% after corrective measures had been taken for adequate pain management, as commonly practiced during routine dressing change to burn patients, in the later clinical studies and occurred at a comparable incidence in both treatment groups. Pain and pyrexia and wound infection are included in the RMP as identified risks and adaequat wordings were provided within the SmPC.

Wound complications occurred more frequently in NexoBrid treated patients in the pivotal study than SOC treated patients. The study DSMB and investigators could not attribute the majority of these events to NexoBrid or other underlying cause.

Table 122.15- Wound complications reported in NexoBrid clinical studies

Preferred term	Patient	Study/Arm	Severity	causality	Outcome	Violation
Open Wound	39A003	MW2004-11-02/ NexoBrid	Mild	Not related	Recovered[12]	2 TWs were treated with SSD
	45A027	MW2004-11-02/ NexoBrid	Mild	Not related	Recovered	No
	24A002	MW2004-11-02/ SOC	Mild	Not related	Recovered	No
Wound Complications	08B015	MW2004-11-02/ NexoBrid	Mild	Not related	Recovered	No
	24A003	MW2004-11-02/ NexoBrid	Mild	Not related	Recovered	No
	08A095	MW2002-04-01/ NexoBrid	Moderate	Not related	Recovered	No
	08A099	MW2002-04-01/ NexoBrid	Mild	Not related	Recovered	No
	08B008	MW2002-04-01/ NexoBrid	Moderate	Not related	Recovered	No
Wound Decomposition	05A002	MW2004-11-02/ NexoBrid	Mild	Remotely related	Recovered	No
	09A001	MW2004-11-02/ NexoBrid	Mild	Remotely related	Recovered	No
	23B001	MW2004-11-02/ NexoBrid	Moderate	Not related	Recovered	No
	06A003	MW2004-11-02/ SOC	Mild	Not related	Recovered	No
	25A007	MW2004-11-02/ SOC	Mild	Not related	Recovered	2 TWs were treated with SSD
Graft Failure	23B014	MW2004-11-02/ NexoBrid	Moderate	Not related	Recovered with sequelae	No
	35A002	MW2004-11-02/ NexoBrid	Mild	Not related	Recovered	No
	40A002	MW2004-11-02/ NexoBrid	Mild	Not related	Recovered	No
	45B017	MW2004-11-02/ NexoBrid	Moderate	Not related	Recovered	No
	09B010	MW2002-04-01/ NexoBrid	Severe	Possibly related	Recovered	No
	14C001	MW2002-04-01/ NexoBrid	Moderate	Not related	Recovered	No
	40B014	MW2004-11-02/ SOC	Mild	Not related	Recovered	No
	23A059	MW2002-04-01/ SOC	Mild	Not related	Recovered	No
Scar events	06B014	MW2004-11-02/ NexoBrid	Severe	Not related	On going at the end of the study	No
	26A012	MW2004-11-02/ NexoBrid	Severe	Not related	Recovered with sequelae	No

To prevent wound complications related to delays in wound closure the SmPC clearly indicates that areas of full-thickness and deep burns should be autografted as soon as possivle after Nexobrid debridement.

Table 7- Wound complications reported in NexoBrid clinical studies

	NexoBrid	SOC
Complications		
Overall	20.4% (67/329)	18.7% (41/219)
Late autografted	23.8% (29/122)	22.0% (15/68)
Time to AE from ICF (days)	10.4 (67)	12.7 (41)
Delay in TTCWC	3.4 (67)	3.5 (41)
Long-term (MVSS) scores[1]		
Overall	3.12	3.38
With wound complications	3.09	2.87

[1] Long term evaluation was performed only on patients participating in study MW2004-11-02.

Wound Infections

Wound infections occurred more frequently in NexoBrid treated patients than SOC treated patients in earlier studies. However, the Applicant presented data to show that after implementation of infection control measures, such as antibacterial soaking of wounds prior to and after NexoBrid treatment, wound infection rates became similar between the study groups in later studies. Wound infection is listed as an identified risk in the RMP and adaequate statements to prevent wound infections are included into the SmPC.

Table 128.2- Wound Infection AEs reported in studies MW2001-10-03 an MW2002-04-01

Outcomes	NexoBrid N= 90		SOC/Vehicle N=70	
	Patients (%)	Events* (%)	Patients (%)	Events* (%)
Recovered with sequelae	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (25.0%)
Recovered without sequelae	7 (7.8%)	7 (100%)	3 (4.3%)	3 (75.0%)

* Events are calculated out of the total infection events reported

Table 128.3- Wound Infection AEs reported in studies MW2005-10-05, MW2004-11-02

Outcomes	NexoBrid N= 110		SOC/Vehicle N=101	
	Patients (%)	Events* (%)	Patients (%)	Events* (%)
Recovered with sequelae	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Recovered without sequelae	9 (8.2%)	10 (100%)	8 (7.9%)	9 (100%)

* Events are calculated out of the total infection events reported

General Infections

The total event rates for Infections & Infestations in the pivotal trial were higher in the NexoBrid groups than in SOC groups (34% vs. 20%). None of the infectious AEs reported on NexoBrid or SOC were considered treatment-related and nominal differences in infection rates between treatment groups depend on very few reports and from open-label trials. Urinary tract infections (UTI, proteus infection), skin and soft tissue infections (burn & wound infection, pustules, cellulitis, graft infection, staphylococcal infection) and systemic infections (sepsis, infection, bacteraemia) occurred with slightly higher frequency in the NexoBrid cohort.

Preferred terms of infectious AEs (under System Organ Class of Infections and Infestations) reported during the pivotal study MW2004-11-02.

Table 1- Infections & Infestations SOC AEs in Pivotal study MW2004-11-02 - normalized per total events and total patients treated in the study

		NexoBrid Tot. events=187		SOC Tot. events=120		NexoBrid Tot. Patients=100		SOC Tot. Patients=81	
SYSTEM ORGAN CLASS	PREFERRED TERM	N	%	N	%	N	Normalized Per patient	N	Normalized Per patient
Infections and infestations	Application site pustules	2	1.07	0	0.00	2	0.02	0	0.00
	Bacteraemia	1	0.53	0	0.00	1	0.01	0	0.00
	Dengue fever	1	0.53	0	0.00	1	0.01	0	0.00
	Fungal infection	2	1.07	0	0.00	2	0.02	0	0.00
	Infection	4	2.14	2	1.67	4	0.04	2	0.02
	Pneumonia	0	0.00	2	1.67	0	0.00	2	0.02
	Proteus infection	1	0.53	0	0.00	1	0.01	0	0.00
	Scarlet fever	1	0.53	0	0.00	1	0.01	0	0.00
	Sepsis	3	1.60	1	0.83	3	0.03	1	0.01
	Skin graft infection	1	0.53	0	0.00	1	0.01	0	0.00
	Staphylococcal bacteraemia	0	0.00	1	0.83	0	0.00	1	0.01
	Staphylococcal infection	2	1.07	1	0.83	2	0.02	1	0.01
	Tinea cruris	1	0.53	0	0.00	1	0.01	0	0.00
	Tonsillitis	1	0.53	0	0.00	1	0.01	0	0.00
	Urinary tract infection	6	3.21	1	0.83	6	0.06	1	0.01
	Wound infection	8	4.28	8	6.67	8	0.08	8	0.10
Total		34	18.2	16	13.3	34	0.34	16	0.20

In the safety database, the rate of general infections was seen to be higher in NexoBrid debrided patients than in SOC debrided patients. Data on timing of occurrence of infections were not available.

Table 8- Burn-related general infection events reported in the clinical development

Burn related infections	NexoBrid (N=218)		SOC (N=127)		Vehicle (N=44)		Vehicle + SOC (N=171)	
	N events	Events per total patients	N events	Events per total patients	N events	Events per total patients	N events	Events per total patients
	13	0.060	4	0.031	3	0.068	7	0.041

Table 9- Non-burn-related general infection events reported in the clinical development

Non-burn related infections	NexoBrid (N=218)		SOC (N=127)		Vehicle (N=44)		Vehicle + SOC (N=171)	
	N events	Events per total patients	N events	Events per total patients	N events	Events per total patients	N events	Events per total patients
	19	0.087	6	0.047	7	0.159	13	0.076

Given the limited size of the safety database for the development programme, a clear pattern that would indicate an increased infection risk associated with a product for local, topical application, cannot be established. Taking into account the still limited information, the need to be observant regarding systemic and local infection following treatment with NexoBrid is highlighted in the SmPC, and infection is included as an identified risk for targeted follow-up within the RMP.

Antibiotic use

Analysis of normalized, total antibiotic use per patient's weight in the pivotal study MW2004-11-02 shows that "normalised" therapeutic use of antibiotics was 1.33 times higher for the NexoBrid arm than for SOC (0.729 vs 0.545) and 1.75 times higher in the phase II pivotal trial.

Table 3- Antibiotics administered during study MW2004-11-02 normalized per patients' weight

	NexoBrid	SOC
Normalized per patient's weight- Prophylactic use (g*day/kg)	0.524	0.510
Normalized per patient's weight- Therapeutic use (g*day/kg)	0.729	0.545

Table 4- Antibiotics administered during study MW2002-04-01 normalized per patients' weight

	NexoBrid	SOC
Normalized per patient's weight- Prophylactic use (g*day/kg)	0.452	0.477
Normalized per patient's weight- Therapeutic use (g*day/kg)	0.625	0.358

However, this difference was not replicated in the normalization per days of antibiotics used (number of Days of Therapy = DOT) where the mean duration of antibiotics per patients was shorter in the NexoBrid group (10.1 vs 11.9 for prophylactic use and 18.2 vs 21.9 therapeutic use). The use of antibiotics in late autografted patients was not increased in the NexoBrid arm.

Pain medication

In order to quantitate the aggregate utilisation of pain medication, the total dose of a specific drug group prescribed to a patient was divided (normalized) by the patient's weight. These scores were summed up together according to the relevant Second level ATC group and divided by the total number of patients at each study group (NexoBrid or SOC), resulting in a normalized Drug/patient/Kg value that represents the actual dose of drugs/patient for the entire treatment duration (Table 122.9.)

Table 122.9- Normalized Analgesia/Anesthesia medications per patient given in study MW2004-11-02

SECOND LEVEL ATC	FOURTH LEVEL ATC	Normalized DGD (N=98)	Normalized SOC (N=78)
Analgesics	Anilides	27.4651	35.9775
	Benzomorphan derivatives	0.0701	0.0079
	Diphenylpropylamine derivatives	0.1420	0.1775
	Natural opium alkaloids/ Other opioids	9.2766	5.7406
	Oripavine derivatives	0.0005	0.0002
	Other analgesics and antipyretics	0.0004	0.0000
	Phenylpiperidine derivatives	4.5399	5.9357
Anesthetics	Amides	0.0770	0.0023
	Barbiturates, plain	0.5174	0.1817
	Halogenated hydrocarbons	0.2993	0.6552
	Opioid anesthetics	0.0782	0.4761
	Other general anesthetics	6.1832	6.9244
	Other opioids	0.0028	0.0000
	Total Analgesia	80.491	85.045
	Total Anesthesia	7.158	8.240

Similar doses of analgesics and anaesthetics were given to patients during the study in the NexoBrid arm as compared to the SOC arm.

Serious adverse event/deaths/other significant events

Serious Adverse Events

Twenty-five subjects had 31 serious adverse events (SAEs), only one of which was considered possibly related to study treatment, i.e. skin graft failure that necessitated re-hospitalization for re-grafting. All other SAEs were considered unrelated or remotely related to study treatment.

Summary of Serious Adverse events occurring in the Clinical Development Program of NEXOBRID

Study No.	**SAE**	**Subject No.**	**Treatment Group**	**Relatedness**
MW 2001-10-03	None	N.A.	N.A.	N.A.
MW 2002-04-01	Skin graft failure	09B010	NEXOBRID	Possibly related
	Pain in extremity, oedema peripheral	10A062	NEXOBRID	Not related

Study No.	SAE	Subject No.	Treatment Group	Relatedness
	Dyspnoea DVT	10A102	NEXOBRID	Not related
	Epilepsy	25A078	NEXOBRID	Not related
	Graft infection	12A001	Vehicle	Not related
	Wound infection	20C003	Vehicle	Not related
	Wound decomposition	35B019	Vehicle	Not related
	Skin graft failure	23A059	SOC	Not related
	Depressed level of consciousness	37B023	SOC	Not related
MW 2005-10-05	Mental disorder	10A003	Vehicle	Unknown
MW 2004-11-02	Disseminated intravascular coagulation	02B015	NEXOBRID	Not related
	Anaphylactic shock		NEXOBRID	Not related
	Systemic sepsis/wound infection	39A005	NEXOBRID	Not related
	Sepsis / systemic inflammatory response syndrome (SIRS)	40B001	NEXOBRID	Remotely related
	Wound opening due to fall	45A027	NEXOBRID	Not related
	Wound breakdown	23B001	NEXOBRID	Not related
	Mental deterioration	03B001	NEXOBRID	Not related
	Psychoactive drug induced acute psychotic event	41A005	NEXOBRID	Not related
	Functional disability in neck movement because of hypertrophic scars	26A012	NEXOBRID	Not related
	DVT	39A006	NEXOBRID	Remotely related
	Tinnitus	26B014	SOC	Not related
	Sepsis	41A012	SOC	Not related
	Atelectasis		SOC	Not related
	Wound infection	25B015	SOC	Not related
	Reopening of the wound	25A007	SOC	Not related

Study No.	SAE	Subject No.	Treatment Group	Relatedness
	Worsening of neurogenic overactive bladder	26A011	SOC	Not related

Source: MW 2001-10-03, MW 2002-04-01, MW 2005-10-05, MW 2004-11-02,

Deaths

Six deaths occurred during the clinical development program. There were 5/362 (1.4%) deaths in the NEXOBRID group (all considered not related to NexoBrid by both the investigator and DSMB) and 1/127 (0.8%) in the SOC group.

Summary of Deaths (final diagnosis) Occurring in the Clinical Development Program of NEXOBRID

Study No.	Subject	SAE name	Treatment Group	Relatedness
MW 2002-04-01	14A021	Multi-system organ failure (MSOF), sepsis	NEXOBRID	Not related
	35B018	Respiratory failure	NEXOBRID	Not related
	37B026	Vomiting and aspiration	NEXOBRID	Not related
	37B089	Tachypnoea	NEXOBRID	Not related
MW 2004-11-02	34B105	MSOF	NEXOBRID	Not related
	45A028	Murdered	SOC	Not related

Four deaths occurred in study MW 2002-04-01 in the NEXOBRID treatment group (Subjects 14A021, 35B018, Subject 37B026, and 37B089)

Subject 14A021 was a 69-year-old male subject with a medical history of heavy smoking (>30 cigarettes/day for 50 years). Existing co-morbidities were emphysema, hypertension, hepatitis C, several bleeding episodes of peptic ulcer which required transfusions, diabetes mellitus type 2, hypercholesterolemia, and mild von Willebrand's disease. This subject probably suffered from Smoke Inhalation (SI) injury during the accident (fell head first into burning pit). The subject was admitted to hospital with deep burns of 28.5% TBSA and was intubated and sedated on the intensive care unit (ICU). Only one TW of 4% TBSA was successfully treated with NEXOBRID while the non TWs were treated by SOC which included five surgical tangential excision and skin grafting procedures. One month post-op, still ventilated and on ICU, the subject developed Methicillin Resistant Staph. Aureus (MRSA) sepsis with and disseminated idiopathic coagulopathy (DIC) leading to MSOF and died 70 days after NEXOBRID treatment with most of his burns healed.

Subject 35B018 was a 45-year-old debilitated (weighing 45 kg), alcoholic, heavy smoker with COPD and a pre-existing purulent bronchopneumonia male. He had a 3-day history of acute purulent bronchopneumonia. He was admitted with 13% TBSA burns, of which only a single 7% TW was treated with NEXOBRID. His bronchopneumonia did not improve and 9 days post NEXOBRID treatment, he developed respiratory failure necessitating intubation and mechanical ventilation. *Klebsiella* was cultured from his tracheobronchial secretions, and may have had a secondary septicaemia. He expired 14 days after NEXOBRID treatment to only one of his wounds.

Subject 37B026 was 49-year-old male subject, admitted with 29.5% TBSA burn of which only 12.5% was defined as a TW and treated with NEXOBRID. Prior to treatment, scant aerobic organisms were detected in blood cultures, and *Klebsiella pneumoniae* were detected in wound cultures. Two days had abdominal distension, severe projectile vomiting and aspiration. The subject expired with acute respiratory failure less than two hours after aspirating. His abdominal distension could not be explained.

Subject 37A089 was a 21-year-old female subject that was admitted with self-inflicted kerosene burns over 27% TBSA of which only 7% were defined as a TW and treated with NEXOBRID. In addition, this subject had pre-existing COPD, pulmonary hypertension and probably smoke inhalation. She expired 12 days post NEXOBRID treatment in an acute respiratory failure. The autopsy report and independent opinions of two experts regarding the cause of death, all point to COPD, pre-existing cardiopulmonary disease, kerosene fumes and smoke inhalation, leading to intra-alveolar haemorrhage and acute respiratory failure and hypoxic encephalopathy.

All four subjects had significant pre-existing co-morbidity present at the time of enrolment including COPD, bronchopneumonia, infection, SI that developed into septicaemia, all of which represented exclusion criteria and very well known as predictors of complications, morbidity and mortality. Subject 37B026 died of acute aspiration pneumonitis following vomiting that is quite frequent in the burn acute phase (acute gastric dilatation, medication etc.). No causal relationship between these deaths and NEXOBRID treatment could be established by the investigators or the DSMB.

Two deaths occurred in study MW 2004-11-02, one in the NEXOBRID group (Subject 34B015) and one in the SOC group (Subject 45A028).

Subject 34B015 was a 51.4-year-old Caucasian male with no medical history, who presented with 25% TBSA II-III degree flame burns to both lower arms, right hand, both thighs, and left leg (target wounds), and to his head and neck (non-target wounds) caused by an explosion of gun-powder he was carrying. Several days after application of NEXOBRID he was transferred to ICU after developing pulmonary dysfunction with dyspnœa and pleural effusion. He suffered a cardiac arrest two days later, and expired. Autopsy revealed upper respiratory tract changes due to the burn. The causes of death were cardiac arrest following burn pulmonary trauma (burn and SI) followed by septic shock (though no bacteraemia has been found) and MSOF. The DSMB concluded unanimously that there was no association between the application of NexoBrid and the subsequent pulmonary damage and the cardiac arrest.

Subject 45A028 was a 23.9-year-old Caucasian male with no medical history, who presented with burns to both arms, including hands (TWs), and to his head and anterior trunk (non-TWs). He received SOC treatment. 95 days after starting study treatment the subject was murdered. This SAE was determined to have not been study treatment-related.

<u>Other Observations Related to Safety</u>

Scarring

Scarring assessments were made on a scale of 0-3, representing 'none' to 'severe' scarring. At all time intervals in study MW 2004-11-02, approximately 50% of subjects in the NEXOBRID and SOC groups had mild scarring, whereas the other 50% had none or moderate scarring. At the final three-month evaluation, there were more subjects in the NEXOBRID group with 'none' (37/179 wounds, 20.7%, vs. SOC 24/137, 17.5%) and fewer with 'severe' (2/179, 1.1%, vs. 4/137, 2.9%).

Summary Statistics in Scarring Assessments per Wound by 3 Groups (Safety Population)

				RANDOMIZED				
		DGD TRAINING N=26 (61 WOUNDS)		DGD N=74 (163 WOUNDS)		SOC N=81 (170 WOUNDS)		
		N (Wounds)	%	N (Wounds)	%	N (Wounds)	%	P VALUE
MONTH 1	N (Wounds)	44	100.0	138	100.0	148	100.0	0.5871
	(0) NONE	16	36.4	27	19.6	39	26.4	
	(1) MILD	15	34.1	88	63.8	88	59.5	
	(2) MODERATE	12	27.3	22	15.9	20	13.5	
	(3) SEVERE	1	2.3	1	0.7	1	0.7	
MONTH 2	N (Wounds)	44	100.0	121	100.0	126	100.0	0.5482
	(0) NONE	12	27.3	23	19.0	30	23.8	
	(1) MILD	23	52.3	75	62.0	67	53.2	
	(2) MODERATE	9	20.5	22	18.2	27	21.4	
	(3) SEVERE	0	0	1	0.8	2	1.6	
MONTH 3	N (Wounds)	41	100.0	138	100.0	137	100.0	0.8068
	(0) NONE	9	22.0	28	20.3	24	17.5	
	(1) MILD	23	56.1	79	57.2	80	58.4	
	(2) MODERATE	9	22.0	29	21.0	29	21.2	
	(3) SEVERE	0	0	2	1.4	4	2.9	

General Functional Disability

General functional disability assessments were made on a scale of 0-3, representing 'none' to 'severe' disability. There was no statistically significant difference between the NEXOBRID and SOC groups for functional disability of the TW ($p>0.17$) in study MW 2004-11-02.

Summary Statistics in General Functional Disability Assessments

		DGD N=100 (224 Wounds)		SOC N=81 (170 Wounds)	
		N (Wounds)	%	N (Wounds)	%
Month 1	N (Wounds)	187	100.0	148	100.0
	(0) None	168	89.8	126	85.1
	(1) Mild	16	8.6	19	12.8
	(2) Moderate	2	1.1	3	2.0
	(3) Severe	1	0.5	0	0
Month 2	N (Wounds)	168	100.0	126	100.0
	(0) None	146	86.9	108	85.7
	(1) Mild	14	8.3	16	12.7
	(2) Moderate	8	4.8	2	1.6
	(3) Severe	0	0	0	0
Month 3	N (Wounds)	179	100.0	137	100.0
	(0) None	153	85.5	123	89.8
	(1) Mild	17	9.5	11	8.0
	(2) Moderate	9	5.0	3	2.2
	(3) Severe	0	0	0	0

In a comparison by wound size, there was no consistent pattern in the proportion or severity of disability associated with %TBSA, time interval, or study group.

Blood Transfusions and clotting parameters

In study MW 2004-11-02 more blood transfusions were required in the NexoBrid arm compared to SOC (20% vs. 17.3%) (mean whole blood transfused 2245ml vs. 714.7ml). Of these subjects a similar numbers in the NEXOBRID and SOC groups had AEs of anaemia (10/20, 50% and 8/14, 57%, respectively). Either whole blood or packed blood cells were administered.

Blood transfusions were less common among subjects with smaller burns compared to greater %TBSA burns.

Summary Statistics in Blood Transfusions (SAFETY POPULATION)

			DGD N=100		SOC N=81		
			N	%	N	%	P VALUE
RECEIVED BLOOD TRANSFUSIONS		N	100		81		0.6418
		YES	20	20.0	14	17.3	
		NO	80	80.0	67	82.7	
VOLUME OF BLOOD TRANSFUSED (mL)	PACKED BLOOD CELLS	N	15		3		0.9227
		MEAN	1142.8		1040.0		
		SD	1743.7		690.9		
		MEDIAN	482.0		1000.0		
		MIN	250.0		370.0		
		MAX	5750.0		1750.0		
	WHOLE BLOOD	N	6		11		0.4295
		MEAN	2245.0		714.7		
		SD	4346.2		631.7		
		MEDIAN	375.0		400.0		
		MIN	270.0		200.0		
		MAX	11100.0		2400.0		

Post hoc analyses undertaken by the Applicant suggest that the majority of blood transfusions that were administered to NexoBrid debrided patients occurred either pre, peri or post-surgically and were not related to debridement with NexoBrid.

Event	NexoBrid	SOC	Comments
Incidence of transfusions:			
Overall	20.0% (20/100)	17.2% (14/81)	Total surgery-related
Late autografted	28.9% (13/45)	40.0% (10/25)	91.2% (31/34)
Surgery-related	85% (17/20)	100% (14/14)	
Mean volume:			
All patients	1,500 mL	832 mL	
Without "outliers" *	439 mL	660 mL	
Late autografted	2,025 mL	968 mL	
Without "outliers" *	448 mL	742 mL	

* The "outliers" represent 4 patients with extensive deep burn >20% TBSA with severe co-morbidities undergoing several surgical procedures (Latex-related anaphylactic shock and DIC, late extensive grafting; severe smoke inhalation)

In the NexoBrid arm, on average, patients received blood transfusion 14 days after the start of NexoBrid application. Based on the PK profile of NexoBrid with T1/2 of approximately 12 hours, at 14 days following NexoBrid application, no material is detected in the blood of treated patients, therefore the need for blood transfusion is probably related to post-debridement surgical procedures that are known to involve blood loss. Out of the 20 patients who received blood in the NexoBrid arm:

Sixteen (16) patients (80%) were transfused as part of the autografting procedure, not in proximity to the debridement (more than 5 days post debridement) as presented in Table below. Six patients out of the 16 who received late blood transfusions (38%) suffered from late anaemia during the wound healing phase.

Two patients (10%) received blood transfusion on the same day as NexoBrid treatment; the blood transfusion was indicated to treat pre-existing anaemia that was diagnosed prior to NexoBrid treatment.

Additional two patients received blood less than 5 days after the start of NexoBrid application, one patient received blood on the same day that surgical excision was performed due to pre-debridement anaemia of 4.7 mmol/L Hb, and one patient due to reported pre existing anaemia (4.5 mmol/L Hb).

Table 12- Timing of blood transfusion per patient

	NexoBrid N=20	SOC N=14
On Debridement day	Anemia on admission 2 (10%)	4 (28.6%)
1-5 days post debridement	2 (10%)	7 (50.0%)
6-10 days	6 (30%)	1 (7.1%)
11-20 days	6 (30%)	2 (14.3%)
>20 days	4 (20%)	0 (0%)

In the NexoBrid group there were three patients who received a large amount of blood: patients 02B015, 05B001 and 40B001. The common denominator among these patients was that all had extensive, deep burns necessitating several episodes of grafting due to burn characteristics (see Table 7).

Table 7- Patients receiving large amounts of blood transfusion

Patient	% TBSA (DPT,FT)	Pre and Co morbidities	Debridement dates	Time to first excision from debridement.	No. of Exc. and date	Autografting dates	Transfusion (Blood & blood products)
05B001	25.5% (3.5, 19.5)	-Gastrectomy -Chr. Anemia -Depression	31/05/2006; 01/06/2006	14 days	14/06/2006; 19/06/2006; 28/06/2006; 12/07/2006; 07/07/2006; 12/07/2006	14/06/2006; 19/06/2006; 28/06/2006; 12/07/2006; 07/07/2006	5750 ml
40B001	23.5% (13.5,6)	-Smoke Inhal. -Leucocytosis	03/06/2006; 04/06/2006	11 days	14/06/2006	14/06/2006	11100ml
02B015	25.5% (17,6.5)	-Epilepsy -DIC (Latex)	18/10/2006	21 days	08/11/2006 27/10/2006 28/11/2006	08/11/2006 27/10/2006 28/11/2006	5000 ml

None of the NexoBrid-treated patients had treatment-related bleeding in the debridement period and no bleeding has been observed following NexoBrid use by the investigators or in the post debridement periods.

Clotting parameters were collected retrospectively from the files of patients previously enrolled into study MW2004-11-02 who agreed to participate in the scar assessment follow-up study MW2012-01-02. PT and PTT results are presented in Table 8 and Table 9.

Available PT and PTT results were within the normal ranges in the 48-hrs period post debridement and in the overall period post debridement.

There were no differences in PT between the 2 arms, NexoBrid and SOC.

Most of the patients (in both arms) with PTT results above the normal ranges that were included in Table 9 were on anticoagulation therapy in the same period that the blood tests were performed.

Table 8- PT Results

	NexoBrid						SOC					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Normal ranges 10- 20 sec.												
Before Treatment	5	13.1	1.1	13.0	11.5	14.2	3	14.0	3.0	13.1	11.6	17.4
48 Hrs post Treat.	2	13.7	1.7	13.7	12.5	14.8	3	12.8	2.2	11.7	11.4	15.4
Post Treatment	12	12.3	3.7	13.1	11.0	15.3	6	13.8	2.7	13.0	11.4	18.2

Table 9- PTT Results

	NexoBrid						SOC					
	N	Mean	Std	Median	Min	Max	N	Mean	Std	Median	Min	Max
Normal ranges 15- 45 sec.												
Before Treatment	35	33.5	7.0	33.3	23.1	59.9	27	35.6	8.3	33.8	23.1	53.1
48 Hrs post Treat.	21	37.4	7.2	36.9	25.9	56.0	17	32.6	8.1	32.2	21.3	48.2
Post Treatment	84	40.9	13.6	37.7	25.9	116*	52	31.1	9.3	29.6	18.9	78.7

* Result was reported as clinically significant with etiology anticoagulant therapy.

Re-admissions in study MW2004-11-02

There were 11 readmissions in the NexoBrid arm. Among these events, 8/11 events (73%) were pre-planned re-admissions for autografting as part of routine burn management. Some patients in the NexoBrid arm were discharged to exploit the epithelialisation potential and to complete this process at home. Grafting was prescheduled post discharge to allow wounds to exhaust their potential for spontaneous epithelialisation and minimize grafting.

Three re-admissions (3/100 patients, 3%) in the NexoBrid arm involved an AE (Wound decomposition/ Scar event/ Open Wound) and following re-admission were reported as SAEs.

In the SOC arm, 3 re-admission had occurred; one was a planned re-admission and 2 cases (2/81, 2.5%) were due to an AE (wound infection/ wound reopening).

Laboratory findings

In general, no clinically significant changes in serum chemistry, haematology and urinalysis occurred in any treatment group at any time point. Results were similar in adults and paediatric population. Mean

levels of stress indicator glucose were elevated in both groups at both time intervals, increasing slightly post-procedure. Levels were slightly higher in the NEXOBRID group at both intervals.

In study MW 2004-11-02, changes in mean haematology parameters between the two time intervals (pre-treatment and 24 hrs post start of treatment) were similar between study groups for the majority of parameters, most being reductions. Exceptions included statistically significant smaller reductions in the NEXOBRID vs. SOC group in haemoglobin, (p=0.0061) and haematocrit (p=0.0374). In children aged 4-18 years, mean reductions from pre-treatment to 24 hrs post-treatment values were smaller in the NEXOBRID vs. the SOC yet without statistical significant due to the small sample size of this very small cohort.

Safety in special populations

Intrinsic Factors

No analyses of clinical safety data have been conducted examining the effects of intrinsic factors such as gender, height, weight, genetic polymorphism, or renal or hepatic impairment on the safety and tolerability of NEXOBRID. Analysis of safety data by age has been performed in study MW 2004-11-02. A small proportion of paediatric subjects experienced AEs relative to adults. Similar results were observed when analysed by intensity or by relation to study treatment.

Extrinsic Factors

No analyses have been performed investigating the effects of extrinsic factors such as use of tobacco, alcohol, or other drugs or dietary habits on the safety and tolerability of NEXOBRID.

Fertility, Pregnancy and Lactation

No human studies evaluating NexoBrid's effect on fertility and pregnancy have been undertaken. No clinical data on pregnancies exposed to Bromelain are available. It is not known whether Bromelain is excreted in breast milk.

Immunological events

Local Tolerance Studies

Local tolerability was evaluated in all clinical studies as part of the safety assessment.

Pruritus was one of the most frequently reported adverse event reported in NexoBrid patients and SOC patients, 15.4% and 18.9% of all subjects, respectively.

Since pruritus is well-known event to be associated with the burn disease (reported incidence of 87% [van Loey et al., 2008][12], especially with healing of dermis, it is difficult to elucidate whether pruritus is caused by the study treatment, as the result of a local intolerability reaction or by the burn disease itself.

Cutaneous, topical hypersensitivity is characterised by additional local symptoms (mainly rash of various forms) and systemic symptoms that were not reported or observed in NexoBrid clinical studies. Therefore due to the absence of local allergic related, AEs reports the cause may be due to the process of wound healing itself.

No allergic reactions to NexoBrid were reported in clinical trials. One case of allergic event was reported during the phase III study MW2004-11-02, which was considered as not related to study

12 Van Loey NE, et al., Itching following burns: epidemiology and predictors. Br J Dermatol, 2008. 158(1): p. 95-100.

drug. The event involved an anaphylactic shock caused by an allergy to Latex, to which the patient was exposed pre-operatively.

Allergic reactions to Bromelain (including anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angio-oedema, urticaria, mucosal and gastrointestinal reactions) have been reported in the literature. Suspected sensitisation following oral exposure and following repeated occupational airway exposure has been reported. In addition, a delayed-type allergic muccosa reaction (cheilitis) after longer-term oral mucosa exposure (mouthwash) has been reported.

Bromelain allergy is believed to be highest in individuals with sensitivity to pineapples. In one study of a specialised tertiary hospital for allergic diseases, it is estimated to affect 1.2% of the general population [Ortega et al, 2004] [13]. Anaphylaxis has been reported in 62.5% (20/32) of cases of systemic pineapple allergic reaction [Kabir et al 1993][14].

The only published incidence of allergy to oral Bromelain are 8 cases of allergic reactions that have been reported after consumption of 3.5 million Bromelain pills over 7 years [Maurer et al, 2001][15]. The allergy was expressed as urticaria/rash and was controlled by antihistamine medication.

The Applicant has included the warning in Section 4.4 of the SmPC of reported cases of allergic reactions to Bromelain in the literature as well as cross-sensitivity between Bromelain and Papain as well as latex proteins. Allergic reaction was also included as important identified risk in the Risk Management Plan.

Safety related to drug-drug interactions and other interactions

Non-clinical studies showed that silver sulphadiazine and povidone-iodine had an inhibitory effect on the debriding activity, whereas mafenide acetate and gentamicin sulphate did not appear to negatively influence the debriding activity when used prior to treatment.

There are no non-clinical studies addressing pharmacokinetic drug interactions. Such interactions affecting the efficacy of the product are not expected owing to the nature of the product (protease enzyme). Nevertheless since Bromelain consists of cysteine proteases, it cannot be excluded that they, if present in sufficiently high circulation concentrations, could inhibit drug metabolising enzymes.

A single in vitro study using human microsomes demonstrated potent inhibition of CYP2C9 activity. To what extent these data predict the ability of NexoBrid to induce clinically relevant enzyme inhibition is not known. A relevant statement was included in the SmPC that this potential for cytochrome CYP2C9 should be considered in patients treated with substrates of CYP2C9, such as warfarin and phenytoin (see 4.5 of the SPC).

Discontinuation due to adverse events

Across all studies, no subject withdrew due to an AE or an SAE except for cases of death. There were two premature discontinuations in study MW 2002-04-01 during administration of study treatment, one in the NexoBrid group (with the subject withdrawing after two minutes of treatment), and one

[13] Ortega EV, et al., Most common allergens in allergic patients admitted into a thirdlevel hospital. Rev Alerg Mex, 2004 **51**(4): p. 145-50.
[14] Kabir I, Speelman P, and I. A., Systemic allergic reaction and diarrhoea after pineapple ingestion. Trop Geogr Med., 1993. **45**(2): p. 77-9.
[15] Maurer HR, Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci, 2001. **58**(9): p. 1234-45.

subject in the SOC group who withdrew during SOC treatment. Subjects who did not complete the studies did so mainly because they did not return to the scheduled visits post-treatment and were lost to follow-up.

Post marketing experience

Post-marketing data are not yet available. NexoBrid has not yet been marketed in any country.

2.6.1. Discussion on clinical safety

Around 350 patients were exposed to NexoBrid of which, a total of 180 patients participated in controlled studies and were exposed to NexoBrid (2 g NexoBrid powder/20 g of Vehicle gel/1% TBSA). The most frequently reported adverse event in the NexoBrid arm was pruritus, occurring at an incidence of 20.9% in the pivotal study, MW 2004-11-02. The next most frequent AE was anaemia occurring at a similar incidence in both treatment groups (6.3% in both groups). Overall, NexoBrid treatment was not found to be associated with a significantly increased risk of serious or severe adverse events compared to standard of care. Serious infections occurred with similar frequency in the SOC and NexoBrid cohorts and the incidence was low (2 NexoBrid; 2 SOC in study MW2004-11-02).

Wound pain and local wound infections were experienced more frequently by NexoBrid treated patients than by those receiving SOC in the phase II study, MW2002-04-01. However, the implementation of corrective measures in the phase III and later studies, including application of dressings soaked with antibacterial solution (e.g. 3-5% sulfamylon or 0.05-0.5% chlorhexidine) to wounds and administration of appropriate preventive analgesia medication as currently used in SOC and now adaequately reflected in the SmPC eradicated any differences between the two treatment arms. Changes to the definitions of certain adverse events (e.g. wound infection classified as such only if supported by confirmatory biopsy and pain reported if only out of keeping with that normally experienced by a burns patient) occurred between the phase II and III studies.

A slightly higher rate of wound complications was observed in the NexoBrid arm, which included graft failure, wound decomposition, scar events and 'wound complications'; however the study DSMB and investigators did not attribute the majority of these events, at least possibly, to NexoBrid or other underlying cause. It is acknowledged by the CHMP that the diagnosis of infection in burn care is difficult and can be ascertained only if well defined criteria are fulfilled. However the CHMP notes that the slightly higher rate in wound complications may be the result of to longer TTCWC seen in certain wounds following delayed grafting (see also discussion on efficacy). Therefore it was considered imperative by the CHMP to make appropriate wound management following the treatment with Nexobrid part of the planned educational material for health care professionals. These adverse events have been clearly labelled in sections 4.4 and 4.8 of the SmPC and appropriate guidance to health care professionals is given in 4.2 of the SmPC to minimise the risk of infection. Further the planned survey drug utilisation study (MW2013-06-01) will evaluate the effectiveness of the applied risk minimisation activities.

Analyses of infectious adverse events from the NexoBrid clinical development programme were presented. For a number of individual infection PTs (e.g. pneumonia) and groups of infections, the incidence rates were lower than reported in the literature. The total event rates were higher in the NexoBrid groups than in SOC groups. (e.g. in the pivotal study: 34% vs. 20%) although causal relationship was not established. In the same context a number of analyses of antibiotic use showed a slightly greater therapeutic use of antibiotics in NexoBrid patients than SOC patients. The therapeutic use of antibiotics (dose administered normalized per patient weight) was 1.75 times higher for the

NexoBrid arm than SOC in the phase II study and 1.33 times higher in the phase III pivotal trial where corrective measures were applied. It is acknowledged by the CHMP that patients randomised to NexoBrid debridement of wounds, especially the ones who had delayed autografting and wound closure (see discussion on efficacy), may have been subject to a number of additional wound dressing changes and interference of wounds. Further CHMP notes that nearly all infections were classified as mild or moderate in intensity and resolved with appropriate treatment and appropriate discussion of infection risks has been incorporated in the SmPC. Further it is considered by the CHMP that this possible excess risk is associated with the delay in TTCWC or in autografting NexoBrid-debrided wounds rather than the product itself. The appropriate statements in SmPC and the planned risk minimisation activities are taking this into account.

In the pivotal study, more blood transfusions were required for the NexoBrid arm than the SOC arm (20% vs. 17.3%) (mean whole blood transfused 2245 ml vs. 714.7 ml). More patients with NexoBrid treated wounds ≥5% - ≤15% TBSA received blood transfusions 12.7% (NEXOBRID) vs. 8%(SOC) and a number of NexoBrid treated patients with wounds >15% TBSA received large transfusions compared to SOC patients. Max. Packed cells transfused: 5750 ml (NEXOBRID) vs. 1750 ml (SOC). Max. whole blood transfused: 11,000 ml (NEXOBRID) vs. 2400 ml (SOC). The Applicant provided further information which did not suggest that NexoBrid treated patients suffered haemorrhages and bleeding events. The information provided instead revealed that a small number of patients with large wounds underwent a number of surgical excisions post-NexoBrid debridement which required large transfusions to correct anaemia or to replace blood lost post-surgical excision. A simple holistic analysis of the data demonstrated that 31/34 (91.2%) of the blood transfusions in the pivotal study were in proximity to and clearly associated with a surgical procedure, regardless of the study arm, vs. 0/20 (0%) in proximity and associated with NexoBrid debridement. The data also showed that NexoBrid treated patients who required transfusions received these approximately two weeks after NexoBrid treatment. The CHMP therefore considers that the observed increase in transfusions in the NexoBrid study arm is not related to a direct effect of NexoBrid, but likely due to increased blood loss known to occur with late grafting (and surgical excision) of wounds. This view was also shared by the ad hoc expert advisory group to CHMP. Adequate warnings were placed in the SPC (section 4.4 & 4.5) and the risk management plan indicates increased tendency to bleeding as important potential risk, which will be further elucidated with studies MW2012-01-01 and MW2008-09-03.

With regard to use of analgesics and anaesthetics, overall use was similar between study arms, where it could have been expected for use of such agents to be lower with a topical treatment than with surgery and other non-surgical treatments. The lack of difference in analgesic and anaesthetics use is considered to be be due to pain medication required for dressing changes which may have occurred more frequently for NexoBrid debrided wounds as time to placement of autografts was significantly longer for these wounds than SOC treated wounds. Current data on use of analgesia and anaesthesia in the pivotal study do not support any assertion that NexoBrid treatment is associated with less pain than SOC. However, data presented during the procedure do show that it is associated with less surgery (whether or not related to debridement) than SOC.

There were 5 deaths from medical reasons in NexoBrid patients vs. none in the SOC group (1 patient in the SOC group was murdered). Neither analysis of the narratives, nor investigator opinion, nor the DSMB have associated NexoBrid with the deaths in patients that received the treatment. Most of the NexoBrid treated subjects who died had significant pre-existing morbidity. 4 of the 5 NexoBrid patients had pulmonary disease or suffered injury related pulmonary consequences (smoke inhalation, burn pulmonary trauma, COPD, bronchopneumonia). Currently, a biologically plausible mechanism for the interaction of NexoBrid and pre-existing pulmonary or cardiopulmonary disease is difficult to establish. However, a caution for use in such patients has been added to the SmPC.

The general functional disability and scarring assessments initially performed in the phase III pivotal study were considered of limited value with regard to the choice of assessment measure or length of assessment period. In study MW2012-01-02 treated wounds of patients originally enrolled in the pivotal study were assessed using the modified Vancouver scar score (MVSS) assessment measure, a modified version of the validated VSS measure using blinded assessors. In addition, quality of life and patient function was evaluated with the SF-36 and Burn outcomes questionnaire (BOQ [paediatric patients only]) measures. In total, approximately 50% and 46% of the originally assessed NexoBrid and SOC treated wounds respectively were re-evaluated. The overall MVSS data suggest no difference in long-term cosmetic outcome between the two groups. However the effect of any bias on the main study results remains difficult to estimate, given the limitations of the study design and methods. Data on the quality of donor site scars were made available showing that they were at least comparable between NexoBrid and SOC and within the expected MVSS range for donor sites. However, from a quantitative standpoint, NexoBrid patients had fewer and smaller donor site scars. Unfortunately like the MVSS treatment wound data only approximately 50% of the patients enrolled into MW2004-11-02 were available for evaluation. The same uncertainties exist for these data as they do for the overall MVSS data from study MW2012-01-02. Analyses presented during the procedure show that a similar amount of time had elapsed post initial treatment in both arms and that there appeared to be minor improvements in scar quality in both arms over time. It should be noted however that the latter results represent one-off data from subgroups of patients at different stages of follow up rather than follow up of a single cohort. In summary CHMP considers the long-term follow-up of cosmetic outcome in patients in the pivotal study not optimal. A number of uncertainties still exist regarding the influence of baseline imbalances on the overall MVSS data presented and the applicability of the presented MVSS data on approximately 50% of the patients initially enrolled in MW2004-11-02 to the entire cohort randomised in the pivotal study. The submitted SF-36 data do not suggested worsening of QoL or function in the NexoBrid arm. However the data suffer the same uncertainties as the MVSS data noted above. The use of the SF-36 to evaluate the adult QOL is accepted but in future studies a clinically accepted, validated burns specific QoL measure should be used in conjunction with the SF-36 to provide supportive data. Nevertheless, the totality of the data does not suggest that the long-term cosmetic outcome of DPT or FT wounds treated with NexoBrid is worse than those treated with SOC. This is in line with sentiments expressed by the ad hoc expert group that the experimental treatment is not expected to impact the outcome of the overall burn treatment. The long-term cosmetic and fiunctional outcome has been addeded as missing information in the risk management plan, and additional data will be generated through studies MW 2014-01-01 and MW 2010-03-02.

2.6.2. Conclusions on the clinical safety

The most commonly reported adverse reactions of the use of NexoBrid are local pain and transient pyrexia/hyperthermia. When NexoBrid was used in a regimen which included recommended preventive analgesia as routinely practiced for extensive dressing changes in burn patients as well as antibacterial soaking of the treatment area before and after NexoBrid application, pain was reported in 3.6% of patients, pyrexia/hyperthermia in 19.1% of patients. The frequency of pain and pyrexia/hyperthermia was higher without these precautionary measures.

Several safety aspects were noted in the NexoBrid treatrment arms of the clinical studies, however the data suggest that at least a part of them are not associated to Nexobrid but to differences in the post-debridement strategy between the study arms, which is now known to be the difference in time to placement of autografts. The SmPC and the planned educational material provide appropriate guidance to the treating physician in specialised burn centers to assure early grafting of wounds with FT areas and the planned risk minimisation activities will be monitored within a retrospective drug utilisation study.

The data on long-term follow-up of cosmetic and functional outcomes indicate no detrimental effects. However CHMP takes into account that the ad hoc expert group rated long term cosmetic and functional outcome the most important clinical outcome measure. Therefore, the Applicant will further investigate long-term cosmetic outcome in a future multicentre randomised control trial as identified in the risk management plan.

The CHMP considers the following measures necessary to address issues related to safety:

Description	Due date
The MAH shall conducts a study on enzymatic debridement in burns patients (children and adults): A comparison to standard of care (protocol MW2010-03-02), based on a CHMP approved protocol.	31/03/2017

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

Details have been provided of the Teva pharmacovigilance system (Version 9 dated June 2010). A statement signed by the Applicant and the qualified person for pharmacovigilance, indicating that the Applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP consider that the Pharmacovigilance system as described by the Applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The CHMP recommends updating the flowcharts illustrating the flow of safety reports with timelines for the major processing steps with the next routine update to the DDPS.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

SUMMARY OF THE EU RISK MANAGEMENT PLAN

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Identified Risks		
Pain	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: ▪ Retrospective, drug utilisation study (MW2013-06-0, titled: "Drug utilisation study in real life burn unit setting in burn patients treated with NexoBrid."	Routine risk minimisation (labelling) ▪ Section 4.2 (Posology and method of administration): - "Pain management must be used as commonly practiced for an extensive dressing change; it should be initiated at least 15 minutes prior to NexoBrid application" ▪ Section 4.8 (Undesirable effects) Educational materials Training
Pyrexia/ hyperthermia	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: ▪ Retrospective, drug utilisation study (MW2013-06-01)	Routine risk minimisation (labelling) ▪ Section 4.2 (Posology and method of administration): - Under 'Preparation of Patient' and Wound Area' and 'Removal of NexoBrid': "Dressing soaked with an antibacterial solution must be applied for 2 hours". ▪ Section 4.8 (Undesirable effects) Educational materials Training
Wound infection	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: Retrospective, drug utilisation study (MW2013-06-01)	Routine risk minimisation (labelling) ▪ Section 4.2 (Posology and method of administration): - "Under Method of administration "Dressing soaked with an antibacterial solution must be applied for 2 hours". ▪ Section 4.4 (Special warnings and precautions for use): - under 'Monitoring': "In addition to routine monitoring …, patients treated with NexoBrid should be monitored for: ▪ Signs of local and systemic inflammatory and infectious processes". Educational materials Training
Delayed time to complete wound closure	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: 1. Retrospective, drug utilisation study (study MW2013-06-01) 2. A multicenter, multinational, randomized, controlled, open-label study, performed insubjects with thermal burns, to evaluate the efficacy and safety of NexoBrid as compared to standard of care (SOC) treatment (study MW2010-03-02)	Routine risk minimisation (labelling) ▪ Section 4.2 Wound care after debridement: "Wounds with areas of full-thickness and deep burn should be autografted as soon as possible after NexoBrid debridement. Careful consideration should also be given to placing permanent skin covers (e.g. autografts) on deep partial thickness wounds soon after NexoBrid debridement." ▪ Section 4.4 (Special warnings and precautions for use): - Under '<u>Prevention of wound complications</u>': "In NexoBrid studies wounds with visible dermal remnants were allowed to heal by spontaneous epithelialisation. In several cases adequate healing did not occur and autografting was required at a later date, leading to significant delays in wound closure which is associated with increased risk of wound-related complications. Therefore, wounds with areas of full-thickness and deep burn should be autografted as soon as possible after NexoBrid debridement."

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		Section 5.1: Pharmacodynamic properties The difference in time to complete wound closure is mainly related to the wound care strategy applied by the physician, where an attempt to minimise grafting and allow for spontaneous epithelialisation of the wound areas that still have dermis may prolong time to first autograft (time to autograft: NexoBrid: 14.7 days vs. SOC: 5.9 days*)* and hence prolong complete wound closure. • Educational materials • Training
Direct Interactions with CYP2C8/CYP2C9 substrates		Routine risk minimisation (labelling): ▪ Section 4.5 (Interaction with other medicinal products): "NexoBrid, when absorbed, is an inhibitor of cytochrome P 450 2C8 (CYP2C8) and P 450 2C9 (CYP2C9). This should be taken into account if NexoBrid is used in patients receiving CYP2C8 substrates (including amiodarone, amodiaquine, chloroquine, fluvastatin, paclitaxel, pioglitazone, repaglinide, rosiglitazone, sorafenib and torasemide) and CYP2C9 substrates (including ibuprofen, tolbutamid, glipizide, losartan, celecoxib, warfarin, and phenytoin)". ▪ Targeted Follow up questionnaire for drug interactions
Important potential risks		
Increased tendency to bleeding	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR. Additional Pharmacovigilance activities will include: 1. A multicenter, multinational, randomized, controlled, open study in Children with Partial Thickness and/or Full Thickness Thermal Burns, to evaluate the efficacy and safety of Enzymatic Debridement. A Comparison to Standard of Care, (Study MW2012-01-01). 2. Feasibility Study: Enzymatic Debridement in Patients with Partial Thickness Burns, (Study MW2008-09-03). 3. Retrospective, drug utilisation study (MW2013-06-01).	Routine risk minimisation (labelling): ▪ Section 4.4 (Special warnings and precautions for use): - Under 'Coagulopathy': "It is not known if NexoBrid application has any clinically relevant effect on haemostasis. Reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported in the literature as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. During the clinical development of NexoBrid, there was no indication of an increased bleeding tendency or bleeding at the site of debridement. Patients should be monitored for possible signs of coagulation abnormalities. ." - under 'Monitoring': "In addition to routine monitoring for burn patients… patients treated with NexoBrid should be monitored for: o Potential effects on haemostasis". • Section 4.5 (Interactions with other medicinal products and other forms of interaction): "Reduction of platelet aggregation and a moderate increase in partial

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		thromboplastin and prothrombin times have been reported as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. Caution and monitoring is therefore needed when prescribing concomitant medicinal products that affect coagulation." • Educational materials • Training
Severe irritation	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: Retrospective, drug utilisation study (MW2013-06-01).	Routine risk minimisation (labelling): ▪ Section 4.2 (Posology and method of administration) under 'Preparation of patient and wound area' subheading: "To prevent possible irritation of abraded skin by inadvertent contact with NexoBrid, such areas can be protected by a layer of a sterile fatty ointment" • Educational materials • Training
Allergic reaction	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: Retrospective, drug utilisation study (MW2013-06-01).	Routine risk minimisation (labelling): ▪ Section 4.3 (Contraindications): "hypersensitivity to the active substance, to pineapples or papain, or to any of the excipients". ▪ Section 4.4 (Special warnings and precautions for use): - Under 'Hypersenstitivity reactions, skin exposure': "There are limited clinical data to assess the sensitization potential of Nexobrid. Allergic reactions to bromelain (including anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angio-oedema, urticaria, and mucosal and gastrointestinal reactions) have been reported in the literature. Suspected sensitisation following oral exposure and following repeated occupational airway exposure has been reported. In addition, a delayed-type allergic skin-reaction (cheilitis) after longer-term dermal exposure (mouthwash) has been reported.. The potential of NexoBrid (a protein product) to cause allergic reactions should be taken into account when re-exposing patients to bromelain-containing products at a later point in time. The use of NexoBrid at a later point in time cannot currently be recommended. In case of skin exposure, NexoBrid should be rinsed off with water to reduce the likelihood of skin sensitization." - Under 'Cross-sensitivity' subheading: "Cross-sensitivity between bromelain and papain as well as latex proteins (known as latex-fruit syndrome), bee venom, and olive tree pollen has been reported in the literature." - under 'Monitoring': "In addition to routine monitoring for burn patients …patients treated with NexoBrid should be monitored for: o Signs of local and systemic allergic reactions" ▪ Section 6.6. (Special precautions for disposal and other handling): "There are reports of occupational exposure to bromelain leading to sensitisation. Sensitisation may have occurred due to inhalation of bromelain powder. Allergic reactions to bromelain include anaphylactic reactions and other immediate-type reactions with manifestations such as bronchospasm, angioedema, urticaria, mucosal and gastrointestinal reactions. This should be considered when

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		mixing NexoBrid powder with the Gel. The powder should not be inhaled. In NexoBrid, the powder containing enriched bromelain proteolytic enzymes is present in the form of a lyophilised cake, reducing the likelihood of inhalational exposure. Accidental eye exposure must be avoided. In case of eye exposure, irrigate exposed eyes with copious amounts of water for at least 15 minutes. In case of skin exposure, rinse NexoBrid off with water." • Educational materials • Training
Increased mortality in patients with cardiopulmonary disease	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR. Additional Pharmacovigilance activities will include: Retrospective, drug utilisation study (MW2013-06-01)	Routine risk minimisation (labelling): ▪ Section 4.4 (Special warnings): "NexoBrid should be used with caution in patients with cardiopulmonary and pulmonary disease, including pulmonary burn trauma and suspected pulmonary trauma". • Educational materials • Training
Off-label use in facial burns, perineum or genital area, single application of NexoBrid/Nexobrid to wounds >15% TBSA in one session, use in repeated applications	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities will include: ▪ Retrospective, drug utilisation study (MW2013-06-01).	Labelled in SmPC in: ▪ Section 4.1 (therapeutic indications): "NexoBrid is indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns." ▪ Section 4.2 (Posology and method of administration): "NexoBrid should not be applied to more than 15% Total Body Surface Area (TBSA) … A total wound area of not more than 15% TBSA can be treated with NexoBrid...A second and subsequent application is not recommended" • Section 4.4 Special warnings and precautions: <u>Burns for which there is limited or no experience</u>: There is no experience of the use of NexoBrid in perineal and genital burns. There is limited information on the use of NexoBrid in: - Facial burn wounds". • Educational materials • Training
NexoBrid Drug interactions with the following: • Anticoagulant/ blood-thinning agents		Routine risk minimisation (labelling): ▪ Section 4.4 (Special warnings and precautions for use): Coagulopathy: "It is not known if NexoBrid application has any clinically relevant effect on haemostasis. Reduction of platelet aggregation and plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported in the literature as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. During the clinical development of NexoBrid, there was no indication of an increased bleeding tendency or bleeding at the site of debridement. NexoBrid should be used with caution in patients with disorders of coagulation, low platelet counts and increased risk of bleeding from other causes e.g. peptic ulcers and sepsis. Patients should be monitored for possible signs of coagulation abnormalities. ." - Under 'Monitoring': "In addition to routine monitoring for burn patients… patients treated with

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		NexoBrid should be monitored for: o Potential effects on haemostasis". ▪ Section 4.5 (Interactions with other medicinal products and other forms of interaction): "Reduction of platelet aggregation and a plasma fibrinogen levels and a moderate increase in partial thromboplastin and prothrombin times have been reported as possible effects following oral administration of bromelain. *In vitro* and animal data suggest that bromelain can also promote fibrinolysis. Caution and monitoring is therefore needed when prescribing concomitant medicinal products that affect coagulation." ▪ Targeted Follow up questionnaire for drug interactions
• NexoBrid Drug interactions with 5-FU and vincristine		Routine risk minimisation (labelling): ▪ Section 4.5 (interaction with other medicinal products): "Bromelain may enhance the actions of fluorouracil and vincristine". ▪ Targeted Follow up questionnaire for drug interactions
• NexoBrid Drug interactions with Antihypertensive medication		Routine risk minimisation (labelling): ▪ Section 4.5 (Interaction with other medicinal products): "Bromelain may enhance the hypotensive effect of ACE inhibitors, causing larger decreases in blood pressure than expected". ▪ Targeted Follow up questionnaire for drug interactions
• NexoBrid Drug interactions with Nervous system depressants		Routine risk minimisation (labelling): ▪ Section 4.5 (Interaction with other medicinal products): "Bromelain may increase drowsiness caused by some medicinal products (e.g. benzodiazepines, barbiturates, narcotics and antidepressants)". ▪ Targeted Follow up questionnaire for drug interactions
Important missing information		
Elderly	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	▪ Routine risk minimisation (labelling): Section 4.2 (Posology and method of administration): "Experience with NexoBrid in elderly patients (>65 years) is limited. Benefit/risk assessment should include consideration of the greater frequency of concomitant disease or other drug therapy in the elderly"
Paediatric (< 18 yrs)	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR. Additional Pharmacovigilance activities will include: 1. Study MW2012-01-01 2. Study MW 2008-09-03 3. Study 2010-02-03	Routine risk minimisation (labelling): ▪ Section 4.2 (Posology and method of administration): "The safety and efficacy of NexoBrid in children and adolescents younger than 18 years have not yet been established. … No recommendation on a posology can be made. NexoBrid is not indicated for use in patients younger than 18 years". ▪ Section 4.8 (Undesirable effects) ▪ Section 5.2 (Pharmacokinetic properties): "Pharmacokinetic parameters and the extent of absorption have not been studied in children."
Pregnancy	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR	Routine risk minimisation (labelling): ▪ Section 4.6 (Fertility, pregnancy and lactation): - "There are no data from the use of NexoBrid in pregnant women. Animal studies are insufficient to properly assess the potential of NexoBrid to interfere with embryonal/foetal development. - Since the safe use of NexoBrid during pregnancy has not yet been established, NexoBrid is not recommended during pregnancy. - It is unknown whether bromelain/metabolites are

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
		excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued for at least 4 days after NexoBrid application. - No studies were performed to assess the effects of NexoBrid on fertility".
Systemic exposure	Additional Pharmacovigilance activities will include: 1. Study MW2012-01-01 2. Study MW2008-09-03 3. Study MW 2010-02-03	Routine risk minimisation (labelling): ▪ Section 4.4 (Special warnings and precautions for use): "Bromelain is systemically absorbed from burn wound areas" Section 5.2 (Pharmacokinetic properties): "The extent of systemic absorption from a burn wound, C_{max}, T_{max}, AUC, and $t_{½}$ of bromelain from NexoBrid have been investigated in 16 burn patients with partial-thickness (mid- and deep-dermal) thermal burns. … These results for C_{max} and AUC_{last} indicate that systemic absorption may depend both on the applied NexoBrid dose (proportional to the covered wound area) and other, patient-specific factors."
Development of Anti-NexoBrid Antibodies	Additional Pharmacovigilance activities will include: 1. Study MW2012-01-01 2. Study MW2008-09-03 3. Study MW2010-02-03	None
Long-term (at least 2 years) cosmetic and functional outcomes	Routine pharmacovigilance including presentation of collated data in the corresponding chapter of the PSUR Additional Pharmacovigilance activities for long-term evaluation (at least 2 years) of cosmetic and functional outcomes will be evaluated in two proposed non-interventional, observational phase 3b: 1. Cosmesis function and Quality of Life Assessments in Children following treatment with NexoBrid Compared to Standard of Care Treatment, (study MW2014-01-01). 2. Cosmesis, function and Quality of Life Assessments in Adults and Children following treatment with NexoBrid Compared to Standard of Care Treatment, (Study MW2010-03-02).	None

The below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The MAH shall conducts a study on enzymatic debridement in burns patients (children and adults): A comparison to standard of care (protocol MW2010-03-02), based on a CHMP approved	Protocol submission not later than 6 month after granting of the marketing authorisation.

Description	Due date
protocol. (Annex II)	Submission for interim study report Q1 2015 Submission of final results 31/03/2017
To address within the planned Phase IIIb paediatric study (protocol MW 2012-01-01) the lack of data on immunogenicity in the MAA dossier. The Applicant will undertake assessment of immunogenicity as laid out in the CHMP guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (RMP)	The Protocol should be submitted for approval by the CHMP before the start of the study. Submission of the final study report Q4, 2016
Retrospective survey (protocol MW2013-06-01) drug utilisation study for further evaluation of the effectiveness of the risk minimisation activities (RMP)	Review within the PSURs Submission of final results June 2014

The following additional risk minimisation activities were required:

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals in specialist burn centres who are expected to use and/or prescribe NexoBrid receive a specific training and are provided with an Educational pack.

The MAH should undertake a controlled distribution of NexoBrid to ensure that the product is not available for use at a centre until at least one surgeon at the centre has received formal training in the use of NexoBrid. This is in addition to the educational material which all potential users should receive.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Healthcare Professional information pack

The Healthcare Professional information pack should be a step by step treatment guide that includes information on the following key elements:

Before prescribing NexoBrid

- The limitation of the total area than can be treated to 15% TBSA
- The risk of allergic reaction and of cross reactivity and the contraindication in patients allergic to pineapple and papain or to previous application of the product
- The risk of increased mortality in patients with cardiopulmonary diseases

Before applying NexoBrid

- The need for pain management
- The need for wound cleansing and preparation before treatment with
    - Application of a dressing soaked with an antibacterial solution for two hours before Nexobrid application
    - Protection of surrounding skin areas
- The method of preparation of NexoBrid and of its application to wound area

After applying NexoBrid

- The removal of NexoBrid and of dissolved eschar
- The wound assessment and the warning against any repeat treatment
- The wound management after NexoBrid treatment with
    - Application of a dressing soaked with an antibacterial solution for two hours
    - Performance of grafting procedures as soon as possible after debridement
- The fact that Nexobrid may cause an allergic reaction, an increased tendency to bleed and severe local irritation and that patients should be monitored for signs or symptoms of these
- The fact that patients should be monitored for signs and symptoms of wound and systemic infections

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of NexoBrid in debriding deep partial thickness (DPT), mixed and full thickness (FT) wounds has been robustly demonstrated. Statistically significant and clinically relevant reductions in the number of DPT wounds that proceeded to surgical excision and in areas of wounds excised at first surgery and in any surgery were seen for NexoBrid debrided wounds. The subgroup data show that efficacy in debriding wounds occurs across a number of key subgroups, full thickness and mixed wounds and in wounds at different sites. This reflects the target indication for Nexobrid and is a direct measure of the pharmacological action.

A graft take success rate of > 90% in wounds autografted within 2 days of debridement was recorded in the main clinical studies for the NexoBrid patients which was comparable to the rate in the SOC group. Data on graft take in early autografted wounds were accepted by the CHMP as a surrogate measure of quality of debridement as supportive pre- and post-debridement histological data from animal studies were additionally provided.

The speed of debridement is also considered a beneficial effect. On average NexoBrid debridement was started within 0.77 days and was completed by 0.8 days after ICF date compared to 1.26 days and 6.7 days respectively for SOC. The much earlier achievement of complete debridement allows the burn surgeon an unobscured assessment of the burn wound depth (and extent) soon after the injury and allows the burn surgeon the choice between different post debridement strategies.

Other factors important for patient management influence outcome in terms of autografting, time to wound closure and other longer-term outcomes. Only small differences were seen in the number of non-mITT (FT & mixed) wounds receiving autografts, as these wounds usually require autografting. These wounds therefore had been excluded from the primary analysis. It has been demonstrated that NexoBrid reduces grafting vs. SOC in DPT wounds (18% of wounds NexoBrid arm vs. 34% SOC). There

were significant differences (although less marked) in the number of DPT wounds that received autografts and in the mean area of wounds autografted. As with efficacy of debridement, differences favouring NexoBrid were also seen across subgroups.

Regarding the treatment of hand wounds, a positive trend was noted regarding the exploratory endpoint of compartment pressure in circumferential burns of the extremities and of note no escharotomy was required for NexoBrid treated hands compared to 9.7% (4 of 41 hands) in the SOC cohort.

Uncertainty in the knowledge about the beneficial effects.

Despite an overall significant superior result in the NexoBrid treatment arm on autografting (driven by results in DPT wounds), the numerical difference between groups was small. Contradictory findings were observed in mixed wounds, a subgroup which was excluded from the primary analysis. As this analysis was based on a non-randomised comparison and baseline imbalances were present, together with the fact, that post debridement wound care was not standardised and determined by individual subjective open-label decisions, overall the results on autografting are not considered to be of the same direct relevance to the efficacy of as the primary endpoint results. The CHMP considers it appropriate to rely primarily on the measures of debridement to quantify the benefit of Nexobrid in the claimed indication. The lesser clinical relevance of the autografting data is supported by the statement of the ad hoc expert group that reduction in autografting is not the primary goal in burn surgery. Besides appropriate risk minimisation measures were established to ensure prompt autografting of all FT wounds and wound areas directly after debridement with NexoBrid (as is standard of care in European burn centers).

Cosmetic and functional outcome is important and data at a 2 year follow up has been provided. Although no difference in the long term cosmetic outcome was observed between NexoBrid and SOC treated wounds and the submitted SF-36 data suggest overall equal outcome on QoL and function in the two treatment arms, the available data is not considered confirmatory. A number of uncertainties exist regarding the influence of baseline imbalances on the overall MVSS data presented and the applicability of the presented MVSS data on approximately 50% of the patients initially enrolled in MW2004-11-02 to the entire cohort randomised in the pivotal study. The ad-hoc expert group supported the assumption that a negative impact of NexoBrid treatment on the outcome of the overall burn treatment is not expected. However the SF-36 measure was not, by itself, considered a suitably valid measure of burn-related or overall function. It is therefore considered that non-inferiority in quality of life and burn related and overall function require further data generation. The CHMP requested this to be addressed through a dedicaeted study to be conducted post-auuthorisation, as indicated in the RMP and also made an obligation to the licence.

Risks

Unfavourable effects

The most commonly reported adverse reactions of the use of NexoBrid are local pain and transient pyrexia/hyperthermia. The data from the clinical development showed that through precautionary measures including preventive analgesia as routinely practiced for extensive dressing changes in burn patients as well as antibacterial soaking of the treatment area before and after NexoBrid application, the frequency of pain and pyrexia/hyperthermia was reduced. These recommendations are included in the SmPC.

NexoBrid treatment was not found to be associated with a significantly increased risk of serious or severe adverse events compared to standard of care. Serious infections occurred with similar frequency in the SOC and NexoBrid cohorts and the incidence was low.

NexoBrid debridement was associated with a slightly higher rate of wound complications, general infections, wound infections /wound cultures and extent in antibiotic-use. The imbalances were only small and wound infections were only mild to moderate in severity. They responded well to treatment. No detrimental effect on long term outcome has been detected for the Nexobrid treated patients (regarding imbalance in mortality see below). The SmPC adequately addresses this point through guidance.

Uncertainties in the knowledge of the unfavourable effects

In general uncertainties surrounding the risks associated with NexoBrid use resulted from low rates of adverse events of interest, small differences between NexoBrid and SOC cohorts and limited size of submitted studies and subgroups in various analyses.

The initial time to complete wound closure (TTCWC) analyses confirmed that NexoBrid debridement was associated with an overall increased TTCWC. However, presented subgroup analyses of comparative TTCWC data for autografted wounds and non-autografted wounds in various wound depth subgroups and similar comparative data for time to placement of autografts make it clear that in the pivotal study the large delays in TTCWC only occurred in two subgroups i.e. late autografted DPT wounds and late autografted mixed wounds. The reason for this was mainly a delay in placing the autografts on the wounds (time to autograft from end of debridement in DPT wounds 15.0 vs. 1.7 days Nexobrid vs. SOC) which impacted TTCWC. The CHMP accepts that the delay in autografting NexoBrid debrided wounds was the principal cause of the increase in TTCWC experienced by such wounds which means that it is not considered a direct effect of NexoBrid treatment itself. In clinical practice, TTCWC can effectively be reduced by ensuring that NexoBrid debrided wounds with any full-thickness areas of burn are autografted early (i.e. within a few days of debridement) as advised in the SmPC and through risk management activities including educational material. In addition, to further address the remaining uncertainty the CHMP requested data generation thorugh a clinical study to confirm the absence of a direct negative impact of Nexobrid on TTCWC and possibly associated adverse events. This study is an obligation to the marketing authorisation.

The pharmacokinetic profile of NexoBrid has been investigated to a limited extent only. Based on the available data it is currently not known whether doses applied to large, deep wounds will result in plasma concentrations of bromelain or other proteolytic enzymes of Nexobrid that approximate or exceed plasma concentrations observed in a non-clinical study in minipigs that were later found to have visceral haemorrhages. Importantly no clinical sign of haemorrhage or coagulopathy in timely relation to the NexoBrid treatment has been observed so far. Nevertheless, the CHMP requested that the use of NexoBrid is restricted to a single application and to a maximum of 15% TBSA. The SmPC contains appropriate guidance and the educational programme will address this concern. Further investigation of the pharmacokinetics of NexoBrid in the indicated population and investigation of clotting parameters will be performed in the clinical post authorisation study which is an obligation to the marketing authorisation.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

NexoBrid significantly reduces the need for excisional surgery in FT, mixed and DPT wounds, and substantially reduces the time to successful eschar removal. It is confirmed to be an effective tool for

debridement with regard to extent and quality of debridement. Non-clinical data combined with a good graft take rate (>90%) are surrogates for a sufficiently good quality of debridement with NexoBrid. Early eschar removal also permits unobscured direct visualisation of the wound bed at an earlier stage and an earlier decision-making on subsequent wound care strategy. CHMP, in line with the SAG, sees the potential benefit to having another (non-surgical) technique for removal of eschar to complement the available surgical techniques.

Based on the available data the CHMP is sufficiently reassured about the absence of relevant detrimental effects in burn wound management through NexoBrid. Additional data to address uncertainties on long-term outcome will be generated.

The safety profile is considered acceptable, since overall, NexoBrid treatment was not found to be associated with a significantly increased risk of serious or severe adverse events compared to standard of care. Serious infections occurred with similar frequency in the SOC and NexoBrid cohorts and the incidence was low. Adequate precautionary measures have been employed to reduce the frequence of the most commonly observed adverse reactions.

The maximum potential treatable wound surface area has been restricted to 15% TBSA and the use is limited to a single application. Experts in the field state that this does not critically diminuish the usefulness as the majority of burn wounds is smaller than 15%TBSA. Further data will be generated through a requested phase IIIb study identified as obligation to the marketing authorisation.

Benefit-risk balance

The benefit-risk of Nexobrid for the removal of eschar in adults with deep partial, mixed and full thickness burns is positive.

Discussion on the benefit-risk balance

The efficacy of NexoBrid in debriding DPT, mixed and FT wounds in good quality, suitable for autografting and in a relatively shorter time period than standard of care has been demonstrated. There is evidence that NexoBrid reduces the extent of grafting vs. SOC particularly in DPT wounds.

Within the dossier a number of adverse outcomes were seen to occur more frequently in the NexoBrid arm than the SOC arm. These are not considered direct effects of NexoBrid but rather to be associated with an altered treatment strategy with delayed wound closure and later placement of autografts on NexoBrid debrided wounds or unrelated chance findings. Therefore the CHMP concludes in an acceptable safety profile of Nexobrid considering the severity of the patients' clinical condition. The Applicant has proposed a sound package of risk minimisation measures, which include efforts to educate specialists in the importance of early autografting of NexoBrid-debrided FT and deep burn areas which are considered to sufficiently address these concerns.

The CHMP has been reassured that some adverse trends observed in the clinical data are not a direct consequence of treatment with NexoBrid, but arise due to chance, or are related to differences in post-debridement wound care in the clinical trial. This highlighted however the importance of an adequate training. Furthermore, it is important that NexoBrid should only be applied by trained healthcare professionals in specialist burn centres. This is adequately addressed by the SmPC as well as the risk minimisation activities to ensure proper management in clinical practice.

Given the clear efficacy of Nexobrid for eschar removal, the demonstrated clinical benefit of the product and the fact that safety concerns can be adequately managed in clinical practice, the demonstrated benefit of NexoBrid outweighs the uncertainties about possible risks.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of NexoBrid indicated for removal of eschar in adults with deep partial- and full-thickness thermal burns is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in Version 1.12 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch in each Member State, the Marketing Authorisation Holder MAH shall agree the content and format of the educational programme with the national competent authority. The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals in specialist burn centres who are expected to use and/or prescribe NexoBrid receive a specific training and are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet
- Educational material for Healthcare Professionals

The Physician information pack should be a step by step treatment guide that includes information on the following key elements:

Before prescribing NexoBrid

- The limitation of the total area that can be treated to 15% TBSA

- The risk of allergic reaction and of cross reactivity and the contraindication in patients allergic to pineapple and papain or to previous application of the product
- The risk of increased mortality in patients with cardiopulmonary diseases

Before applying NexoBrid

- The need for pain management
- The need for wound cleansing and preparation before treatment with
    - Application of a dressing soaked with an antibacterial solution for two hours before Nexobrid application
    - Protection of surrounding skin areas
- The method of preparation of NexoBrid and of its application to wound area

After applying NexoBrid

- The removal of NexoBrid and of dissolved eschar
- The wound assessment and the warning against any repeat treatment
- The wound management after NexoBrid treatment with
    - Application of a dressing soaked with an antibacterial solution for two hours
    - Performance of grafting procedures as soon as possible after debridement
- The fact that Nexobrid may cause an allergic reaction, an increased tendency to bleed and severe local irritation and that patients should be monitored for signs or symptoms of these

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
The MAH shall conducts a study on enzymatic debridement in burns patients (children and adults): A comparison to standard of care (protocol MW2010-03-02), based on a CHMP approved protocol.	Submission of final results 31/03/2017

Divergent position to the majority recommendation is appended to this report.

New Active Substance Status

The applicant requested the active substance concentrate of proteolitic enzymes enriched in bromelain contained in the above medicinal product to be considered as a new active substance in itself.

Appendix – divergent position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the Marketing Authorisation for NexoBrid.

The reasons for divergent opinion were as follows:

The limited benefits are not considered to outweigh the risk of adverse effects and the considerable uncertainties.

Benefits:

the claimed beneficial effects of Nexobrid treatment are the selective removal of eschar with better preservation of viable tissue and better chances for spontaneous re-epithelisation than in surgical debridement. Therefore, fewer autografts are expected to be necessary. It is expected that the shift of the treatment strategy from early covering with autografts to spontaneous healing without or with less grafting will cause some delay, i.e. increase the time to complete wound closure.

It has been shown that effective debridement and less wound excision is achieved by Nexobrid treatment for full thickness (FT), deep partial thickness (DPT) and mixed burn wounds.

For the clinically relevant parameters decrease in autografting and time to complete wound closure the benefical effect of the Nexobrid treatment is less clear. The beneficial effect on number and size of autografts was driven by the subgroup of DPT wounds only, whereas there was no difference in FT wounds and an increased in autografts in mixed wounds. A possible explanation for the increase in grafting in the mixed wound group may be an imbalance in the study groups, see uncertainties below. Graft failure and multiple grafting procedures were few. Multiple grafting was more frequent for Nexobrid treatment in patients with DPT and mixed wounds, there was no difference in patients with FT wounds. In patients with FT wounds, graft failure occurred in 8.9% in the Nexobrid treatment group and in 2.5% in SOC group.

In patients with DPT or mixed wounds who received autografts there was a clearly longer time to complete wound closure, as expected (see above). In patients with DPT or mixed wounds who did not received autografts there was no difference in time to complete wound closure. On the one hand, this indicates that Nexobrid has no detrimental effect on the wound, on the other hand the presumed better preservation of viable tissue with Nexobrid than with SOC resp. surgical debridement does not translate into a more rapid healing.

Differentiating the burn wounds the effects of Nexobrid treatment versus SOC on autografting and wound healing are:

1. For FT wounds, there was no difference in autografting and time to complete wound closure. Graft failures were few but more frequent in the Nexobrid group.
2. For DPT wounds that were autografted, there were overall fewer autografts, more multiple grafting procedures (possibly reflecting a treatment strategy with more emphasis on spontaneous re-epithelisation, see uncertainties below) and a significantly longer time to complete wound closure for Nexobrid-treated patients.
3. For DPT wounds that were not autografted, there was no difference between Nexobrid and SOC.
4. For mixed wounds that were autografted, there were overall more autografts, more multiple grafting procedures and a significantly longer time to complete wound closure for Nexobrid-treated patients (a possible explanation may be an imbalance in the study groups, see uncertainties below).
5. For mixed wounds that were not autografted, there was no difference between Nexobrid and SOC.

There are considerable uncertainties of regarding the beneficial effects: the clinical relevance of less wound excision per se seems uncertain, when less wound excision that is not translated in less grafting

or more rapid healing. Avoiding the surgical procedure must be set against the Nexobrid treatment, which takes longer and requires pronounced anaesthesia.

Any quantification of differences in benefits between the Nexobrid arm and the SOC arm has considerable uncertainty. The different treatment strategies, early covering with autografts in the SOC arm versus more emphasis on to spontaneous re-epithelisation and temporary graft placement in the Nexobrid arm in the (unavoidably) unblinded study design are obvious confounders. Depending on the endpoint, this may favour Nexobrid (less autografts) or SOC (earlier wound closure). Imbalances in the study population add further uncertainty.

As the overall reduction in autografts (number of procedures and size) in the pivotal study was driven by the effect on DPT wounds it is important that there was an imbalance in the proportion of DPT wounds between study arms (61.9 vs. 44.9 Nex vs. SOC), favouring a better outcome for NexoBrid. On the other hand, the inferior outcome of Nexobrid treatment versus SOC in the mixed wounds is probably at least in part due to an imbalance with more severe mixed wounds in the Nexobrid arm.

Risks:

There is no clear clinical evidence for unacceptable risks of Nexobrid. The combination of several findings, however, may indicate the possibility of harmful effects.

For different bromelain products anti-inflammatory, antithrombotic and anticoagulant effects have been explored. Pharmakokinetic studies demonstrated highly variable serum levels of bromelain after administration to burn wounds. The highest concentration observed was Cmax 13.5 µg/ml. This is approx. a third of the concentrations observed in non-clinical studies with intravenous administration at NOEL.

There have been numerical imbalances favouring SOC versus Nexobrid for several adverse effects including mortality, blood transfusions, wound related complications (including graft failure), general infections, pain, pyrexia, antibiotic use, hospital discharge and total re-admissions Most concerns remain for mortality and blood transfusions: in the development program, there were five deaths of patients treated with Nexobrid for medical reasons versus no death for medical reasons in the SOC patients (one SOC patients was murdered). There were more and larger blood transfusions in the Nexobrid group (mean whole blood transfused 2245 ml vs. 714.7 ml). For neither of these adverse effects a clear link to Nexobrid treatment could be established. The explanations provided during the procedure are not completely reassuring. Examples: For mortality it has been argued that these were patients with pre-existing co-morbidities that should not have been included in the study. However, if the exclusion criteria were not (always) followed in the Nexobrid arm in the clinical trials, it must be assumed that similar patients have been included in the SOC group and may be treated post-approval in clinical practice. For blood transfusions, it has been agued that the increase in blood transfusions were caused by outliers and linked to surgical procedures which supposedly make an effect of Nexobrid implausible. However, high variability in pharmacokinetics with individual C_{max} estimates ranging from 951 to 13500 ng/ml and apparent mean terminal half-life of from 8.8 to 19.9 h are compatible with manifestation of effects only in (very) few patients under special circumstances (e.g. surgery).

The uncertainty is further increased as burn wounds in the Nexobrid arm of the one pivotal study were less severe (more DPT wounds, less full thickness and mixed wounds) than the burn wounds in the SOC arm (less DPT wounds, more full thickness and mixed wounds).

Conclusion:

The benefit-risk for this produce is negative and a marketing authorisation should not be granted.

London, 20 September 2012

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