09 November 2023
EMA/560965/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

NexoBrid

International non-proprietary name: Concentrate of proteolytic enzymes enriched in bromelain

Procedure No. EMEA/H/C/002246/II/0058

Note

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

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List of abbreviations

ABL	Actual blood loss
ADA	Anti-drug antibodies
APTT	Activated Partial Thromboplastin Time
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CRF	Case report form CSR Clinical study report
CSR	Clinical Study Report
CTD	Common Technical Document
DSMB	Data Safety Monitoring Board
DPT	Deep partial thickness
EBA	European Burns Association
eCRF	Electronic case report form
EMA	European Medicines Agency
ER	Eschar removal
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPI	First patient in
FT	Full thickness
FU	Follow-up Hb Hemoglobin
ICF	Informed consent form
ISE	Integrated Summary of Efficacy
ITT	Intent-to-treat
K-M	Kaplan-Meier
LS	Least square
M/F	male/female
MAA	Marketing Authorisation Application
Max	Maximum
MeDRA	Medical Dictionary for Regulatory Activities
MCI	Mass casualty incidence
Min	Minimum

MITT	Modified intent-to-treat
MVSS	Modified Vancouver Scar Scale
NI	Non-inferiority
NXB	NexoBrid
PDCO	Paediatric Committee
PK	Pharmacokinetics
PI	Principal Investigator
PIP	Paediatric investigation plan
POSAS	Patient and Observer Scar Assessment Scale
PP	Per protocol
PT	Prothrombin time
QoL	Quality of life
RBCV	Red blood cell volume
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SD	Standard deviation
SE	Standard error of the mean
SOC	Standard of care
SPT	Superficial partial thickness
SSD	Silver sulphadiazine
TBSA	Total body surface area
TW	Target wound
UK	United Kingdom
USA	United States of America

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, MediWound Germany GmbH submitted to the European Medicines Agency on 27 July 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of current indication for removal of eschar in adults with deep partial- and full-thickness thermal burns to the paediatric population for NexoBrid based on interim results from study MW2012-01-01 (CIDS study), listed as Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2 arm study aiming to demonstrate the superiority of NexoBrid treatment over SOC treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA).
As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 9 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0189/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0189/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

Scientific advice

The MAH did seek Scientific Advice at the CHMP. The Scientific Advice (EMA/SA/0000067318) pertained to the following Clinical aspects:

- Submission plan for NexoBrid label extension to the paediatric population based on the efficacy and safety data from completed and ongoing studies.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Janet Koenig

Timetable	Actual dates
Submission date	27 July 2022
Start of procedure:	17 September 2022
CHMP Rapporteur Assessment Report	11 November 2022
PRAC Rapporteur Assessment Report	11 November 2022
PRAC members comments	23 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	25 November 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 December 2022
Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	30 May 2023
PRAC Rapporteur Assessment Report	30 May 2023
PRAC Outcome	8 June 2023
CHMP members comments	8 June 2023
Updated CHMP Rapporteur Assessment Report	16 June 2023
Request for supplementary information (RSI)	22 June 2023
CHMP Rapporteur Assessment Report	10 October 2023
PRAC Rapporteur Assessment Report	10 October 2023
PRAC members comments	n/a
PRAC Outcome	26 October 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	1 November 2023
CHMP Opinion	9 November 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

This variation concerns an application for extension of the current indication to the paediatric population.

The therapeutic indication initially claimed by the MAH was: "NexoBrid is indicated in all age groups for removal of eschar in patients with deep partial- and full-thickness thermal burns."

The initially proposed dose regimen was the same as in adults.

2.1.2. About the product

One vial contains 2 g or 5g of concentrate of proteolytic enzymes enriched in bromelain, corresponding to 0.09 g/g concentrate of proteolytic enzymes enriched in bromelain after mixing (or 2 g/22 g gel or 5 g / 55 g gel).

The proteolytic enzymes are a mixture of enzymes from the stem of Ananas comosus (pineapple plant).

The mixture of enzymes in this medicinal product dissolves burns wound eschar. The specific components responsible for this effect have not been identified. The major constituent is stem bromelain.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Please refer to the section 'Scientific advice' above.

2.1.4. General comments on compliance with GCP

The MAH stated that the submitted clinical study MW2012-01-01 was conducted according to ICH GCP standards and procedures, and that a GCP audit program was undertaken to ensure compliance with these procedures.

2.2. Non-clinical aspects

2.2.1. Introduction

To support this application, a juvenile repeated dose toxicity study was submitted (study 1990-003). The findings of this study were compared to those of older studies with single or multiple IV dosing.

2.2.2. Toxicology

The objective of study 1990-003 was to evaluate the potential toxicity and toxicokinetics of the test article, Debrase powder (another forerunner product to NexoBrid), after three times weekly intravenous administration in juvenile (28 to 36 days of age on Day 1) farm pigs and to evaluate reversibility, progression, or delayed appearance of any observed changes following a 14-day post-dose observation period. The age of the piglets at treatment start corresponds to a human age of 2 years[1]. Table 1 provides an overview on the study design and the relevant results.

Table 1: Overview on the study design and relevant results of the repeated dose toxicity study "Debrase powder: a 2-week intravenous toxicity study in juvenile farm pigs with a 2-week recovery period"

Study no. / year / GLP	1990-003	2012	yes
Study design			

[1] Developmental reproductive toxicology: a practical approach. 3rd edition, page 310, edited by R.D. Hood, published by Informa Healthcare 2012

Species	Domestic Yorkshire Crossbred Swine (farm pigs)
Age of the piglets at treatment start	28 – 36 days
No. of piglets / group	Co + HD: 6 m + 6 f with 2/sex for recovery; LD + MD 4 m + 4 f
Doses (mg/kg/d)	0 – 4 – 8 – 12
Route	slow bolus IV via a femoral vein top access port
Treatment duration	3 x / week for 2 weeks
Parameters evaluated	morbidity, mortality, clinical signs, body weights, food consumption, ophthalmoscopy pretest + prior to necropsy; ECG pretest, prior to 1st + 5th dosing + 1 – 2 h post-dose (day 1 + 10) and during recovery (day 21); haematology + serum chemistry; TK day 1 + 8, macroscopic + microscopic pathology, organ weights
Major findings	
Mortality	none
Clinical signs	unremarkable until the 5th dose **➔5th dose in 1st set (=1 m + 1 f) of piglets / group**: male (m): ≥ 4: in each dose group the first dosed m had convulsions, difficult breathing, and developed reddening skin at the time of the injection. Some piglets also had watery feces, audible breathing, salivation and ataxia. Female (f): 4: no convulsions or other adverse effects after the 5th dose 8: 1 f with ataxia + difficult breathing 12: 1 f with a convulsion and developed reddening of the skin during the injection ➔ next set of 1m/1f per group pre-treatment with oral + IM antihistamines prior to dosing ➔ m: ≥ 4 reddening of the skin as before 12: 1 m with a convulsion f: ≥ 4 ↓ activity and ataxia 4 + 8: 1 f each with breathing difficulty ➔ remaining piglets received no antihistamines and no 5th dose
ECG	Trend of increasing QT and QTc intervals on Day 10 post-dose in treated piglets. However, values obtained following clinical signs (e.g. convulsions in some piglets after the 5th dose). → When these values were evaluated by sex, there were no statistically significant changes identified.
Coagulation	≥ 4: mild to marked prolongation of APTT + PT ≥ 8: fibrinogen ↓ effects were dose related, apparent up to 24 h post-dose, resolved or partially resolved at 48h post-dose → more dramatic on day 8 relative to day 1 suggesting cumulative effect
Macroscopic / microscopic pathology	≥ 4: sporadic haemorrhages in several tissues (lungs, tracheobronchial lymphnodes, gallbladder, pancreas, kidneys, ileum and urinary bladder) → not seen in recovery piglets → reversible effect
NOEL	none

TK

Mean[a] Serum Debrase Toxicokinetic Parameters on Day 1 and Day 8 during Intravenous (Slow Bolus) Administration of Debrase Powder to Male and Female Juvenile Farm Pigs Three Times a Week

Group	Dose Level (mg/kg/day)	Gender	C_{max} (ng/mL)[b]	t_{max} (h)[c]	t_{last} (h)[c]	AUC_{last} (ng·h/mL)	AUC_{inf} (ng□h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	Cl (mL/h·kg)
Day 1										
2	4	M	12100	0	24	18600	18700	3.8	1210	224
		F	11900	0	24	17200	17200	4.0	1350	233
3	8	M	26400	0	24	40000	40200	4.0	1180	208
		F	25600	0	24	40300	40500	4.0	1170	206
4	12	M	42100	0	24	69400	69800	3.9	975	174
		F	31700	0	24	54200	54600	4.2	1380	227
Day 8										
2	4	M	13800	0	24	23100	23300	4.6	1140	174
		F	14400	0	24	22000	22500	5.4	1390	184
3	8	M	27300	0	24	46100	46600	4.6	1160	174
		F	28100	0	24	55200	55800	4.3	909	148
4	12	M	49200	0	24	103000	105000	4.8	790	115
		F[d]	40300	0	24	89000	90400	4.5	951	148

[a] Median for t_{max} and t_{last}; n=4 for Groups 2 and 3; n=6 for Group 4.
[b]The concentration at the end of dosing (time zero) was estimated by extrapolation of observed data.
[c]Time from the end of dosing
[d]n=5

For comparison, Table 2 below provides an overview on the study design and major findings of intravenous single and repeated dose toxicity studies conducted previously in adolescent/adult minipigs. In adult minipigs repeated IV administration of Debrase (another forerunner product to NexoBrid) at 4, 8, and 12 mg/kg/d was associated with convulsions only in male at 8 mg/kg/day. Due to decreased activity, ataxia, salivation, laboured breathing, and haemorrhage in multiple tissues, no NOEL was established (study 20002068).

Table 2: Overview on toxicity studies performed with IV administration of Debrase in minipigs

Kind of study GLP	Study no Study year	Species Age at treatment start	n / sex / group	Route Doses (mg/kg/d)	Major effects	NOAEL (mg/kg/d) AUC (ng*h/ml)
Single dose yes	20002067 2010	minipigs 13 weeks	3	slow bolus IV 0 – 4 - 12 - 24	24: activity ↓, shivering (m), faeces ↓, food consumption ↓ → in m until d 7, in f until d 2	12 m: 73400 f: 77500
Single dose yes	20006035 2010	minipigs 16 weeks	1	2 h IV infusion 0 – 24 – 48 – 96	96: both pigs died / euthanized (purple skin discoloration, red discharge from eyes + nostrils, gasping, retching, vomiting + tremors) 24, 48: Prothrombin time + activated PTT slightly ↑; normal on day 8	48 m: 66600 f: 63900

Repeated dose yes	20002068 2010	minipigs 17 – 19 weeks	Co + HD: 6 (2 for recovery) LD + MD: 4	IV: 3 x / week for 2 weeks 0 – 4 – 8 – 12	≥4:↓ activity, ataxia, salivation, laboured breathing, defecation, ↓ food consumption –haemorrhage in multiple tissues, pancreatic acinar cell degeneration + single cell necrosis + lymphoid depletion in cortex of thymus. Recovery not complete after 2 weeks, findings not dose but treatment related 8: 1/4 minipig euthanized for welfare reasons because of convulsions + cyanosis	no NOAEL 4 mg/kg/d → day 1: m: 14900 f: 16200 day 14: m: 39100 f: 39900

To further support the extension of the indication in children from birth until adulthood with preclinical data, single dose studies with dermal or IV route of administration were conducted in non-weaned domestic pigs and minipigs which could be considered juvenile (3 months old).

Topical application of NexoBrid (0.09 g/g) to young pigs (2 months of age) did not cause any local and systemic toxicological relevant findings when applied to burn wounds in a formulation and in a dosage regimen relevant for the human use of the product.

2.2.3. 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.

2.2.4. Discussion on non-clinical aspects

To support this extension of indication, the MAH conducted a juvenile toxicity study (study 1990-003) in a species (although not in the same strain) that had been used before in older toxicity studies. This facilitates comparison of study results obtained in adolescent/adult with those obtained in juvenile animals (28-36 days old at treatment start). Except for convulsions, noted at all dose levels in juvenile pigs, the results of the juvenile toxicity study do not differ from those obtained previously in adolescent / adult (mini)pigs in single and repeated dose IV studies and exposure data are also in the same range. Contrary to the findings in the juvenile study, where convulsions occurred at all dose levels, only a single adolescent / adult pig of the mid dose group (8 mg/kg/day) showed convulsion.

In the juvenile toxicity study (study 1990-003), one male piglet each at 4, 8, and 12 mg/kg/day (1/4, 1/4 and 1/6, respectively) had convulsions, difficulties to breathe, and developed reddening skin at the time of the 5th injection. Some of the animals also had findings that included watery faeces, audible breathing, salivation and ataxia. In the females, there were no convulsions or other adverse effects after the 5th dose at 4 mg/kg/day. However, at 8 mg/kg/day 1/4 female developed ataxia and difficulty to breathe, and at 12 mg/kg/day 1/6 female had a convulsion and developed reddening of the skin during the injection, as was seen in the males after the 5th dose.
Based on the possibility of some type of allergic/anaphylactoid reaction, as none of the control animals were affected, a decision was made to pretreat the next stagger set of animals (1/sex/group) with oral and intramuscular injections of antihistamines prior to dosing to see if the adverse clinical signs, particularly the convulsions and reddened skin, could be averted. The second set of animals receiving a 5th dose were pretreated with antihistamines; however, all the males showed reddening of the skin as before, and one male at 12 mg/kg/day had a convulsion. The females from this second set showed decreased activity and ataxia at all dose levels (4, 8, and 12 mg/kg/day). At 4 and 8 mg/kg/day, one

female each also had difficulty to breathe. Reddened skin was seen in one female each at 4 and 12 mg/kg/day. Based on the continued adverse clinical outcome, the remaining animals in the first two sets were not administered any additional injections as originally scheduled. For human reasons, the remaining set of animals only received four doses to avoid these adverse effects after the 5th dose. One female at 12 mg/kg/day from the last set of animals did show signs of decreased activity, ataxia, difficulty to breathe, and reddened skin after the 4th dose on Day 8. In the study report, these clinical findings were considered to be test article related.

As a consequence, a No-Observed-Effect-Level (NOEL) for general toxicity could not be established in the juvenile toxicity study due to significant clinical findings following the 5th injection in all treatment groups as well as alterations in the coagulation parameters and microscopic findings in the terminal animals.

It is agreed that the animals were juvenile, but not all non-weaned in the single dose studies with dermal or IV route of administration. Although in nature, weaning in pigs is a gradual process that occurs around 10 to 12 weeks of age, coinciding with the near complete maturation of the gastrointestinal tract, in commercial pig production, weaning is abrupt, occurring at around 2 to 4 weeks of age[2]. As these studies were performed in laboratories, pigs should be considered to be weaned. According to Hood[1], the age of 3 months in minipigs corresponds to a 12-year-old child.

It might be reassuring that convulsions were noted in juvenile pigs only following repeated administration keeping in mind that according to SmPC section *4.2 Posology and method of administration* a second and subsequent application is not recommended in humans. However, prior to final risk assessment on the relevance of the convulsions observed in pigs for the use of NexoBrid in children, the MAH was requested by CHMP to provide a discussion on this issue taking into account the small number of children treated so far, the small amount of PK data available in children as well as the fact that no NOEL was established in the juvenile toxicity study and consequently the exposure at the NOEL is unknown. The MAH has provided a discussion on convulsions observed in pigs and the reason for lack of study results. The reason for missing data was explained by sopping of dosing of animals which suffered from severe adverse effects. Therefore, a final analysis was not performed. This is understood and acceptable. Regarding convulsions, the mechanism and reasons for these convulsions is still not clear and human relevance cannot be fully excluded. However, it was discussed that convulsion occurred after repeated i.v injections, while NexoBrid is used topically and just once for 4 hours. It can therefore reasonably be assumed that exposure of patients is significantly lower than exposure of pigs in the juvenile study, despite the lack of TK data. Based on these considerations and the lack of clinical correlates in paediatric patients thus far, convulsions observed in pigs are considered to be of minor relevance for patients. In addition, these findings were adequately included in section 5.3. of the SmPC.

Topical application of NexoBrid (0.09 g/g) to young pigs (2 months of age) did not cause any local and systemic toxicological relevant findings when applied to burn wounds in a formulation and in a dosage regimen relevant for the human use of the product. This information has been adequately added to SmPC section 5.3.

The trend of increasing QT and QTc intervals obtained on Day 10 post-dose in treated piglets were not judged treatment-induced but were considered to be due to the substantial clinical signs (e.g., convulsions) following the 5th dose. Those findings were included in SmPC section 5.3. Furthermore, study 2010-03-02 (DETECT) included an evaluation of QT prolongation and no signal was identified.

Test article-related effects were observed in the coagulation parameters of all treated groups (4, 8, 12 mg/kg/day) showing dose responsive prolongation of APTT and PT, as well as decreases in fibrinogen

[2] Faccin Jamil EG et al. *Impact of increasing weaning age on pig performance and belly nosing prevalence in a commercial multisite production system*; Journal of Animal Science, 2020, Vol. 98, No. 4, 1–8

levels. The changes in the coagulation parameters were generally more important on Day 8, in comparison to Day 1, suggesting a cumulative effect.

At necropsy, possible test article-related findings were limited to sporadic haemorrhages in several tissues noted macro- and microscopically in terminal animals. These changes were not seen in recovery animals, indicating a reversible effect. The haemorrhagic events may be correlated to the changes in the coagulation parameters observed (prolongation of PT and APTT and decrease in fibrinogen).

Phase 3 2010-03-02 (DETECT) study included assessment of coagulation (PTT/INR) and no signal was identified.

A warning on Coagulopathy is already included in the SmPC section 4.4 Special warnings and precautions for use.

The toxicokinetic investigations confirmed dose responsive exposure to Debrase (another forerunner product to NexoBrid) following intravenous administration at 4, 8, and 12 mg/kg/day in both male and female piglets on Days 1 and 8. Mean C_{max} and AUC_{last} were comparable for males and females at each dosage, indicating gender independence for both parameters, with similar half-lives on each day of evaluation. Debrase was detected in treated animals up to 24 hours after injection. At this time point, the mean values were slightly higher on Day 8 as compared to the first day of dosing (Day 1). Exposure levels at the lowest dose tested were well above those obtained in pharmacokinetic investigations in children following a single administration of NexoBrid. However, as no NOEL could be established in the repeated dose toxicity study in juvenile pigs, the exospore at the NOEL is unknown.

2.2.5. Conclusion on the non-clinical aspects

To support this extension of indication in the paediatric population, the results of a juvenile repeated IV dose toxicity study covering children of 2 years of age were submitted. Except for convulsions, noted at all dose levels in juvenile pigs, the results of the juvenile toxicity study do not differ from those obtained previously in adolescent / adult (mini)pigs in single and repeated dose IV studies and even exposure data are in the same range. Contrary to the findings in the juvenile toxicity study, in adolescent / adult minipigs, convulsion was limited to a single male in the mid dose group. Given that convulsion occurred after repeated i.v injections and taking into account that patients receive NexoBrid topically and just one application for 4 hours, it can reasonably be concluded that exposure of patients is significantly lower than exposure of pigs in the juvenile study, despite the lack of TK data. Based on the above considerations and the lack of clinical correlates in paediatric patients thus far, convulsions observed in pigs are considered to be of minor relevance for patients. Topical application of NexoBrid (0.09 g/g) to young pigs (2 months of age) did not cause any local and systemic toxicological relevant findings when applied to burn wounds in a formulation and in a dosage regimen relevant for the human use of the product. In addition, these findings were adequately included in section 5.3. of the SmPC.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

Type of Study	Study Identifier	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Products; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and Efficacy in Paediatric patients	MW2012-01-01	NA	To evaluate the safety and clinical benefit of NexoBrid in hospitalized children (0-18 years) with deep partial and/or full thickness thermal burns of 1-30% TBSA and to compare NexoBrid to standard of care (SOC).	Phase 3, Multicenter, Multinational, Controlled, Open label study, performed in Children with Thermal Burns including 2 arms: NexoBrid and SOC in a ratio of 1:1 Controlled (SOC)	**NexoBrid:** Two grams or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle to obtain NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2g NexoBrid/20g Gel per 180cm² for four hours. **SOC:** Included surgical and/or nonsurgical eschar removal procedures	Total of 139 paediatric patients: NXB=69 treated SOC=70 treated	Paediatric patients age birth to <18 hospitalized in burn units with DPT and/or FT burns (≥3% to ≤30% TBSA)	4 hours per application	12M CSR is available.

CSR = clinical study report, DPT = deep partial thickness, F = female, FT = full thickness, M = male, PK = pharmacokinetic, PT = partial thickness, QoL = quality of life, SOC = standard of care, TBSA = total burn surface area

2.3.2. Pharmacokinetics

Substudy on Pharmacokinetics in the paediatric population

This substudy was integrated in the submitted study (interim report) MW2012-01-01. PK blood samples were collected from 16 out of 72 NexoBrid treated patients (of the 145 patients randomised in the study). All 16 patients received a single dose (and PK samples were not available from the one patient who was treated with a second application). Blood samples from patients weighing over 35 kg at screening were taken at pre-treatment (time 0) and at 2, 4, 12, 24, 48, and 72 hours after start of treatment. For some patients, not all time points were collected. In protocol version 9.0 (26 August 2019), a sparse sampling approach was implemented for patients >7 kg and <35 kg at screening. These patients were split between the 2 sub-groups (A and B). The 'A' sub-group had blood samples taken at 2 and 12 hours while the 'B' subgroup had blood samples taken at 4 and 24 hours post treatment. Due to the timing of the protocol amendment, this only applied to 2 patients (<2 years of age).

In addition to the main analysis that used valid samples (n=10), there were an additional 6 patients with PK samples analysed outside of the stability period for long term storage in an exploratory analysis. The ECL assay used in this analysis as well as the analytical site (Q2 Solutions, Marrietta, GA, USA) were the same as described in trial MW2008-09-03 (assessed in EMA-procedure EMEA/H/C/002246/II/0023).

PK analysis was performed for NexoBrid serum concentration versus time data using standard non-compartmental methods. PK outcome parameters included:

T_{max}: Time at which the maximum concentration was observed.

C_{max}: Maximum observed concentration.

C_{max}/D: Dose normalised C_{max}.

AUC_{last}: Area under the concentration-time curve from the start of dose administration to the last quantifiable point within the dosing day, using the trapezoidal rule.

AUC_{last}/D: Dose normalised AUC_{last}.

AUC_{0-4}: Area under the concentration-time curve from the start of dose administration to 4 hours after dosing (end of treatment) within the dosing day, using the trapezoidal rule.

AUC_{0-4}/D: Dose normalised AUC_{0-4}.

AUC_{0-24}: AUC from time zero to time 24 hours post dose administration.

AUC_{0-24}/D Dose normalised AUC_{0-24}:

All values reported as below the LLOQ were set equal to zero for descriptive statistics and for PK analysis. Nominal sample times and nominal dose values were used in the PK calculations (nominal dose values were calculated based on wound area treated and not based on actual reported dose; dose was calculated as 2 g NexoBrid/180 cm^2 of wound area).

Patients with less than 3 consecutive quantifiable concentrations were included in the concentration tables only and were excluded from the PK analysis. Phoenix WinNonlin (version 8.3) was used to estimate all PK parameters using the non-compartmental analysis tool following the Linear Trapezoidal Linear Interpolation calculation method. For the 2 patients with sparse sampling, their values were merged to create a composite PK profile (resulting in one PK profile for patients < 2 years of age).

Peak plasma concentrations post-dose (C_{max}) and the corresponding T_{max} were determined by direct assessment (no calculations) of the concentration versus time data. All AUC calculations were performed using the linear trapezoidal rule. For the calculation of partial areas (e.g. AUC_{0-4}), if the plasma concentration value at the last nominal hour post-dose time point of the desired interval was missing but was followed by at least one measurable concentration at a later time point, the partial area was calculated using linear interpolation. However, if no measurable concentration was available beyond the missing value to define the partial area interval (e.g. post the 4-hour value is missing and there are no more values beyond that for an AUC_{0-4} partial area), a partial area was not calculated. Due to limited data, λz could not be assessed for a majority of the patients; as such half-life, AUC from time zero to infinity (AUC_{INF}), total body clearance, and the volume of distribution were not reported. A correlation analysis of the NexoBrid dose applied and AUC_{0-4} values was performed in WinNonlin using a Least Squares Regression Model (Linear Regression) to obtain a r value. Using a non-validated version of GraphPad Prism (Version 9.3.1), the same data set was used in a correlation analysis to obtain the Pearson r value and a two-tailed p-value.

Summary statistics (i.e. N, arithmetic mean, median, SD, CV%, minimum, and maximum) were calculated for plasma concentrations for each nominal time point and separated by age group. All concentration and descriptive statistic values were reported to 3 significant figures. Summary statistics (i.e. N, arithmetic mean, median, SD, CV%, minimum, maximum, geometric mean, and geometric mean CV%, confidence interval [CI] 90% lower mean and CI 90% upper mean) were presented for all PK parameters and separated by age group. All PK parameters and descriptive statistic values are reported to 3 significant figures, except for individual T_{max} values which are reported to 2 significant figures. An evaluation of C_{max} and AUC with respect to age group and dose applied was performed.

Main Analysis

PK data were collected from 11 patients, all received a single application of NexoBrid; data from patients with less than 3 consecutive quantifiable concentrations were excluded. In addition, data from one patient included outliers and this patient was not included in further analysis. Descriptive statistics were therefore calculated using PK data from 10 patients (Table 3). This included 2 patients who were less than 2 years

of age (which were used to make a single composite PK profile), 5 evaluable patients aged 4 to 11 years, and 3 patients aged 12 to 18 years. PK data were not available from patients < 20 months and aged 2 to 3 years.

There were only 10 PK profiles available in the paediatric PK study. The treated TW area ranged from 4 to 11% TBSA (5.3% in the one profile ~2 years of age), up to 9% in children 4-11 years and up to 11% TBSA in the age group 12-18 years; the overall mean was 6.31% TBSA.

The median T_{max} values were 4.0 hours in the full PK profile patients (4 to 18 years) and 2 hours in the composite profile (<2 years). The arithmetic mean C_{max} ±SD values were 200, 205±169, and 180±114 ng/mL in the <2, 4 to 11 and 12 to 18 age groups, respectively. Normalising for estimated dose applied (g NexoBrid), the mean dose normalised C_{max} ± SD values were 66.7, 32.8±23.9, and 19.2±7.50 ng/mL/g, respectively.

To allow for comparison between paediatric and adult burn patients treated with NexoBrid, partial areas (AUC_{0-4}) were calculated consistently with study MW2010-03-02. The arithmetic mean AUC_{0-4} (time of treatment) ± SD values were 476, 416±259 and 499±315 h·ng/mL in the <2, 4 to 11 and 12- to 18-year age groups, respectively, while the mean dose normalised values were 159, 67.9±44.7 and 53.3±20.4 h·ng/mL/g, respectively. The arithmetic mean AUC_{0-24} ± SD values were 1020, 1850±1510, 1560±887 h·ng/mL in the <2, 4 to 11, and 12- to 18-year age groups, respectively, with mean dose normalised values of 340, 308±252 and 174±67.4 h·ng/mL/g, respectively. The arithmetic mean AUC_{last} ± SD values were 876, 2240±2220, and 1560±887 h·ng/mL in the <2, 4 to 11, and 12- to 18-year age groups respectively, with mean dose normalised values of 292, 366±350 and 174±67.4 h·ng/mL/g, respectively. When normalised for the dose applied (treatment area), the AUC values were within 2-fold between age groups.

Table 3: Summary Serum Pharmacokinetic Parameters Following Topical Administration of NexoBrid (Main Analysis)

Age Group (years)	Dose (g)	TW Area (cm^2)	T_{max} (h)	C_{max} (ng/mL)	C_{max}/ Dose (ng/mL/g)	AUC_{0-4} (h·ng/mL)	AUC_{0-4}/ Dose (h·ng/mL/g)	AUC_{0-24} (h·ng/mL)	AUC_{0-24}/ Dose (h·ng/mL/g)	AUC_{last} (h·ng/mL)	AUC_{last}/ Dose (h·ng/mL/g)
<2 (n=2; sparse)	3.0	271	2.0	200	66.7	476	159	1020	340	876	292
4 – 11 (n=6[a])	6.89± 3.01	620± 271	4.0 (2.0-4.0)	205±169	32.8±23.9	416±259	67.9±44.7	1850±1510	308±252	2240±2220	366±350
12 – 18 (n=3)	12.2± 12.6	1100± 1140	4.0 (2.0-4.0)	180±114	19.2±7.50	499±315	53.3±20.4	1560±887	174±67.4	1560±887	174±67.4

Values are reported as Mean ± SD, which the exception of T_{max}, which is reported as Median (Min-Max). The <2 year age group is a composite profile (n=2); 4-11 year old group represents n=5 and 12-18 year old group represents n=3.

The interindividual variability was very high, which can be seen e.g. in the C_{max}/dose and C_{max}/TBSA ranges. In the adult study, values for C_{max}/dose ranged from 5.19 to 40.9 ng/mL/g (a factor of almost 8); in the CIDS study, the range was from 9.18 to 66.7 ng/mL/g (a factor of 7). Values for C_{max}/TBSA ranged from 10.23 to 88.80 ng/mL/%TBSA in adults (a factor of almost 9) vs. 9.68 to 68.86 ng/mL/%TBSA (a factor of 7) in the CIDS study.

Correlation analyses showed that in the CIDS study there were no correlations between C_{max} and the treated TW area (in %TBSA) nor between AUC and %TBSA. However, there was a correlation between age and C_{max}/dose (p-value 0.0765) and between age and AUC_{0-4}/dose (p-value 0.0796).

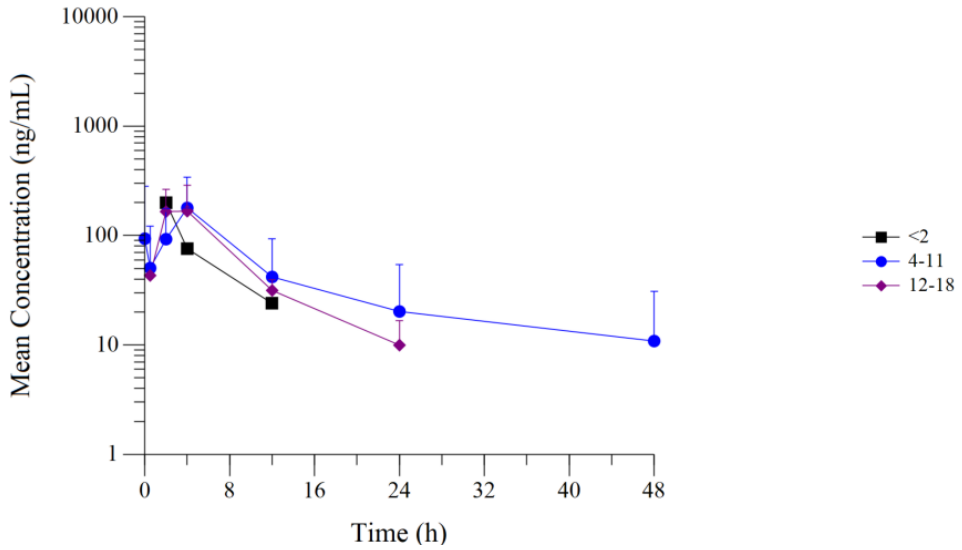
The r value for the relationship between C_{max} and dose applied was 0.3349, with a p-value of 0.3783, indicating a lack of correlation. The r value for the relationship between AUC_{0-4} and the dose applied was 0.5926, with a p-value of 0.0926, indicating no correlation.

When systemic exposure was normalised for the dose applied (treatment area), the AUC values decreased with age (but remained within 2-fold between age groups).

Since less than a third of the patients had sufficient data (as defined in the PK analysis plan) to reliably determine λz, additional disposition parameters (e.g. terminal half-life and AUC_{INF}) were not reported.

Due to the high interindividual variability (e.g. ~factor 7 between lowest and highest C_{max}/dose), conclusions regarding differences in PK profiles between age groups are difficult to make.

Figure 1: Mean serum NexoBrid concentration versus time profile data following a single topical NexoBrid administration (main analysis)



Legend: Age group (years); Error bars represent standard deviation

Exploratory Analysis

There were 6 patients (3 4 to 11-years of age and 3 12- to 18-years) whose serum samples were analysed outside of the stability window for the analytical assay. The PK analysis of those samples was therefore exploratory only. Evidence of systemic plasma exposure was observed in all patients (Table 4). The median T_{max} values were 2.0 and 4.0 hours in the 4 - 11 and 12 - 18-year age groups, respectively.

The arithmetic mean C_{max} (±SD) values were 170±103 and 774±866 ng/mL in the 4 to 11 and 12- to 18-year age groups, respectively, and normalising for estimated dose applied (NexoBrid, g), the mean dose normalised C_{max} values were 29.5±27.9 and 53.7±39.5 ng/mL/g, respectively. The arithmetic mean AUC_{0-4} values were 525±351 and 2260±2600 h·ng/mL (mean ± SD) in the 4 to 11 and 12 to 18-year age groups, respectively, while the mean dose normalised AUC_{0-4} values were 92.6±91.4 and 157±118 h·ng/mL/g. The arithmetic mean AUC_{0-24} values were 2000±1890 and 9700±11900 h·ng/mL in the 4 to 11 and 12- to 18-year age groups, respectively, while the mean dose normalised values were 379±436 and 558±353 h·ng/mL/g. The arithmetic mean AUC_{last} values were 2370±2630 and 11900±14500 h·ng/mL in the 4 to 11 and 12- to 18-year age groups, respectively, while the mean dose normalised values were 463±587 and 629±369 h·ng/mL/g.

There was a positive correlation/relationship between serum C_{max} and AUC_{0-4} values and the dose applied, suggesting a dose or treatment area dependent increase in exposure. The r value for the relationship between C_{max} and dose applied was 0.7227, with a p-value of 0.1047, indicating a lack of significant

correlation. The r value for the relationship between AUC_{0-4} and the dose applied was 0.7053, with a p-value of 0.1175, indicating a lack of significant correlation.

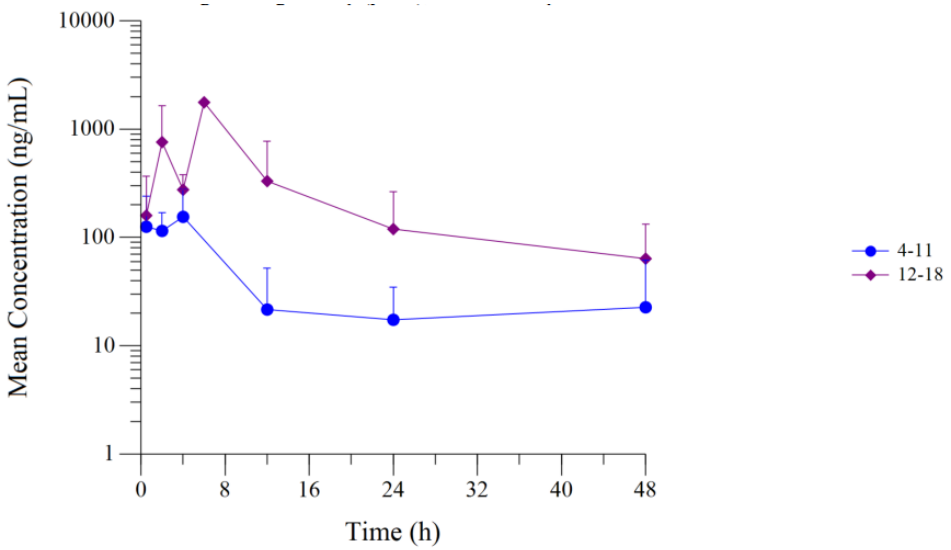
Systemic exposure between the age groups increased with age, concurrent with increased treatment area. However, when normalised for the dose applied (treatment area), the AUC values remained within 2-fold between age groups, suggesting no significant age-related differences in exposure.

Table 4: Summary of Serum Pharmacokinetic Parameters Following Topical Administration of NexoBrid (Exploratory Analysis)

Age Group (years)	Dose (g)	TW Area (cm^2)	T_{max} (h)	C_{max} (ng/mL)	C_{max}/ Dose (ng/mL/g)	AUC_{0-4} (h·ng/mL)	AUC_{0-4}/ Dose (h·ng/mL/g)	AUC_{0-24} (h·ng/mL)	AUC_{0-24}/ Dose (h·ng/mL/g)	AUC_{last} (h·ng/mL)	AUC_{last}/ Dose (h·ng/mL/g)
4 – 11 (n=3)	8.90± 5.87	801± 528	2.0 (2.0-4.0)	170± 103	29.5± 27.9	525± 351	92.6± 91.4	2000± 1890	379± 436	2370± 2630	463± 587
12 – 18 (n=3)	20.0± 15.7	1800± 1410	4.0 (2.0-4.0)	774± 866	53.7± 39.5	2260± 2600	157± 118	9700± 11900	558± 353	11900± 14500	629± 369

Values are reported as Mean ± SD, which the exception of T_{max}, which is reported as Median (Min-Max). 4-11 year old group represents n=3 and 12-18 year old group represents n=3.

Figure 2: Mean serum NexoBrid concentration versus time profile data following a single topical NexoBrid administration (exploratory analysis)



Legend: Age group (years); Errors bars represent standard deviation

Analyses across studies

The paediatric PK data from the CIDS sub-study were compared to adult PK data.

Since the PK study MW2008-09-03 contained adult PK data plus paediatric PK data, a meaningful comparison of PK data (paediatric vs. adult) was only possible with the data from the paediatric CIDS PK sub-study (MW2012-01-01) and from the adult PK sub-study MW2010-03-02.

The administered dose per skin wound area (cm^2) in the paediatric population was the same as in adults (i.e. the gel has the same concentration and the amount applied per cm^2 is also the same).

Table 5: Summary of PK parameters measured in all patients from Study MW2010*

Study ID	N	T_{max} Median (range) (h)	C_{max} (ng/mL)	C_{max}/Dose (ng/mL/g)	AUC_{0-4} (h*ng/mL)	AUC_{0-4}/Dose (h*ng/mL/g)	AUC_{last} (h*ng/mL)	AUC_{last}/Dose (h*ng/mL/g)
MW2010-	21	4.0 (0.50 - 12)	200±184 (Min=30.7) (Max=830)	16.4±11.9	516±546	39.8±29.7	2500±2330	215±202

*Values are reported as Mean ± SD, which the exception of T_{max}, which is reported as Median (Min-Max).

Table 6: Summary of PK parameters measured in patients from study MW2012

(Age group years)	T_{max} (h)	C_{max} (ng/mL)	Cmax/Dose (ng/mL/g)	AUC $_{0-4}$ (h*ng/mL)	AUC $_{0-4}$/ Dose (h*ng/mL/g)	AUClast (h*ng/mL)	AUClast/Dose (h*ng/mL/g)
<2[a]	2.00	200	66.7	476	159	876	292
4-11[b]	4.0 (2.0-4.0)	205±169	32.8±23.9	416±259	67.9±44.7	2240±2220	366±350
12-18[c]	4.0 (2.0-4.0)	180±114	19.2±7.50	499±315	53.3±20.4	1560±887	174±67.4

[a]The <2 years age group is a composite profile of samples collected from 2 patients.
[b] PK samples were available for 5 patients in the age 4 to 11 years group.
[c] PK samples were available for 3 patients in the age 12 to 18 years age group.

Comparability of these two studies is corroborated by the fact, that for the oldest subgroup of paediatric patients (12-18 years of age in MW2012-01-01 PK sub-study) after administration of a mean dose of 12.2 g, mean C_{max} was 180 ng/mL, compared to adult C_{max} of 200 ng/mL (after the same mean dose of 12.2 g in MW 2010 PK sub-study).

In the adult PK-study there was a statistically significant correlation between serum C_{max} or AUC_{0-4} values and dose or %TBSA, suggesting a dose or treatment area dependent increase in exposure. The same trend was observed in the CIDS study, although not statistically significant (likely due to the smaller sample size). Analysis of samples by wound depth (all TWs mixed depth [DPT and FT, MIXED], and all TWs DPT [ALL DPT]), comparison of the dose-normalised serum C_{max} and AUC_{0-4} values suggest that the depth of the NexoBrid treated-wound has no significant impact on systemic exposure.

Overall, the PK profile of the age groups 4-11 and 12-18 years of age from the paediatric study was very similar to the PK profile of the adults in study MW 2010-03-02. T_{max} at 4 hours in both populations, C_{max} 180 vs. 200ng/mL (adolescents vs. adults), C_{max}/dose: 19.2 vs. 16.4 ng/mL/g (adolescents vs. adults), AUC_{0-4}/dose 53.3 vs. 39.8 ng/mL/g (adolescents vs. adults) and AUC_{0-24}/dose 174 vs. 178 ng/mL/g.

However, there was a correlation between age and C_{max}/dose (p-value 0.0765) and between age and AUC_{0-4}/dose (p-value 0.0796). The dose normalised C_{max} values e.g. were higher in the age groups < 12 years of age (paediatric vs. adults: 67 ng/mL/g [0-2 years] and 32 ng/mL/g [4-11 years] vs. 16.4 ng/mL/g in adults). When normalised for the dose applied (treatment area), the exposure values increased with lower age.

Table 7 summarizes the normalised PK parameters per treated dose (g) in paediatric and adult patients

Table 7: Summary of normalised PK parameters per treated dose (g) in paediatrics PK patients, paediatric age groups and adults

Mean Normalized PK parameters /dose	Adults PK patients (MW2010-03-02)	Total paediatric PK patients (MW2012-01-01)	Paediatric PK population by age groups		
			0-23 months	4-11 years	12-18 years
C_{max}/dose (ng/mL/g.)	16.4	32.03	66.7	32.8	19.2
AUC_{0-4}/dose (h*ng/mL/g.)	39.8	73.2	159	68.0	53.3
AUC_{0-24} /dose (h*ng/mL/g.	178.0	266.9	340	308.22	173.7
AUC_{last} /dose (h*ng/mL/g)	215.0	293.7	292	366.06	173.7

In general, in the DETECT study, mean elimination half-life values ranged between 12 and 17 hours, supporting low presence of NexoBrid in serum 72 hours post treatment. In CIDS, less than a third of the patients had sufficient data to reliably determine λz.

2.3.3. Pharmacodynamics

Immunogenicity sub-study within MW 2012-01-01

The ADA (anti-drug antibody) evaluable population for study MW2012-01-01 comprised a total of 17/69 patients treated with NexoBrid. Samples were scheduled to be collected at multiple time points to enable the time-course and maximal extent of the treatment-emergent ADA response - relative to the pre-treatment levels - following treatment with NexoBrid. According to the MAH, a highly sensitive assay was used to detect antibodies reactive with NexoBrid. Evaluation of PK was included as an exploratory endpoint, to assess the relationship of ADA signals to the concentration of NexoBrid measured in the systemic circulation. The relationship of pre- and post-treatment levels of ADA to efficacy (time to eschar removal) and incidence and severity of hypersensitivity reactions were also assessed. The CIDS protocol specified that blood samples for ADA testing would be collected only from patients with a body weight of over 18 kg at the screening visit. ADA samples were actually collected from 19 patients, with a total of 69 samples tested in the ADA screening assay. Out of these, 5 patients (29.4%) had an ADA positive result pre-treatment, and 14/17 patients (82.4%) had either treatment-induced or treatment-boosted ADA positive status. For these patients the time of onset occurred relatively soon after NexoBrid administration, with 13/15 patients (86.7%) with ADA results available at Week 4 having a positive ADA result (Table 8).

Table 8: ADA results by sample timepoint for NexoBrid treatment arm (N=17 patients in ADA Evaluable Population)

		Sampling Time Post-treatment				
Statistic	**Baseline**	**1-week**	**4-week**	**8-week**	**6-month**	**24-month**
Number of patients with ADA result	17	4	15	11	10	6
% of ADA evaluable population	100%	23.5%	88.2%	64.7%	58.8%	35.3%
ADA positive	5	1	13	9	9	6
ADA negative	12	3	2	2	1	0
% of ADA positive patients with result at given time point	29.4%	25.0%	86.7%	81.8%	90.0%	100%

ADA = anti-drug antibodies

At 24-months, 6/6 patients (100%) were ADA positive, indicating persistence of the treatment-emergent ADA response. There was a trend for higher post-treatment ADA titres in ADA positive-patients at baseline. Patients with highest baseline ADA titres had dose-adjusted C_{max} values that fell within the range of dose-adjusted C_{max} values observed for ADA negative patients (assigned as ADA titre=1) at baseline. There was no statistically significant difference in time to eschar removal between ADA positive patients at baseline vs. ADA negative at baseline (unpaired t-test, p=0.3539).

As expected, there was no influence of maximal post-treatment ADA titre on time to eschar removal. The ADA report focused on describing the relationship between incidence of adverse events (AEs) related to hypersensitivity and allergic reactions and ADA positive versus negative status at baseline and maximal ADA titre post-treatment. AEs related to hypersensitivity and allergic reactions refer to the following Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries: Anaphylactic reaction, Anaphylactic/anaphylactoid shock conditions, Hypersensitivity, Angioedema, Periorbital and eyelid disorders, Shock-associated circulatory or cardiac conditions (excluding torsade de pointes), Eosinophilic pneumonia and AEs in the MedDRA System Organ Class of Immune Disorders.

The incidence of hypersensitivity reactions, including allergic reactions and cases of rash, was approximately 5% (4/69) of NexoBrid treated patients; 2/69 were considered related. All were mild or moderate in intensity. No cases of anaphylaxis were reported. The only hypersensitivity AEs that occurred within 1 day after study treatment were 4 cases of pruritus treated with antihistamines, and one case of local rash treated with topical hydrocortisone. However, pruritus is a common symptom in patients with burns and 3 out of these 4 pruritus cases were assessed by the investigators as not related to NexoBrid. Overall, the detection of only 2 possibly/probably treatment-related local hypersensitivity reactions (local rash and local pruritus) of mild intensity does not suggest a relationship between pre- or post-treatment ADA status or titre and antibody-mediated AEs.

2.3.4. Discussion on clinical pharmacology

PK substudy

Exploratory PK analyses were performed in a subset of patients who participated in study MW2012-01-01. The substudy included PK blood samples collected from 16/72 NexoBrid treated patients. For the main analysis valid samples from only 10 patients were available (one combined PK profile for subjects < 2 years of age and no PK profile for the age group 2-3 years of age). Additional PK samples (from 6 patients), which were outside the stability period for long term storage were analysed in an additional ancillary analysis.

The ECL assay used in this analysis as well as the analytical site (Q2 Solutions, Marrietta, GA, USA) were the same as described in trial MW2008-09-03 which was assessed in EMA-procedure EMEA/H/C/002246/II/0023. In this procedure the methods were assessed as being acceptable.

The adult PK data from MW2008-09-03 are not comparable with the data from the paediatric CIDS PK-sub-study (e.g. four times higher C_{max} values). A meaningful comparison of adult PK data with paediatric PK data is therefore only possible with the DETECT data and the CIDS data (see discussion below).

Evidence of systemic serum exposure was observed in all paediatric patients. Concentrations increased relatively rapidly, with median T_{max} values between 2 to 4 hours, comparable with adult PK data (median T_{max}: 4.0 hours).

The majority of the patients had no quantifiable concentrations after 48 hours, and no quantifiable concentrations were observed in any patient at 72 hours. Since less than a third of the patients had sufficient data to determine λz, additional parameters (e.g. terminal half-life and AUC_{INF}) could not be reliably determined.

The administered dose per skin wound area (cm^2) in the paediatric population is the same as in adults (i.e. the gel has the same concentration and the amount applied per cm^2 is also the same). The paediatric subjects <12 years of age, in the PK substudy were treated with smaller amounts of NexoBrid (compared to adults): 3 g in p. < 2 years of age, 6.9 g in p. 4-11 years, 12.2 g in p. 12-18 years compared to 12.2 g in adults.

Systemic exposure was correlated to the dose. In the main analysis - when normalised for the dose applied - the exposure values increased with lower age (<12 years).

Overall, the PK profile of the age groups 4-11 and 12-18 years of age from the paediatric study was very similar to the PK profile of the adults in study MW 2010-03-02. Exposure results for C_{max} and AUC were comparable between adults and older children (C_{max} in adults [DETECT]: 200 ± 184 ng/mL vs. C_{max} in children [CIDS]: 180±114 [12-18 years of age], 205±169 [4-11 years of age]) and 200 ng/mL [<2 years of age]. The absolute AUC_{0-4} values in the paediatric patients were lower than in adults (AUC_{0-4} in adults [DETECT]: 516±546 h·ng/mL vs. AUC_{0-4} in children [CIDS]: 499±315 [12-18 years of age], 416±259 [4-11 years of age] and 476 h·ng/mL [<2 years of age]).

However, there was a correlation between age and C_{max}/dose (p-value 0.0765) and between age and AUC_{0-4}/dose (p-value 0.0796). There were higher C_{max}/dose values and higher AUC $_{0-4}$/dose values in the younger children as compared to older children/adolescents and adults. Why this correlation was not also shown for age by Cmax/%TBSA (nor between age by AUC/%TBSA) remains unclear, but it might be related to the small numbers of paediatric PK-profiles.

There is no PK data in children at the age group of 0-12 months and also no PK data in children at the age group for 2-3 years available. It is acknowledged that collection of blood samples for PK in paediatric patients with severe burns is problematic. Furthermore, the lack of PK data does not prevent approval as the safety data for these age groups do not indicate an increased safety risk, which is reassuring.

Due to the high interindividual variability (~factor 7 between lowest and highest C_{max}/dose e.g.), conclusions regarding differences in PK profiles between adults and the paediatric population are difficult to make.

Therefore, the decision on safe use in the different paediatric age groups must not only be based on the scarce PK profiles and the comparison of PK data between adults and children. The assessment of the TEAEs in the pooled paediatric study data, especially the comparison between age groups and the dose subgroups must be taken into consideration as well.

Based on the limited PK and safety results, children 0-3 years of age can be safely treated up to 10% TBSA and children over 4 years of age can be safely treated up to 15% TBSA. The section 4.2 Posology of the SmPC (subsection 'Paediatric population') has been updated accordingly. See discussion on clinical safety.

A summary of paediatric PK data (from the Main Analysis) was incorporated in section 5.2 Pharmacokinetic properties of the SmPC (subsection 'Paediatric population'), which is considered acceptable. In addition, upon CHMP's request, the MAH agreed to only retain PK data from study MW2010 and to remove the PK data from study MW2008 which are considered to be less reliable when compared to data from PK sub-study MW2012.

Immunogenicity substudy

A total of 17 of the 69 patients treated with NexoBrid in study MW2012-01-01 comprised the subset for the Immunogenicity substudy. In the protocol for MW2012-01-01 subjects with a history of allergy and/or known sensitivity to pineapples, papaya, bromelain, or papain were excluded.

The outcomes in this substudy were comparable to the immunogenicity substudy in MW2010-03-02, which was assessed in procedures EMEA/H/C/002246/II/0049 and EMEA/H/C/002246/II/0057.

The ADA-positive status or the ADA-titers did not influence clinical efficacy nor were they related to (severe) hypersensitivity reactions. ADA status or titers were not discriminatory to detect clinically relevant sensitisation or to predict hypersensitivity reactions. No conclusions can therefore be drawn regarding correlation between positive ADA-antibody status (or high titer values) and clinically relevant sensitisation or symptomatic hypersensitivity reactions.

The clinical relevance of the ADA test is therefore considered as insignificant.

Since currently there is no specific immunogenicity test commercially available with a sufficiently good positive predictive value for occurrence of allergic reactions to bromelaine, and specific IgE antibody levels are not seen as reliable in predicting clinical symptoms by clinical experts, hypersensitivity adverse-reaction–monitoring is viewed as the most reliable method for assessing the risk of allergic / anaphylactic reactions. Pre-screening of patients for antigen-specific IgE is considered unnecessary due to the observed low clinical relevance.

In this clinical study AEs in two patients that occurred within one day after treatment (local rash and local pruritus, both of mild intensity) were assessed as possibly/probably related to NexoBrid. Only one of these subjects had available ADA results, and was negative for ADA at pre-dose. The proportion of NexoBrid-treated subjects with ADA results however was low (24.6%).

No cases of anaphylaxis were reported in clinical studies, and the frequency of serious allergic reactions is based on post-marketing data; therefore, the frequency of serious allergic reactions including anaphylaxis in the EU SmPC section 4.8 is labelled as "not known".

The MAH's proposal to omit 'rosiglitazone' since it was withdrawn from the market and 'sorafenib' since there are no records in literature that sorafenib is a substrate for CYP2C8 and CYP2C9 from SmPC section 4.5 was agreed by the CHMP. The patient leaflet was updated accordingly.

No interaction studies have been performed in children/adolescents, which is agreed. This information has been adequately added to SmPC section 4.5.

2.3.5. Conclusions on clinical pharmacology

Exploratory pharmacokinetic analyses were performed in a PK sub-study of study MW2012. PK blood samples were collected from 16 patients treated with a single application of Nexobrid. Summary of paediatric PK data was incorporated in section 5.2 Pharmacokinetic properties of the SmPC (subsection 'Paediatric population').

Based on the (limited) PK and safety results, children 0-3 years of age can be safely treated up to 10% TBSA and children over 4 years of age can be safely treated up to 15% TBSA. The section 4.2 Posology of the SmPC (subsection 'Paediatric population') has been updated accordingly.

2.4. Clinical efficacy

2.4.1. Main study

Paediatric study MW2012-01-01 (CIDS) - a multicenter, multinational, randomised, controlled, open label study, performed in children with thermal burns, to evaluate the efficacy and safety of NexoBrid as compared to Standard of Care (SOC) treatment.

Methods

A 3-stage, multi-center, multi-national, randomised, controlled, open label, 2-arm, superiority efficacy and safety study.

Study participants

Hospitalised paediatric burn victims with DPT and/or FT thermal burns who met the entry criteria below. A total of 145 patients from 36 sites were enrolled, stratified, and randomised 1:1 to NexoBrid or SOC

1. Stage I: Males and females between 4 years to 18 years of age,

   Stage II (upon DSMB review): Males and females between 1 year to 18 years of age,

   Stage III (upon DSMB review): Males and females between 0 years to 18 years of age,

2. Thermal burns caused by fire/flame, scalds or contact,

3. Patient total burns area ≥ 1% DPT and/or FT,

4. Patient total burns area were ≤ 30% TBSA; SPT, DPT and/or FT in depth,

5. Signed written informed consent by a legal guardian obtained within 84 hours of the burn injury.

Treatments

1. 2 or 5 g of NexoBrid sterile powder mixed in 20 or 50 g of sterile Gel Vehicle (ratio of 1:10), to obtain sterile NexoBrid gel (also referred to as NexoBrid). The gel was applied to the burn wound at a dose of 2 g NexoBrid sterile powder mixed with 20 g sterile Gel Vehicle per 180 cm^2 for 4 hours. The NexoBrid powder and the Gel Vehicle were mixed at the patient's bedside ≤15 minutes prior to use. NexoBrid was not applied to more than 15% TBSA in 1 session.

   Prior to the treatment of the first patient at the participating study centres, all investigators and study site staff were trained on the proper application and removal procedures for NexoBrid.

2. SOC included surgical and/or nonsurgical eschar removal procedures. Surgical procedures included tangential, minor, avulsion, Versajet, and dermabrasion excisions. Nonsurgical procedures included the application of antimicrobial solutions (e.g. Dakin's Solution and Sulpha-Nystatin Solution), ointments/creams (e.g. Bacitracin, Polysporin, and Silvadene), and/or silver dressings (e.g. Mepilex Ag, Aquacel Ag, and Acticoat). The need for either nonsurgical or surgical procedures or both was determined by the burn specialists and could have been repeated as needed until complete debridement.

Objectives

- To demonstrate superior enzymatic eschar removal efficacy of NexoBrid by providing earlier, complete eschar removal as compared to SOC.
- To demonstrate superior enzymatic eschar removal efficacy by reducing patients' surgical burden, eschar removal related blood loss and resulting in non-inferior final outcomes of cosmesis and function as compared to SOC.
- To assess the safety of NexoBrid compared to SOC.

Outcomes/endpoints

The co-primary and secondary endpoints in the CIDS study are displayed in Table 9 below.

Table 9: Main study endpoints

Type of Endpoint	Endpoint
Primary Efficacy Endpoint(s)	• Time to complete ER compared to SOC • The % wound area surgically excised for ER • Cosmesis and function using MVSS at 12 months from wound closure
Secondary Efficacy Endpoint(s)	• Incidence of surgical excision performed for ER • Blood loss related to ER • Incidence of autograft performed in DPT wounds • Percent area of Autograft performed in DPT wounds • Cosmesis and function using MVSS at 24 months from wound closure[a]

Sample size

In accordance with the European regulatory requests and planned age distribution, originally a sample size of 80 patients per group was selected to detect with a 90% power a difference on each of the primary endpoints based on the results from the previous study.

However, the COVID-19 pandemic significantly affected all study sites' ability to enrol additional patients. There was a great uncertainty when restrictions would be lifted and study sites would be able to resume enrolment. Therefore, the MAH updated the sample size calculation taking into account the recently completed 12 month follow up of the phase 3 study MW2010-03-02 (DETECT, with 175 adult patients randomised). Power calculations were updated also using data from this latest phase 3 study.

Actual age distribution in the CIDS study was as follows (NexoBrid vs. SOC): 0-11 months 4 vs. 4, 12-23 months 19 vs. 18, 24 months–3 years: 15 vs. 15, 4-11 y. 25 vs. 25 and 12-18 years: 9 vs. 11.

Time to Complete Eschar Removal (estimate based on study MW2010-03-02)

Since the proportional hazards assumption was rejected in study MW2010-03-02 trial, the sample size calculation based in the CIDS study assumed this also to be the case here, and that a generalised Wilcoxon-Gehan test should be used in the analysis. Based on the data from MW2010-03-02, simulations were conducted, resulting in a total sample size of 94 (47 per group) to achieve a power of 90%. The updated sample size calculation confirmed that with a sample size of 145 patients, the study should be sufficiently powered to meet the primary and main secondary and safety endpoints as originally planned.

The enrolment of patients into the study was completed with a total of 145 patients (age distribution: 45 patients ≥0 months and ≤23 months, 30 patients ≥24 months and ≤3 years, 50 patients ≥4 years and ≤11 years and 20 patients ≥12 years and <18 years).

Randomisation

Eligible subjects were stratified into different groups in order to balance the treatment groups with respect to factors that may be related to efficacy and safety outcomes. Four factors were used to stratify the subjects.

A. Age group: A1: 0 to 23 month, A2: 24 months to 3 years, A3: 4 to 11 years, A4: 12 to 18 years,

B. Overall total area of burns measured by % of TBSA: B1: (1% to 15%), inclusive, B2: (> 15% to ≤ 30%),

C. The proportion of the FT area out of the total burned area of a patient: C1: < 20% of the burned area defined as FT, C2: ≥ 20% of the burned area defined as FT,

D. Clinical centre, to address possible differences in SOC procedures between sites (if any), to allow comparison of the results within centre and to reduce the likelihood of a centre including patients in only one arm of the study. D1, D2,…, Dm (m being the number of participating clinical centres).

Following the stratification, patients were randomised (as per their stratification group) in a 1:1 ratio (NexoBrid : SOC).

Treatment allocation was performed using the method of minimisation (Pocock and Simon, 1975; White and Freedman, 1978) with stratification by the factors A, B, C and D: age group, overall % TBSA, % TBSA of all TW wounds, overall % of FT area, and clinical centre. Randomisation was conducted using an interactive web-based response system.

Blinding (masking)

Study treatment randomisation was not blinded in this study due to the visual differences between NexoBrid and surgical and non-surgical SOC. Eschar removal and wound closure assessments were not blinded assessments.

Cosmesis, Function and QOL were assessed by an assessor blinded to the original treatment arm at 6 and 12 weeks from reaching complete wound closure and at 6, 12, 18, 24, and ≥30 months from reaching complete wound closure.

Statistical methods

A hierarchical testing procedure for the primary endpoints was used, in which *Timely Eschar Removal* was tested first using a two-tailed superiority test at the significance level of 0.05 and then - if the effect was statistically significant - *% wound area excised* was tested. If the effect on both was statistically significant, then *scar assessment by MVSS* was tested using a one-tailed non-inferiority test at the significance level of 0.025. The outcome of the trial was to be declared successful only if all three endpoints reached the significance levels mentioned.

Time to complete eschar removal

Time until complete eschar removal refers to all TWs (time from randomisation in days). Kaplan-Meier curves were to be presented to display the distribution under the two treatments (using the FAS). Median time to complete eschar removal was to be estimated for each treatment group with a 95% confidence interval. The treatment groups were compared using a Cox regression model. The comparison should be adjusted for centre, age, %TBSA, proportion of the FT area of a patient and number of TWs (1,2,3-4, ≥5) by including each of them in the Cox regression model together with the treatment variable (NexoBrid vs. SOC). The treatment groups were to be compared by testing the null hypothesis of no difference, comparing the ratio of the estimated treatment coefficient to its standard error to a standard normal distribution. The Cox Regression analysis was to be performed, if the proportional hazards assumption appeared to hold. This was to be checked by including in the regression model a variable representing the interaction between time since randomisation and treatment group. This coefficient should be tested to be non-zero. Additionally, a log likelihood test comparing the model fit of a model with time dependent factors with a model with constant factors should be computed. The proportionality assumption was to be rejected if one of these tests yielded a significant result at the 10% level. If both tests produced non-

significant results, then the time-treatment group interaction should be significant, then a generalised Wilcoxon-Gehan test was to be used.

Supportive analyses included adjustment for other baseline variables that were imbalanced, and investigating interactions between baseline variables and the treatment groups. The comparison between treatments using Cox regression should also be conducted on the time of complete eschar removal measured from the date of ICF as secondary analysis.

Percent Wound Area Surgically Excised for Eschar Removal

Descriptive statistics of the observed values on a subject level (including the number of missing values) should be provided by treatment group (in the FAS). Missing values were to be imputated involving the multiple imputations procedure. An overall estimate of the treatment difference with its standard error should be reported, together with the final combined p-value. As a sensitivity analysis, the main analysis should be repeated using the PP as analysis population instead of the FAS. Secondary analyses of this primary endpoint should include adding other baseline variables that are imbalanced, all within the re-randomisation test framework. In another secondary analysis, a percent wound area surgically excised for eschar removal should be analysed on a TW level. The difference in the means of the treatment groups should be compared using a linear mixed model, with the correlations between TWs within the same patient being described by the compound symmetry pattern. The explanatory variables in the model should include treatment group (NexoBrid vs. SoC), treatment centre and %TBSA. This analysis should yield an estimate of the difference in means between the two groups, adjusted for centre and %TBSA. The re-randomisation test procedure should then be applied as in the primary analysis.

Cosmesis and Function at 12 Months from Wound Closure

Descriptive statistics of MVSS score at 12 months should be provided by treatment group, for both observed and imputed data. The treatment groups should be compared (using the FAS) using a linear model with imputed MVSS score at 12 months as the dependent variable. The explanatory variables in the model should include treatment, and the following variables: treatment centre, age, %TBSA, proportion of the FT area of a patient and number of TWs (1, 2, 3-4, ≥5). The coefficient corresponding to the treatment group should be estimated and should represent the estimated mean difference in MVSS score at 12 months between NexoBrid and SoC (adjusted for any imbalance in the stratification factors). A clinically meaningful difference should be incorporated into the analysis (1.9 or more units advantage to SOC), so that the analysis will show whether the NexoBrid group is estimated to have on average a MVSS score not worse than 1.9 units vs. SoC. The following hypotheses are about to be tested: H_0: $\Delta \geq 1.9$ vs. H_1: $\Delta < 1.9$, where Δ is the mean difference in MVSS score between NexoBrid and SoC adjusted for any imbalance in the stratification factors. These hypotheses should be tested by comparing the 95% confidence interval for the coefficient of the treatment group from the linear model outlined above to the clinically meaningful difference 1.9. The null hypothesis will be rejected if the upper bound of this interval is smaller than 1.9. As sensitivity analysis, the procedure should be repeated using the PP instead of the FAS. The analyses should be performed using both on-site and remotely collected evaluations, with missing values imputed. In addition, a sensitivity analysis should be performed (similar to the main analysis described above) to explore the possible influence of remotely captured data. For this, the remote evaluations should be "corrected", and missing values at 12 months should be imputed on observed on-site evaluations and "corrected" remote evaluations.

Secondary Analyses

Incidence of Surgical Excision

This is a binary yes/no variable and the proportion of patients who need excision will be compared using logistic regression. The explanatory variables in the model will include treatment, center, age, %TBSA, proportion of the FT area of a patient and number of TWs (1,2,3-4, ≥5). The odds ratio of requiring

surgery for NexoBrid versus SoC will be estimated from the model, as well as a 95% confidence interval and the level of statistical significance. As sensitivity analysis, the procedure will be repeated using the PP instead of the FAS population. A supportive analysis will be performed adjusting for other baseline variables that are imbalanced. As an additional analysis, the incidence of surgical excision will be compared on a wound level using a mixed logistic regression model with a random effect for patient.

Blood Loss

The measure of blood loss per patient will be computed using two different methods:

- Method 1: treating the whole eschar removal process as one continuous procedure.

- Method 2: summing the blood loss computed per procedure over all procedures carried out to remove eschar. Descriptive statistics of the blood loss values will be provided by treatment group. The imputation of missing values should be done involving the multiple imputations procedure. An overall estimate of the treatment difference with its standard error will be reported, together with the final combined p-value. The analysis with less missing values will be regarded as more reliable and is therefore considered the main analysis. The other analysis is considered supportive. As sensitivity analysis, the analysis outlined above will be repeated using the PP instead of the FAS as analysis population. A supportive analysis will be performed adjusting for other baseline variables that are imbalanced.

Note: No wound level analysis of this endpoint is possible, since blood loss cannot be attributed to single target wounds.

Incidence of Autograft in DPT Wounds

This is a binary yes/no variable and the proportion of Deep Partial Thickness TWs that were autografted will be compared (on a wound level). The comparison of NexoBrid vs. SOC will be conducted using logistic regression within the generalised estimating equations framework that accounts for within-subject correlation between target wounds. The explanatory variables in the model will include treatment, center, age, %TBSA (wound level), proportion of the FT area of a patient and number of TWs (1,2,3-4, ≥5). The odds ratio of requiring Autograft for NexoBrid vs. SOC will be estimated from the model, as well as 95% confidence intervals and the level of statistical significance. As sensitivity analysis, the procedure will be repeated using the PP instead of the FAS. Supportive analyses will include adjustments for baseline variables which are found to be imbalanced. These analyses will only take into account DPT target wounds.

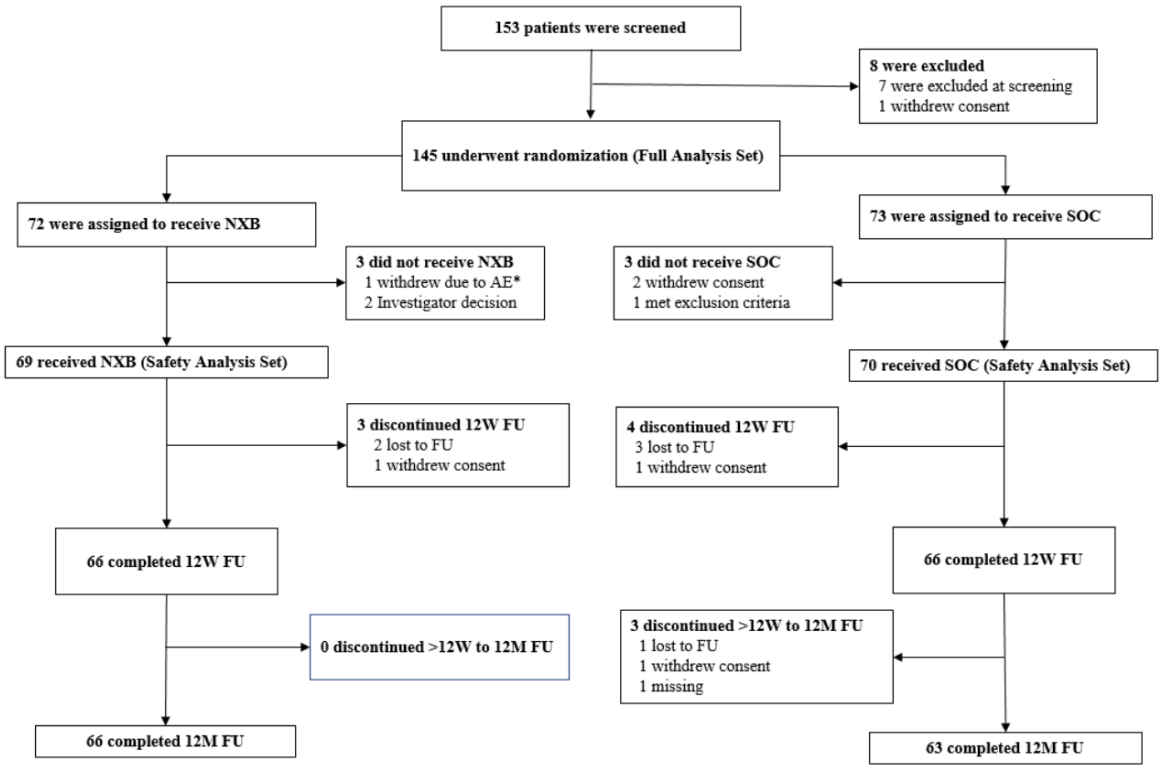
Area of Autograft in DPT Wounds

For the purpose of the main analysis, the mean %area of autograft in DPT wounds will be compared on a subject level between NexoBrid and SOC. This analysis will be restricted to subjects having at least one DPT target wound. Descriptive statistics of the observed values on a subject level (including the number of missing values) will be provided by treatment group. The imputation of missing values will be done involving the multiple imputations procedure. An overall estimate of the treatment difference with its standard error will be reported, together with the final combined p-value. As sensitivity analysis, the main analysis will be repeated using the PP instead of the FAS, also restricted to subjects having at least one DPT target wound. Supportive analyses on a subject level will include adjustments for additional baseline variables which are found to be imbalanced.

As an additional analysis, the percent area autografted in DPT target wounds will be analysed on a target wound level. This analysis will be restricted to DPT target wounds only. Descriptive statistics will be provided on a target wound level for each treatment group. The differences in the distribution of %area autografted in DPT wounds between the treatment groups will be tested using a mixed linear regression model with patient as the random effect that accounts for within-subject correlation between target wounds.

Results

Participant flow



* Patient 1103-001 was randomised but discontinued from the study due to an adverse event prior to receiving study treatment. 12M = 12 month follow-up period; 12W FU = 12 weeks following wound closure follow-up period, AE = adverse event, FU = follow-up, NXB = NexoBrid, SOC = standard of care

Recruitment

Inclusion criteria:

Inclusion criteria at the patient level:

- Stage 1: Males and females between 4 - 18 years; Stage 2 (upon DSMB review): males and females between 1 - 18 years; and Stage 3 (upon DSMB review): males and females between 0 years - 18 years of age,
- Thermal burns caused by fire/flame, scalds or contact,
- Patient total burns area ≥1% DPT and/or FT,
- Patient total burns area were ≤30% TBSA; SPT, DPT and/or FT in depth,
- Signed written informed consent by a legal guardian obtained within 84 hours of the burn injury.

Inclusion criteria at the wound level:

At least one wound (a continuous burn area which could have been treated in one session; may have included several anatomical areas) in a patient should have met all the following criteria:

- Wound that was ≥1% TBSA (DPT and/or FT) (not including face, perineal or genital),
- Wound was composed of DPT and/or FT in depth. Superficial partial thickness areas may have been included in the wound area only if it could not be separated from deeper areas (e.g. surrounded by or mixed with DPT areas) and may have interfered with the treatment of the deeper areas,
- Wound that was intended for surgical ER,
- Wound's blisters could have been unroofed, as judged by the investigator.

Exclusion criteria

Exclusion criteria included standard clinical study exclusion (e.g. pregnant patients or nursing mothers, drug or alcohol abuse, current suicide attempt, participation in other clinical studies), and other burn-specific or safety criteria including exclusion of patients with:

- Patients who weighed less than 3 kg,
- Diagnosis of smoke inhalation injury,
- History of allergy and/or known sensitivity to pineapples, papaya, Bromelain, or papain,
- Cardiopulmonary disease, pre-existing disease which interfered with circulation, immediate life-threatening conditions, chronic systemic steroid intake, poorly controlled diabetes,
- Facial, perineal, and/or genital burns. A patient with these wounds may have been enrolled but the wounds were not to be designated as target wounds,
- Electrical or chemical burns,
- Patient with a continuous burn area above 15% TBSA,
- Patients with no DPT and/or FT burn area (only SPT wounds),
- Patient with circumferential anterior/posterior trunk fire/flame burns, >15% TBSA (circumferential is defined as encircling ≥ 80% of the trunk circumference),
- Serious pre-existing infection that impaired the patient's safety or interfered with study procedures,
- Pre-enrolment wounds which were covered by eschar heavily saturated with iodine or by SSD pseudoeschar (e.g. pseudoeschar as a result of >12h SSD treatment) or with pre-enrolment dressings with flammacerium or silver nitrate,
- Pre-enrolment escharotomy.

Conduct of the study

The study was conducted in 3 stages; with only children aged 4 to 18 years, hospitalised in burn units, enrolled in Stage 1. A safety analysis was performed on these patients by a DSMB. If the DSMB did not have any safety concerns Stage 2 started, enrolling children between the ages of 1 to 18 years of age. After the 50th patient had reached wound closure, an additional safety analysis was performed by the DSMB. If no safety concerns were raised Stage 3 commenced, this time enrolling children ages 0 to 18 according to study procedures.

After reviewing the entry criteria, eligible patients were stratified based on age, overall total area of burns (% TBSA), proportion of the FT area (out of the total burned area) and clinical centre groups. Following the stratification and identification of TW(s), patients were randomised as per their stratification group in a 1:1 ratio to NexoBrid or SOC. Patients in both treatment arms were treated in a similar way except for

the eschar removal stage. All of a patient's DPT and FT burns that met the specified entry criteria were defined as TWs and were to receive study treatment per the randomised treatment arm. Prior to initiation of eschar removal treatment, patients were medicated with appropriate analgesia and underwent wound cleansing and dressing of all wounds with antibacterial solutions.

Baseline data

Overall, patients' age, ethnicity, height, weight and body mass index (BMI) were similar between treatment arms. The majority of patients were male (NexoBrid: 58.3% vs. SOC: 65.8%), and the median age was 3.54 years (NexoBrid: 3.37 years vs. SOC: 3.94 years). The mean BMI was 16.88 kg/m^2 and 17.09 kg/m^2, respectively (NexoBrid vs. SOC). Most patients were white (NexoBrid: 70.8% vs. SOC: 68.5%), with 4.2% and 9.6%, respectively Hispanic or Latino ethnicity.

Table 10: Patient Demographics (FAS)

Variable Statistics	NexoBrid (N=72)	Standard of Care (N=73)	Overall (N=145)
Age (years)			
n	72	73	145
Mean	5.71	5.83	5.77
SD	4.838	4.909	4.857
Median	3.37	3.94	3.54
Min, Max	0.6, 18.6	0.7, 16.7	0.6, 18.6
Quantiles 25%, 75%	1.67, 9.46	1.77, 9.66	1.70, 9.51
Age Group, n (%)			
0 - 23 Months	23 (31.9)	22 (30.1)	45 (31.0)
24 Months - 3 Years	15 (20.8)	15 (20.5)	30 (20.7)
0 - 3 Years	38 (52.8)	37 (50.7)	75 (51.7)
4 - 11 Years	25 (34.7)	25 (34.2)	50 (34.5)
12 - 18 Years	9 (12.5)	11 (15.1)	20 (13.8)
Gender, n (%)			
Female	30 (41.7)	25 (34.2)	55 (37.9)
Male	42 (58.3)	48 (65.8)	90 (62.1)
Race, n (%)			
White	51 (70.8)	50 (68.5)	101 (69.7)
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3 (4.2)	3 (4.1)	6 (4.1)
Asian	17 (23.6)	16 (21.9)	33 (22.8)
American Indian or Alaska Native	0	1 (1.4)	1 (0.7)
Other	1 (1.4)	3 (4.1)	4 (2.8)
Ethnicity, n (%)			
Hispanic or Latino	3 (4.2)	7 (9.6)	10 (6.9)
Not Hispanic or Latino	69 (95.8)	66 (90.4)	135 (93.1)

Variable Statistics	NexoBrid (N=72)	Standard of Care (N=73)	Overall (N=145)
Height (cm)			
n	72	73	145
Mean	110.6	111.9	111.3
SD	31.65	32.92	32.19
Median	100.0	102.0	101.0
Min, Max	65, 186	65, 180	65, 186
Quantiles 25%, 75%	85.0, 140.0	86.0, 128.0	85.0, 133.0
Weight (kg)			
n	72	73	145
Mean	23.49	24.82	24.16
SD	19.544	20.351	19.896
Median	14.75	15.00	15.00
Min, Max	7.0, 102.0	7.0, 85.0	7.0, 102.0
Quantiles 25%, 75%	11.00, 32.00	12.00, 30.00	11.00, 30.00
BMI (kg/m^2)			
n	72	73	145
Mean	16.88	17.09	16.99
SD	4.368	4.108	4.226
Median	16.32	16.22	16.22
Min, Max	2.4, 32.2	10.4, 32.6	2.4, 32.6
Quantiles 25%, 75%	14.24, 18.51	14.13, 19.38	14.20, 18.75

BMI = body mass index, FAS = Full Analysis Set, Max = maximum value observed, Min = minimum value observed, SD = standard deviation.

The majority of physical examinations in all categories were normal (and similar between treatment arms). Of the abnormal physical examinations, 2 (1 patient each for NexoBrid and SOC) were considered clinically significant with the remaining 4 (1 patient for NexoBrid vs. 3 patients for SOC) considered not clinically significant. The majority of patients (in both treatment arms) were assessed as having normal vital signs and pain assessments (and no patient had abnormal CS vital sign or pain assessments at baseline). The vital signs and baseline pain assessments were similar in both treatment arms. No patient had a positive diabetes status at baseline.

Several baseline factors (gender, percent SPT area [as % of the total TW-area, classified as <25% or ≥ 25%], time from injury to randomisation and number of TWs [1, 2, 3-4 and ≥5]) were compared between the two treatment arms (Table 11).

None of the pre-specified baseline factors were found to be significantly different between the treatment arms at the 0.15 significance level.

Table 11: Results of Baseline Tests for Homogeneity (FAS)

Variable	Test	p-value	Inhomogeneous
Gender	Chi-Square Test	0.3572	No
Time from Injury to Randomisation	One-way ANOVA	0.2186	No
% SPT Area (classified as <25% or ≥25%)	Chi-Square Test	0.5640	No
Number of TWs (1, 2, 3-4, or ≥5)	Chi-Square Test	0.4731	No

ANOVA = analysis of variance, FAS = full analysis set. SPT = superficial partial thickness, TW = target wound

The mean time since injury to randomisation was 41.0 and 37.3 hours (NexoBrid vs. SOC) respectively. The majority of patients in both treatment arms had burns caused by scald (NexoBrid: 68.1% vs. SOC: 65.8%), followed by fire/flame (NexoBrid: 25.0% vs. SOC: 26.0%). For the majority of patients, the place of injury was indoors (NexoBrid: 75.0% vs. SOC: 76.7%).

Target Wound Description at Baseline

Target wounds were assessed and analysed on a TW level (N=192) and a patient level (N=145). There was a total of 98 TWs in the NexoBrid arm vs. 94 TWs with SOC. The average number of TWs per patient was 1.36 with NexoBrid (98 TWs/72 patients) vs. 1.29 with SOC (94 TWs/73 patients). The descriptive statistics of the % TBSA of an average TW are presented in Table 12.

Table 12: Target Wound Description, Target Wound Level (FAS)

Variable Statistics	NexoBrid (N=98)	SOC (N=94)
Percent TBSA of 2° SPT Burns[a]		
n	98	94
Mean	0.88	0.93
SD	1.312	2.010
Median	0.00	0.00
Min, Max	0.0, 5.3	0.0, 10.0
Quantiles 25%, 75%	0.00, 2.00	0.00, 1.00
Percent TBSA of 2° DPT Burns[a]		
n	98	94
Mean	2.91	2.72
SD	2.502	2.567
Median	2.00	2.00
Min, Max	0.0, 14.5	0.0, 14.0
Quantiles 25%, 75%	1.50, 4.00	1.00, 4.00
Percent TBSA of 3° FT Burns[a]		
n	98	94
Mean	0.50	0.47
SD	1.667	1.265
Median	0.00	0.00
Min, Max	0.0, 11.0	0.0, 9.0
Quantiles 25%, 75%	0.00, 0.00	0.00, 0.10

DPT = deep partial thickness, FAS = full analysis set, FT = full thickness, Max = maximum, Min = minimum, SOC = standard of care, SPT = superficial partial thickness, TBSA = total body surface area a Percent TBSA based on clinical assessment.

Target Wound Description at Baseline - Patient Level

Overall, the mean TW area (% TBSA of SPT+DPT+ FT TWs) was 5.85% (SD 4.431) for NexoBrid-patients vs. 5.30% (SD 4.273) in SOC-patients. Mean % TBSA of all TWs was similar across treatment arms for each variable (DPT, FT, and SPT). The descriptive statistics of the % TBSA of all TWs (on a patient level) are shown by treatment arm and wound depth in Table 13.

Each TW was composed of DPT and/or FT areas. However, SPT areas that could not be separated from the DPT areas were included in the TW. SPT areas of TWs were not considered for this analysis. If the FT was 0 then the TW was considered DPT; if the DPT was 0, then the TW was considered FT; and if the TW had both DPT and FT it was considered mixed.

Table 13: Target Wound Description as % TBSA– Patient Level (FAS)

Variable Statistics	NexoBrid (N=72)	Standard of Care (N=73)	Overall (N=145)
Total wounds (% TBSA)			
n	72	73	145
Mean	7.01	6.20	6.60
SD	4.879	4.777	4.828
Median	5.75	4.70	5.10
Min, Max	1.3, 23.5	1.0, 29.1	1.0, 29.1
Quantiles 25%, 75%	3.00, 9.35	3.10, 7.70	3.00, 8.60
TWs DPT total area (% TBSA)			
n	72	73	145
Mean	3.96	3.50	3.73
SD	3.857	3.684	3.765
Median	2.20	2.50	2.50
Min, Max	0.0, 23.5	0.0, 23.0	0.0, 23.5
Quantiles 25%, 75%	1.50, 5.00	1.00, 5.00	1.50, 5.00
TWs FT total area (% TBSA)			
n	72	73	145
Mean	0.69	0.60	0.64
SD	1.966	1.442	1.717
Median	0.00	0.00	0.00
Min, Max	0.0, 11.0	0.0, 9.0	0.0, 11.0
Quantiles 25%, 75%	0.00, 0.00	0.00, 0.50	0.00, 0.00
TWs SPT total area (% TBSA)			
n	72	73	145
Mean	1.20	1.20	1.20
SD	1.637	2.242	1.958
Median	0.50	0.00	0.00
Min, Max	0.0, 7.3	0.0, 10.0	0.0, 10.0
Quantiles 25%, 75%	0.00, 2.00	0.00, 1.00	0.00, 2.00

Variable Statistics	NexoBrid (N=72)	Standard of Care (N=73)	Overall (N=145)
Overall TW area (% TBSA)[a]			
n	72	73	145
Mean	5.85	5.30	5.57
SD	4.431	4.273	4.346
Median	4.00	4.00	4.00
Min, Max	1.0, 23.5	1.0, 23.0	1.0, 23.5
Quantiles 25%, 75%	3.00, 8.00	2.00, 6.50	2.60, 8.00

FT = full thickness, DPT = deep partial thickness, Max = maximum value observed, Min = minimum value observed, SPT = split partial thickness, TBSA = total body surface area, TW= target wound

[a] Overall TW area = SPT+DPT+ FT.

The TW depth of the majority of TWs (on a patient level) was DPT for both treatment arms; however, the proportion of patients with DPT TWs was higher in the NexoBrid arm (80.6%) vs. SOC (71.2%). The proportion of patients with mixed thickness TWs was lower in the NexoBrid arm (13.9%) vs. SOC

(21.9%). The proportion of patients with full thickness TWs was 5.6% with NexoBrid arm vs. 6.2% with SOC respectively.

Numbers analysed

Of the 153 patients enrolled, 145 patients were randomised and included in the FAS: NexoBrid 72 vs. SOC: 73. Of the 145 patients randomised, 139 (95.9%) patients were treated and included in the SAS: NexoBrid: 69 (95.8%) vs. SOC: 70 (95.9%). Six patients were randomised (NexoBrid :3 vs. SOC: 3) but did not receive treatment. Among these 6 patients:

• 1 NexoBrid-patient withdrew due to AE prior to treatment, according to Investigator decision.

• 1 NexoBrid-patient experienced a fever and possible wound infection after randomisation and the PI decided not to treat according to the randomisation,

• 1 NexoBrid-patient was not treated because the PI falsely thought that the site did not have an ethics committee approval in place.

• 2 SOC-patients had their consent withdrawn by parent,

• 1 SOC-patient met 1 or more exclusion criteria.

Of the patients randomised in the study, 132 patients (NexoBrid: 66 [91.7%] patients vs. SOC: 66 [90.4%]) completed the 12 weeks post wound closure FU period and 129 patients (NexoBrid: 66 [91.7%] vs. SOC: 63 [86.3%]) completed the 12 months FU period. The most common reasons for discontinuation from the study were "lost to follow up" and "patient withdrew consent to continue in the study". No patients who received study treatment discontinued due to AEs, deaths, protocol deviations, or left hospital against advice.

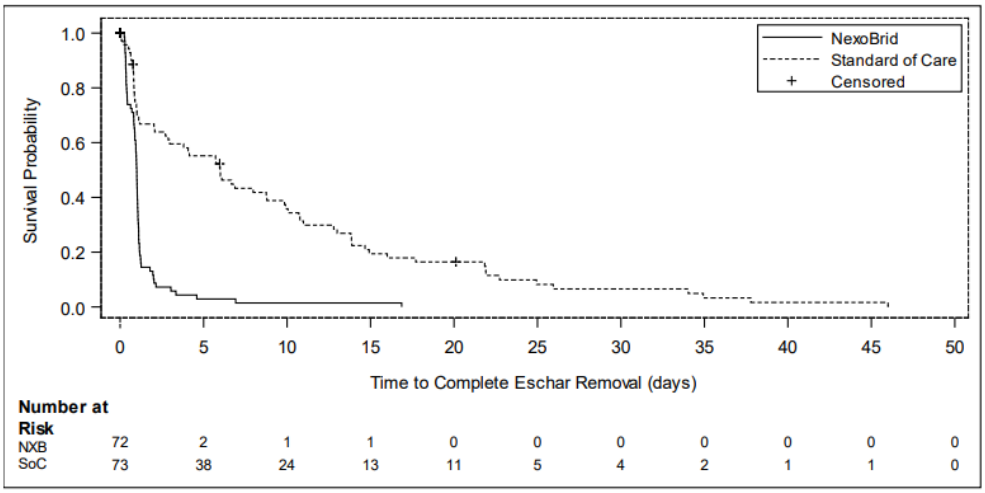
Outcomes and estimation

Co-Primary Efficacy Endpoints

Time to Complete Eschar Removal

The Kaplan-Meier estimates for time to complete eschar removal (in days from randomisation until complete eschar removal in all TWs) in the FAS (main analysis) are shown in Figure 3. The estimated median time to complete eschar removal (Kaplan-Meier method) was 0.99 days (95% CI: 0.88 to 1.04) for NexoBrid vs. 5.99 days (95% CI: 2.71 to 9.84) for SOC.

Figure 3: Kaplan-Meier Curves for Time (in days) to Complete Eschar Removal - Main Analysis, Patient Level (FAS)



FAS = full analysis set, NXB=NexoBrid, SOC=Standard of Care

The proportional hazards assumption for time to complete eschar removal was checked by including in a Cox regression model adjusted for clinical centre, age, % TBSA, proportion of the FT area of a patient, and number of TWs (1, 2, 3-4, ≥5). The coefficient of the time-treatment interaction of this model was significant at the 5% level (p-value <0.0001). Therefore, a generalised Wilcoxon-Gehan test was performed. The results demonstrated superiority of NexoBrid over SOC. The effect was statistically significant (p-value = 0.0008 at the significance level of 0.05).

Table 14: Time to complete eschar removal (main analysis), results of the generalised Wilcoxon-Gehan test adjusted for clinical centre, age, % TBSA, proportion of the FT area of a patient and number of TWs (FAS)

Treatment	Value of the Test Statistics	p-value
NexoBrid vs SOC	77.0	0.0008

FAS = full analysis set, FT = full thickness SOC = standard of care, TBSA = total body surface area, TW = target wound

Four sensitivity analyses were performed for the primary endpoint "Time to complete Eschar Removal" according to the SAP. Results of all sensitivity analyses showed that the time to complete eschar removal in the NexoBrid arm was statistically significantly shorter than with SOC (Table 15). These sensitivity analyses support the results of the main analysis.

Table 15: Time to complete eschar removal (sensitivity analyses): results of the Generalised Wilcoxon-Gehan test adjusted for clinical centre, age, % TBSA, proportion of the FT area of a patient and number of TWs (FAS)

Analysis	Analysis Set	Treatment	Value of the Test Statistics	p-value
First Sensitivity[a]	FAS, Patient Level	NexoBrid vs SOC	85.0	0.0004
Second Sensitivity[b]	FAS, Patient Level	NexoBrid vs SOC	86.0	0.0003
Third Sensitivity[c]	FAS, Patient Level	NexoBrid vs SOC	86.0	0.0003
Fourth Sensitivity[d]	PP Set, Patient Level	NexoBrid vs SOC	67.0	0.0010

FAS = full analysis set, FT = full thickness SOC = standard of care, TBSA = total body surface area, TW = target wound.

Percent Wound Area Surgically Excised

Analysis results of the percent wound area surgically excised (on a patient level, FAS) is presented in Table 16. The mean (SD) percent wound area surgically excised was statically significantly lower for NexoBrid (1.5 [12.13]) vs. SOC (48.1 [46.58]) (p-value <0.0001).

Table 16: Percent Wound Area Surgically Excised for Eschar Removal – Main Analysis, Patient Level (FAS)

Statistics	NexoBrid (N=72)	Standard of Care (N=73)
n[a]	68	68
Mean	1.5	48.1
SD	12.13	46.58
Median	0.0	40.0
Min, Max	0, 100	0, 160
Quantiles 25%, 75%	0.0, 0.0	0.0, 100.0
Number of Missing Observations	4	5
Analysis Results[b]		
Treatment Difference Estimate	-45.5	
SE of Treatment Difference Estimate	6.83	
p-value	<0.0001	

ANOVA = analysis of variance, FAS = Full Analysis Set, Max = maximum value observed, Min = minimum value observed, SE = standard error. Descriptive statistics summarise the observed endpoint values on a patient level. Unit of measurement is percent. b Analysis statistics were estimated in 3 steps. In the first step, missing values were imputed using multiple imputations procedure. In the second step, each imputed dataset was analysed with ANOVA model, using the re-randomisation test. The model included the following covariates: treatment arm, centre group, age group, % TBSA group, proportion of FT area group and number of TWs group. In the third step, the results across imputed datasets were pooled. Since each imputed dataset's re-randomised p-value was zero, the re-randomised p-values were replaced with 1E-11 to enable further computations.

A sensitivity analysis of this co-primary endpoint was performed using the PP set instead of the FAS. In the PPS, the mean (SD) percent wound area surgically excised for eschar removal on a patient level in the NexoBrid arm was 1.7 (12.60) vs. 48.5 (46.73) in the SOC arm. The results indicate that the mean % wound area surgically excised is lower in the NexoBrid arm compared to SOC (p-value <0.0001) in the PPS, supporting the main analysis of this endpoint.

An additional analysis for this co-primary endpoint was performed on the TW level, using all TWs with observed endpoint values from patients included in the FAS. The mean % wound area surgically excised on a TW level was 1.1 (SD 10.38) for NexoBrid vs. 51.4 (SD 46.67) for SOC. The results indicate that the mean % wound area surgically excised on a TW level is lower in the NexoBrid arm vs. SOC (p-value <0.0001) in the FAS set, supporting the main analysis of this endpoint.

Cosmesis and Function (MVSS) at 12 Months from Wound Closure

The main analysis (using the FAS) consisted of linear regression analysis of 12-month MVSS scores using imputation for missing data as outlined in the SAP (Note: Lower MVSS scores indicate better clinical outcome). The coefficient corresponding to the treatment arms represent the estimated mean difference in MVSS score at 12 months between NexoBrid and SOC adjusted for any imbalance in stratification factors. The descriptive statistics for the imputed data show the mean 12-month MVSS score for NexoBrid was lower (3.83 [SD 2.876]) than for SOC (4.86 [SD 3.256]) (Table 17). The regression results show an estimated treatment difference for NexoBrid vs. SOC of -2.76 (Table 18). The 95% CI for this treatment difference estimate is -3.67 to -1.85. Since the upper bound of this CI does not include the pre-defined NI margin of 1.9 points, NI of NexoBrid treatment compared with SOC was established at the predefined one-sided significance level of 0.025 (p-value<0.0001).

Table 17: Descriptive Statistics of MVSS Scores at 12 Months (FAS)

Treatment	MVSS (at 12 Months)								
	N	Missing	Mean	SD	Min	Q 25%	Median	Q 25%	Max
Observed[a]									
NexoBrid	56	16	3.70	2.931	0.00	1.00	3.00	6.00	11.0
SOC	52	21	4.52	3.306	0.00	2.00	4.00	7.00	12.0
Imputed[b]									
NexoBrid	72	NA	3.83	2.876	0.0	1.04	3.11	6.00	11.0
SOC	73	NA	4.86	3.256	0.0	2.00	4.92	7.00	12.0

Max = maximum value observed, Min = minimum value observed, MVSS = Modified Vancouver Scar Scale, Q 25% = first quartile, Q 75% = third quartile, SAS = safety analysis set, SD = standard deviation, SOC = standard of care

[a] Descriptive statistics for observed data.

[b] Descriptive statistics based on imputed data. Data imputed with prediction of linear regression modelling, as detailed in the SAP.

Table 18: MVSS Regression Results at 12 Months (FAS)

	Analysis Results[a]			
Variable	Treatment Difference Estimate	Lower 95% Confidence Bound	Upper 95% Confidence Bound	p-value
Treatment: NexoBrid vs SOC	-2.76	-3.67	-1.85	<0.0001

MVSS = Modified Vancouver Scar Scale, NI = non-inferiority; SAS = safety analysis set, SOC = standard of care

[a] Analysis results obtained using linear model with imputed data at 12 months as dependent variable, and treatment arm, centre group, age group, % TBSA group, proportion of FT area group and number of TWs group as explanatory variables. A clinically meaningful difference was incorporated into the model to represent a 1.9 or more units advantage to the Standard of Care treatment arm. P-value is a one-sided p-value, obtained from the analysis model based on re-randomisation allocation, for testing the NI hypotheses, as detailed in the SAP, at the significance level of 0.025.

Best case and worst-case imputations were performed on the FAS as sensitivity analyses for this co-primary endpoint. For the best-case imputation missing MVSS at 12M was imputed as 0 (observed minimum MVSS value for SOC in previous Study MW2004-11-02). The descriptive statistics for the imputed data showed the mean 12-month MVSS score for NexoBrid was lower (2.88 [SD 3.008]) than for SOC (3.22 [SD 3.462]). The regression results show an estimated treatment difference for NexoBrid vs. SOC of -2.13 (95% CI: -3.21 to -1.05). Since the CI does not include the pre-defined NI margin of 1.9 points, NI of NexoBrid treatment compared with SOC was established at the one-sided significance level of 0.025 (p-value<0.0001), supporting the main analysis of this endpoint.

For the worst-case imputation, missing MVSS at 12M was imputed as 9 (observed maximum MVSS value for SOC in study MW2004-11-02). The descriptive statistics for the imputed data showed that the mean 12-month MVSS score for NexoBrid was lower (4.88 [SD 3.403]) than for SOC (5.81 [SD 3.452]). The regression results showed an estimated treatment difference for NexoBrid vs. SOC of -2.60 (95% CI: -3.58 to -1.63). The CI does not include the NI margin of 1.9 points. NI of NexoBrid treatment was therefore shown at the one-sided significance level of 0.025 (p-value<0.0001), supporting the main analysis of this endpoint.

An additional sensitivity analysis was performed using the PP set. The descriptive statistics for the imputed data showed that the mean 12-month MVSS score for NexoBrid was lower (3.67 [SD 2.869]) than for SOC (4.54 [SD 3.127]). The treatment difference for NexoBrid vs. SOC is -2.59 (95% CI: -3.54 to -1.64), which was similar to the main, and best case and worst-case analyses. Again, NI of NexoBrid vs. SOC was shown at the one-sided significance level of 0.025 (p-value<0.0001), supporting the main analysis.

Based on the hierarchical testing procedure, the main analysis was considered as confirmatory. Each of the co-primary endpoints can be interpreted inferentially only if a statistically significant treatment effect was detected in the preceding endpoint. The outcome of the study was considered successful since all three co-primary endpoints were met.

Secondary Efficacy Endpoints

Incidence of surgical excision

The proportion of patients who needed excision for ER was compared between NexoBrid and SOC using logistic regression. Patients with missing values (NexoBrid: 3 patients vs. SOC: 3 patients) were assumed to have received surgery as was pre-defined in the SAP. The proportion and number of patients who required surgical excision for ER was 8.33% (6/72 patients) with NexoBrid vs. 64.38% (47/73 patients) with SOC (Table 19).

Table 19: Incidence of Surgical Excision for Eschar Removal for NexoBrid vs SOC – Main Analysis (FAS)

n	Incidence Rate (NexoBrid/SOC)[a]	Odds Ratio[b]	p-value[b]	Lower 95% Confidence Bound	Upper 95% Confidence Bound
72 NexoBrid 73 SOC	6/72 (8.33%)/ 47/73 (64.38%)	0.025	<0.0001	0.007	0.090

ER = eschar removal, FAS = full analysis set, SOC = standard of care
Incidence of surgical excision was defined per patient as a binary variable, indicating whether this patient needed surgical excision for ER. Patients with missing values were assumed to have received surgery. The time frame for this analysis is the time until complete ER has been achieved.
[a] The percentages are based on the number of patients in the FAS by treatment arm.
[b] Analysis statistics were estimated from a logistic regression model, including the following covariates: treatmen arm, centre group, age group, % TBSA (patient level), proportion of the FT area of patient and number of TWs, where % TBSA (patient level) and proportion of the FT area of a patient are continuous values on which the stratification factors were based. P-value was calculated using the re-randomisation test.

In the main analysis, the odds ratio of requiring surgical excision for ER for NexoBrid vs. SOC was 0.025 (95% CI: 0.007 to 0.090, p-value <0.0001), indicating a 97.5% lower likelihood of having an excision in the NexoBrid arm compared with SOC.

The results of three sensitivity analyses were similar to the results of the main analysis (odds ratios were in a range of 0.014 to 0.023 [p-value of <0.0001] for NexoBrid vs. SOC). The odds ratios were statistically significant, and supportive of the main analysis. An additional analysis was performed on a TW level, using all TWs with observed endpoint values (from patients included in the FAS). The proportion and number of TWs which required surgical excision for ER was 3.19% (3/94 TWs) with NexoBrid vs. 63.22% (55/87 TWs) with SOC. The odds ratio was estimated as 0.011 (95% CI: 0.002 to 0.056, p-value <0.0001), indicating a 98.9% lower likelihood of excision with NexoBrid compared with SOC, which supports the main analysis. Based on the hierarchical testing procedure, the main analysis of this endpoint was considered as confirmatory.

Blood Loss Related to Eschar Removal

The mean (SD) blood loss with NexoBrid (32.26 [284.757] mL) was numerically lower than with SOC (202.55 [409.147] mL). However, the difference was not statistically significant (p-value = 0.1374). Notably there were multiple missing values for the blood loss analysis in both treatment arms (NexoBrid: 30/72 vs. SOC: 49/73), resulting in a small population for the analysis. Physicians tend to draw less blood routinely, especially in young children. Missing values derived from missing samples, samples that were not analysable, and/or samples that were not collected within the required timeframe. As was pre-defined in the SAP, the approach with the least missing values (the subject-oriented analysis) was used as the main analysis. The results of the main analysis are presented in Table 20.

Table 20: Blood Loss (in mL) – Main Analysis, Blood Loss Calculated Using Subject-Oriented Method, Subject Level (FAS)

Statistics	NexoBrid (N=72)	SOC (N=73)
n[a]	42	24
Mean	32.26	202.55
SD	284.757	409.147
Median	1.01	65.76
Min, Max	-531.3, 1272.1	-311.1, 1205.2
Quantiles 25%, 75%	-69.86, 64.09	-32.36, 243.48
Number of Missing Observations[b]	30	49
Test for Normality[c]		
Shapiro-Wilk test p-value	0.0004	
Analysis Results[d]		
Treatment Difference Estimate	-47.13	
SE of Treatment Difference Estimate	32.137	
p-value	0.1374	

FAS = full analysis set, max = maximum, min =minimum, SOC = standard of care

Results of sensitivity analyses using the PP set showed similar results compared to the main analysis: the mean (SD) blood loss with NexoBrid (36.85 [301.932] mL) was numerically lower than with SOC (126.71 [340.620] mL), however, the effect was not statistically significant (p-value = 0.3081).

Two additional supportive analyses were conducted, which evaluated procedure-oriented blood loss on the FAS and PP set. The mean (SD) blood loss in the NexoBrid arm was numerically lower than in the SOC arm; however, the effect was not statistically significant (p-value = 0.3166 [FAS] and 0.3476 [PP set]).

Since the main analysis of the blood loss did not demonstrate superiority of NexoBrid over SOC at the significance level of 0.05, the hierarchical testing procedure stops.

Incidence of Autograft in DPT Wounds

The main analysis was performed on a TW level using DPT TWs from patients included in the FAS. The frequency distribution and analyses results are presented in Table 21. The proportion and number of DPT TWs that had been autografted was 25.93% (21/81 DPT TWs) for NexoBrid vs. 37.68% (26/69 DPT TWs) for SOC. The odds ratio of requiring autograft for NexoBrid vs. SOC was estimated as 0.414 (95% CI: 0.163 – 1.054, p-value = 0.0545.

Table 21: Incidence of Autograft in DPT Wounds – Main Analysis, TW Level (FAS, DPT TWs Only)

n	Incidence Rate	Odds Ratio	p-value	Lower 95% Confidence Bound	Upper 95% Confidence Bound
NexoBrid: 81	21/81 (25.93%)[a]	0.414[b]	0.0545[b]	0.163[b]	1.054[b]
SOC: 69	26/69 (37.68%)[a]				

DPT = Deep Partial Thickness, FAS = Full Analysis Set, TW = Target Wound.
Note: Incidence of autograft was defined per TW as a binary variable, indicating whether this TW needed autografting. TWs with missing values were assumed to have received autograft.

The results of three sensitivity analyses were similar to the main analysis. The incidence rate of autograft in DPT wounds was numerically lower in the NexoBrid arm than in the SOC arm.

Percent Area of Autograft Performed in DPT Wounds

The main analysis was performed using the FAS patients with at least one DPT TW. The descriptive statistics and results of the analysis are presented in Table 22. The mean percent DPT wound area autografted with NexoBrid (15.9% [SD 38.57%]) was numerically lower than with SOC (22.8% [SD 43.72%]). The treatment difference between NexoBrid and SOC was estimated as –3.7% (SE=7.60, p-value = 0.5045).

Table 22: Percent Area of Autograft Performed in DPT Wounds - Main Analysis, Patient Level (FAS, Only Patients with at Least one DPT TW)

Statistics	NexoBrid (N=60)	Standard of Care (N=55)
n[a]	56	50
Mean	15.9	22.8
SD	38.57	43.72
Median	0.0	0.0
Min, Max	0, 200	0, 200
Quantiles 25%, 75%	0.0, 0.0	0.0, 20.0
Number of Missing Observations	4	5
Analysis Results[b]		
Treatment Difference Estimate	-3.7	
SE of Treatment Difference Estimate	7.60	
p-value	0.5045	

DPT = Deep Partial Thickness, FAS = Full Analysis Set, Max = maximum value observed, Min = minimum value observed, SD = standard deviation, SE – standard error, TW = Target Wound.

A sensitivity analysis was performed using the PP set, instead of the FAS. Similar to the main analysis, the mean % area with NexoBrid (15.8% [SD 39.11%]) was numerically lower than with SOC (23.7% [SD 44.38%]) in the PP set. The results of this sensitivity analysis were similar to the results in the main analysis. The treatment difference between NexoBrid and SOC was estimated as –3.1% (SE=7.73, p-value = 0.6857).

Ancillary analyses

Subgroup Analyses of the Co-primary Endpoints by Age Group

The treatment arms were compared using a log rank test, separately for each age group (0 to 23 months, 24 months to 3 years, 0 to 3 years, 4 to 11 years, and 12 to 18 years on patients from the FAS). The results of this subgroup analysis indicate that for each age group the median (SD) time to complete eschar removal in the NexoBrid arm was shorter than in the SOC arm (Table 23), supporting the main analysis of this endpoint.

Table 23: Time to Complete Eschar Removal (Subgroup Analysis by Age Group), Estimated Median Time for NexoBrid vs SOC (FAS)

Age Group	Treatment (n)	Median (Days)[a]	Lower 95% Confidence Bound[a]	Upper 95% Confidence Bound[a]	Log-Rank Test Statistic[a]	p-value[a]
0 – 23 months	NexoBrid (23)	1.03	0.36	1.11	8.3	0.0017
	SOC (22)	5.98	0.89	13.82		
24 months – 3 years	NexoBrid (15)	0.82	0.33	1.16	6.7	0.0031
	SOC (15)	2.07	0.78	10.05		
0 – 3 years	NexoBrid (38)	1.00	0.70	1.06	15.1	<0.0001
	SOC (37)	5.98	0.97	10.05		
4 – 11 years	NexoBrid (25)	0.97	0.82	1.03	13.1	<0.0001
	SOC (25)	5.99	2.71.	10.77		
12 – 18 years	NexoBrid (9)	1.23	0.42	2.03	3.9	0.0244
	SOC (11)	7.97	0.81	14.92		

FAS = full analysis set, SOC = standard of care

Percent Wound Area Surgically Excised for Eschar Removal by Age Group

For each age group the mean % wound area surgically excised for eschar removal in the NexoBrid arm was lower than in the SOC arm (Table 24).

Table 24: Percent Wound Area Surgically Excised for Eschar Removal – Subgroup Analysis by Age Groups, Patient Level (FAS)

Age Group	Treatment	Wound Area Surgically Excised for Eschar Removal									Analysis Results		
		n[a]	Missing	Mean	SD	Min	Q25%	Median	Q75%	Max	Treatment Difference[b]	SE of Treatment Difference[b]	p-value[b]
0 – 23 months	NexoBrid	20	3	0.0	0.00	0	0.0	0.0	0.0	0	-42.1	9.55	0.0002
	SOC	22	0	42.1	44.77	0	0.0	32.5	100.0	100			
24 months -3 years	NexoBrid	15	0	0.3	1.29	0	0.0	0.0	0.0	5	-52.2	12.07	0.0007
	SOC	15	0	52.5	46.72	0	0.0	60.8	100.0	102			
0 – 3 years	NexoBrid	35	3	0.1	0.85	0	0.0	0.0	0.0	5	-46.2	7.44	<0.0001
	SOC	37	0	46.3	45.22	0	0.0	40.0	100.0	102			
4 – 11 years	NexoBrid	25	0	4.0	20.00	0	0.0	0.0	0.0	100	-41.2	11.85	0.0019
	SOC	21	4	45.2	51.10	0	0.0	40.0	100.0	160			
12 – 18 years	NexoBrid	8	1	0.0	0.00	0	0.0	0.0	0.0	0	-61.0	13.98	0.0018
	SOC	10	1	61.0	44.21	0	0.0	75.4	100.0	100			

FAS = Full Analysis Set, Max = maximum, Min = minimum, Q25% = 25% quantile, Q75% = 75% quantile, SD = standard deviation, SE= standard error, SOC = standard of care.

Cosmesis and Function (MVSS) at 12 Months by Age Group

The results of this subgroup analysis were similar to the results obtained in the main analysis. The cosmesis and function (MVSS score for TWs) at 12 months from wound closure was not worse by more than 1.9 points for NexoBrid vs. SOC. Only in the age group 12 to 18 years, after adding the NI margin of 1.9 MVSS points to the values in the SOC arm, the results show that NexoBrid had a 2.79 MVSS point advantage over SOC, however, the 95% CI was -6.00 to 0.42. The upper bound of this CI is slightly above 0 (p=0.0424, one-sided).

Table 25: MVSS Regression Results at 12 Months-Subgroup Analysis by Age Groups (FAS)

Age Group	Treatment (N)	Variable	Analysis Results[a]			
			Treatment Difference Estimate	Lower 95% Confidence Bound	Upper 95% Confidence Bound	p-value
0 – 23 months	NexoBrid (23) SOC (22)	NexoBrid vs SOC	-2.90	-4.67	-1.14	0.0009
24 months – 3 years	NexoBrid (15) SOC (15)	NexoBrid vs SOC	-3.94	-5.95	-1.93	0.0002
0 – 3 years	NexoBrid (38) SOC (37)	NexoBrid vs SOC	-3.31	-4.61	-2.02	<0.0001
4 – 11 years	NexoBrid (25) SOC (25)	NexoBrid vs SOC	-2.41	-4.28	-0.53	0.0065
12 – 18 years	NexoBrid (9) SOC (11)	NexoBrid vs SOC	-2.79	-6.00	0.42	0.0424

FAS = Full Analysis Set, MVSS = Modified Vancouver Scar Scale, NI = non-inferiority, SAS = safety analysis set, SOC = standard of care

Incidence of Surgical Excision by Age Group

Results of incidence of surgical excision by age group indicated that for each age group the incidence of surgical excision performed for ER in the NexoBrid arm was (significantly) lower vs. SOC, supporting the main analysis in all age groups.

Blood Loss Related to Eschar Removal by Age Group

The results of this subgroup analysis by age group were similar to the results obtained in the main analysis: for each age group the blood loss in NexoBrid arm was numerically (but not significantly) lower than in SOC.

Incidence of Autograft Performed in DPT Wounds by Age Group

The results of this subgroup analysis by age group were similar to the results obtained in the main analysis of this endpoint. For each age group, the proportions of TWs autografted were numerically (but not significantly) lower in the NexoBrid arm than in the SOC arm.

Percent Area of Autograft in DPT Wounds by Age Group

The mean area (in %) of autograft in the NexoBrid arm was (not significantly) lower than in the SOC arm in the age groups 0 to 23 months and 1 to 3 years (and in the 0 to 3 years group). For the age group 4 to 11 years, the mean area of autograft in the NexoBrid arm was (not significantly) higher than in the SOC arm.

Further Exploratory Endpoints

1. Patient and Observer Scar Assessment Scale (POSAS) for TWs were analysed at 6-week FU, 12-week FU, 6-month FU, and 12-monthFU.

- POSAS total score: the mean POSAS total score of TWs decreased over time. The mean (SD) total score at 12-months was lower in the NexoBrid arm (29.54 [17.655]) vs. SOC (34.54 [19.995]). However, no significant difference was observed between treatment arms at any visit.

- POSAS patient score: the mean (SD) POSAS patient score of TWs decreased over time. At the 12-month FU it was lower in the NexoBrid arm (15.53 [10.091]) vs. SOC (17.18 [9.719]). However, no significant difference was observed between treatment arms at any visit.

- POSAS observer score: the mean (SD) POSAS observer score of TWs decreased over time. At the 12-month FU it was lower in the NexoBrid arm (13.99 [8.720]) vs. SOC (17.22 [11.610]). However, no significant difference in POSAS total score of TWs was observed at any visit. Similar results were observed in a repeat analysis that excluded patients with remotely collected data. For the 12-months visit, the mean POSAS observer score in the NexoBrid arm (15.94 [9.797]) was significantly lower than in the SOC arm (21.83 [11.774]; p-value = 0.0317).

The exploratory analyses of POSAS (total, observer, and patient) of TWs at 6 weeks, 12 weeks, 6 months, and 12 months post wound closure showed a numerical advantage of NexoBrid over SOC, the gap between treatment arms increasing towards the 12-month assessments.

2. Incidence of surgical escharotomy procedures on circumferential extremities TWs: no surgical escharotomy procedures were performed during the study.

3. Incidence of reduction in interstitial/compartment pressure in circumferential extremities TWs: 13 patients with NexoBrid vs. 3 patients with SOC had at least one circumferential extremity TW. Interstitial/compartment pressure was reduced for at least one circumferential extremity in 4/13 (30.8%) NexoBrid-patients vs. 1/3 (33.3%) SOC-patients. No significant difference between arms was detected.

4. Reduction in surgical need as measured by analysis of incidence of harvested donor sites: less patients with NexoBrid had at least 1 donor site wound (19/72 patients [26.4%]) compared with SOC (27/73 patients [37.0%]). The difference was not statistically significant.

5. Reduction in surgical need as measured by analysis of % area of harvested donor site: the mean (SD) % area of donor site wounds with NexoBrid (0.88 [2.187]) was numerically lower than with SOC (3.28 [(12.477]). The difference was not statistically significant.

6. MVSS scores for TWs at the 6-week, 12-week, and 6-month FU were analysed. No significant difference for TWs were observed between groups at any visit (by ANOVA superiority test).

7. Duration of hospitalisation: the estimated median duration of hospitalisation (using the Kaplan-Meier method) was 12 days (95% CI: 9 - 16) for NexoBrid vs. 10 days (95% CI: 8 - 14) for SOC. There was no statistically significant difference between treatment arms.

Some endpoints with connection to the clinical efficacy [Time to reach complete wound closure; Lower Extremity Function Scale (LEFS); Disabilities of the Arm, Shoulder, and Hand (QuickDash); Range of Motion (ROM) and Quality of Life (EQ-5D)] were evaluated in the study as safety parameters; and are presented below.

Time to Reach Complete (>95%) Wound Closure (TW Level) - Main Analysis CIDS

In the CIDS study time to reach complete wound closure (defined as % wound area epithelialized and/or closed by graft is >95% without drainage or dressing requirements confirmed at 2 consecutive study visits, 2 weeks apart) was compared at a TW level using a survival analysis with clustered data (for the multiple TWs that can occur in a patient) based on appropriate assumptions. The mean time to reach complete wound closure was 30.24 days with NexoBrid vs. 27.93 with SOC. The estimated median time to complete wound closure on a TW level (using the Kaplan Meier Method) was 32 days (95% CI: 28.00 – 42.00) for NexoBrid vs. 41 days (95% CI: 35.00 – 45.00) for SOC, when the NI margin of + 7 days for SOC was included. Non inferiority for NexoBrid was shown (Table 26).

Table 26: Time (in Days) to Reach Complete Wound Closure (>95%) – Main Analysis, Target Wound Level (FAS)

Statistics	NexoBrid (N=98)	Standard of Care (N=94)
n[a]	98	94
Mean	30.24	27.93
SD	17.562	18.081
Median	28.00	24.00
Min, Max	0.0, 74.0	0.0, 85.0
Quantiles 25%, 75%	17.00, 39.00	16.00, 36.00
Number of Censored Observations	31	36
Median Time Estimate (days, including 7-day NI margin) (95% CI)[b]	32.00 (28.00 - 42.00)	41.00 (35.00 - 45.00)
PH Assumption Checks[c]		
Time by treatment arm interaction p-value	<0.0001	
Log likelihood test p-value	<0.0001	
Parametric Frailty Model[d]		
Hazard Ratio Estimate (95% CI) (NexoBrid vs. SOC)	2.86 (1.23 - 6.67)	
p-value	0.0149	
Underlying PH Assumption Checks (Conditional on frailty term)[e]		
Time by treatment arm interaction p-value	<0.0001	
Accelerated Failure Time Model with Shared Frailty[f]		
Coefficient for Treatment Effect (95% CI) (NexoBrid vs. SOC)	-1.92 (-3.46 - -0.38)	
p-value	0.0151	

FAS = Full Analysis Set, Max = maximum value observed, min = minimum value observed, PH = proportional hazard, SD = standard deviation, SOC = standard of care, TW = Target Wound

[a] Descriptive statistics are based on pooled Time to event data, both for TWs with events and those with censored observation.

[b] Analysis statistics were estimated using Kaplan-Meier method. A 7-day NI margin for the SOC arm was incorporated.

Additional Analysis – Time to Complete (>95%) Wound Closure (Patient Level)

However, the additional analysis of this endpoint on a patient level (using the FAS) showed that a Wilcoxon test statistic (estimated from the generalised Wilcoxon-Gehan test) was 32, indicating that for the time to complete wound closure in the NexoBrid arm NI was not established (p-value =0.1114).

Supportive Analysis – Time to Reach 100% Wound Closure (TW Level)

The estimated median time reach 100% wound closure on a TW level (using the Kaplan Meier Method) was 44.00 days (95% CI: 31.00 – 65.00) for NexoBrid vs. 50.00 days (95% CI: 41.00 – 77.00) for SOC, including the NI margin of + 7 days for SOC. The hazard ratio of NexoBrid vs. SOC - estimated from the parametric frailty model - was 2.25 (95% CI: 1.01 to 5.00), indicating that the time to 100% wound closure with NexoBrid was not longer (by more than 7 days) than with SOC (p-value = 0.0475, establishing the NI of NexoBrid vs. SOC), supporting the result obtained in the main analysis.

Supportive Analysis – Time to Reach 100% Wound Closure (Patient Level)

The results of this supportive analysis were similar to the results obtained for the additional analysis on a patient level. The Wilcoxon test statistic, estimated from the generalised Wilcoxon-Gehan test, was 18.00. NI was not established (p-value = 0.3095). This analysis had a high number of missing values (44/72 missing value in NexoBrid, 45/73 missing in SOC, around 61% missing values in both treatment arms).

Lower Extremity Function Scale (LEFS)

The mean LEFS scores were compared between treatment arms (for each visit separately) by a one-way analysis of variance. No statistically significant difference in mean LEFS score was observed between the treatment groups at any visit; however, the number of patients included in this LEFS score analysis was notably small (NexoBrid and SOC: both N=6), therefore, no conclusion can be drawn from the study data.

Disabilities of the Arm, Shoulder, and Hand (QuickDash)

No statistically significant difference in mean QuickDASH score was observed between the two groups at any visit; however, again low numbers of patients (NexoBrid: N=5 vs. SOC: N=4) preclude any conclusion.

Range of Motion (ROM)

For the majority of patients all measurement were normal in both treatment arms. At least 1 abnormal finding was observed in 6/21 (28.6%) in NexoBrid patients vs. 3/13 (23.1%) with SOC. The odds ratio for at least one abnormal finding for NexoBrid vs. SOC was estimated as 0.750 (95% CI: 0.151 – 3.716, p=0.7246).

Quality of Life (EQ-5D)

The mean EQ-5D VAS scores were similar between NexoBrid and SOC both overall and when evaluated by age group (0 – 23 months, 24 months – 3 years, 0 – 3 years, 4 – 11 years, and 12 – 18 years). There were no statistically significant differences in the EQ-5D mobility, self-care, usual activities, pain/discomfort, or anxiety/depression scores between the treatment arms overall or for any group.

Summary of main study

The following Table 27 summarises the efficacy results from the main study (MW2012-01-01) 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).

Table 27: Summary of Efficacy for trial MW2012-01-01

Title: A multicenter, multinational, randomised, controlled, open label study, performed in children with thermal burns, to evaluate the efficacy and safety of NexoBrid as compared to Standard of Care (SOC) treatment		
Study identifier	MW2012-01-01	
Design	Multicenter, multinational, randomised, controlled, parallel group open label study, performed in children	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable 24 months
Hypothesis	Superiority	
Treatments groups	NexoBrid	Topical NexoBrid gel. Duration: 4 hrs, number randomised: 72
	SOC	Standard of Care. Duration: variable, number randomised: 73

Endpoints and definitions	Co-Primary endpoints:	1 2 3	-Time to complete eschar removal -Percent wound area surgically excised for eschar removal -Scar score MVSS at 12 months
	Secondary other: specify endpoint	4 5 6 7 8	-Incidence of surgical excision -Blood loss -Incidence of Autograft in DPT wounds -Area of Autograft in DPT wounds -Scar score MVSS at 24 months
Database lock	Last patient with 12 months follow up assessment		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (FAS) time point: 12 months post wound closure (follow up)		
Descriptive statistics and estimate variability	Treatment group	NexoBrid	SOC
	Number of subject	72	73
	Estimated median time for eschar removal	0.99 days	5.99 days
	95% CI	0.88 – 1.04	1.04 – 9.84
	% area surgically excised	1.5 %	48.1 %
	SD	12.13	46.58
	MVSS 12 months SD	3.7 2.93	4.52 3.31

Effect estimate per comparison	1 median time for eschar removal	Comparison groups	NexoBrid vs. SOC
		Generalized Wilcoxon-Gehan Test	77.0
		P-value	0.0008
	2 % area surgically excised	Comparison groups	NexoBrid vs. SOC
		ANOVA	-45.5
		SE of Treatment Difference	6.83
		P-value	<0.0001
	3 MVSS 12 months	Comparison groups	NexoBrid vs. SOC
		Treatment Difference Estimate	-2.76
		95% CI for Treatment Difference Estimate	-3.67 - -1.85
		P-value	<0.0001
Analysis description	**Secondary analysis**		

		NexoBrid	SOC
	4 Incidence of surgical excision	6/72 (8.33%) Odds ratio 0.025 P value <0.0001	47/73 (64.38%) 95% CI 0.0007 – 0.090

	5 Blood loss mean (SD) Treatment Difference Estimate (SE)	32.26 (284.757) mL -47.13 (32.14) p-value = 0.1374	202.55 (409.147) mL ns
	6 Incidence of Autograft in DPT wounds	21/81 (25.93%) Odds ratio 0.414 P value 0.0545	26/69 (37.68%) 95% CI 0.163 - 1.054 ns
	7 Area of Autograft in DPT wounds mean (SD) Treatment Difference Estimate (SE)	15.9% (38.57%) -3.7 (7.60) P value 0.5045	22.8% (43.72%) ns
	8 Scar score MVSS at 24 months	Results not available yet as interim report 12 months	

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

Patient demographic and baseline characteristics for paediatric patients (from pooled studies MW2012-01-01 (CIDS) and MW2010-03-02 (DETECT)) and adult patients (≥18 years old, from pooled studies DETECT, MW2004-11-02, and MW2002-04-01) are presented in Table 28. The demographic and baseline characteristics were generally similar across the 2 treatment arms in both paediatric studies. The mean (SD) age in the MW2012-01-01 (CIDS) study was 5.71 (4.8) and 5.83 (4.9) years in the NexoBrid and SOC arms respectively vs. study MW2004-11-02: 10.0 (4.49), and 10.8 (4.74) years (NexoBrid and SOC, respectively; N= 15 vs. N=16). The majority of paediatric patients in both studies were males (CIDS: 42/72 [58.3%] and 48/73 [65.8%] NexoBrid and SOC respectively vs. MW2004-11-02: 10/15 [66.7%] and 14/16 [87.5%] NexoBrid and SOC respectively, and Caucasians (CIDS: 51/72 [70.8%], 50/73 [68.5%] NexoBrid and SOC respectively, vs. MW2004-11-02: 10/15 [66.7%], 9/16 [56.3%] NexoBrid and SOC respectively). This was consistent with demographics observed for the adult population, where the majority of patients were male and Caucasians. The majority of paediatric patients in the CIDS study had burns resulting from scald (49/72 [68.1%] and 48/73 [65.8%] NexoBrid and SOC respectively), while the majority of paediatric patients in study MW2004-11-02 had burns resulting from fire/flame (8/15 [53.3%] and 10/16 [62.5%] NexoBrid and SOC respectively), similar to the etiology in the adult population.

Table 28: Summary of demographics and baseline characteristics (abbreviated)

	Paediatric Patients				Adult Patients		
	CIDS (FAS)		MW2004-11-02 Paediatric Subgroup[a] (ITT)		Pooled Studies[b] Adult Subgroup (ITT)		
Parameter Statistics[c]	NexoBrid (N=72)	SOC (N=73)	NexoBrid (N=15)	SOC (N=16)	NexoBrid (N=208)	SOC (N=178)	Gel Vehicle (N=62)
Age (years)							
n	72	73	15	16	208	178	61
Mean (SD)	5.71 (4.838)	5.83 (4.909)	10.0 (4.49)	10.8 (4.74)	38.3 (14.09)	37.9 (13.80)	38.8 (13.90)
SE	-	-	1.16	1.19	0.98	1.03	1.78
Median (Min, Max)	3.37 (0.6, 18.6)	3.94 (0.7, 16.7)	9.0 (4, 18)	10.7 (5, 18)	37.5 (18, 76)	36.5 (18, 73)	37.6 (18, 70)
Age Group							
0-23 months	23 (31.9)	22 (30.1)	-	-	-	-	-
24 months-3 years	15 (20.8)	15 (20.5)	-	-	-	-	-
0-3 years	38 (52.8)	37 (50.7)	-	-	-	-	-
4-11 years	25 (34.7)	25 (34.2)	-	-	-	-	-
12-18 years	9 (12.5)	11 (15.1)	-	-	-	-	-
Gender							
Female, n (%)	30 (41.7)	25 (34.2)	5 (33.3)	2 (12.5)	61 (29.3)	44 (24.7)	21 (33.9)
Male, n (%)	42 (58.3)	48 (65.8)	10 (66.7)	14 (87.5)	147 (70.7)	134 (75.3)	40 (64.5)
Missing, n (%)	0	0	0	0	0	0	1 (1.6)
Race[d]							
Asian, n (%)	17 (23.6)	16 (21.9)	0	1 (6.3)	29 (13.9)	18 (10.1)	13 (21.0)
Black, n (%)	3 (4.2)	3 (4.1)	1 (6.7)	1 (6.3)	19 (9.1)	17 (9.6)	8 (12.9)
Caucasian, n (%)	51 (70.8)	50 (68.5)	10 (66.7)	9 (56.3)	149 (71.6)	133 (74.7)	39 (62.9)
Middle Eastern, n (%)	NA	NA	3 (20.0)	3 (18.8)	3 (1.4)	1 (0.6)	0

Weight (kg)							
n	72	73	15	16	208	178	61
Mean (SD)	23.49 (19.544)	24.82 (20.351)	36.03 (18.355)	46.68 (30.383)	76.23 (18.210)	77.82 (16.687)	76.66 (18.121)
SE	-	-	4.739	7.596	1.263	1.251	2.320
Median (Min, Max)	14.75 (7.0, 102.0)	15.00 (7.0, 85.0)	27.90 (16.0, 80.0)	35.00 (16.0, 110.0)	74.05 (28.3, 132.2)	77.06 (42.0, 140.0)	77.70 (42.0, 127.2)
Etiology							
Contact, n (%)	5 (6.9)	5 (6.8)	1 (6.7)	0	14 (6.7)	14 (7.9)	5 (8.1)
Fire/Flame, n (%)	18 (25.0)	19 (26.0)	8 (53.3)	10 (62.5)	147 (70.7)	123 (69.1)	51 (82.3)
Scald, n (%)	49 (68.1)	48 (65.8)	6 (40.0)	6 (37.5)	46 (22.1)	40 (22.5)	5 (8.1)
Multiple	0	1 (1.4)	-	-	-	-	-
Other, n (%)	0	0	0	0	1 (0.5)	1 (0.6)	0
Missing, n (%)	0	0	0	0	0	0	1 (1.6)
Total Number of TWs							
1, n (%)	51 (70.8)	57 (78.1)	3 (20.0)	2 (12.5)	132 (63.5)	100 (56.2)	50 (80.6)
2, n (%)	17 (23.6)	13 (17.8)	8 (53.3)	6 (37.5)	43 (20.7)	49 (27.5)	6 (9.7)
≥3, n (%)	NA	NA	4 (26.7)	8 (50.0)	33 (15.9)	29 (16.3)	6 (9.7)
3-4, n (%)	4 (5.6)	2 (2.7)	-	-		-	-
≥5, n (%)	0	1 (1.4)	-	-	-	-	-
% TBSA of All TWs							
n	72	73	15	16	208	178	62
Mean (SD)	5.85 (4.431)	5.30 (4.273)	12.8 (5.89)	12.7 (5.80)	7.7 (4.62)	7.8 (4.51)	6.3 (3.35)
SE	-	-	1.52	1.45	0.32	0.34	0.43
Median (Min, Max)	4.00 (1.0, 23.5)	4.00 (1.0, 23.0)	12.5 (5, 30)	11.0 (6, 26)	6.8 (1, 25)	7.0 (2, 27)	6.0 (2, 18)
% TBSA Group of All TWs, subject level							
≤15%, n (%)	-	-	13 (86.7)	12 (75.0)	194 (93.3)	169 (94.9)	61 (98.4)
>15%, n (%)	-	-	2 (13.3)	4 (25.0)	14 (6.7)	9 (5.1)	1 (1.6)
Overall TW Depth							
All TWs DPT, n (%)	58 (80.6)	52 (71.2)	30 (75.0)	22 (53.7)	109 (52.4)	82 (46.1)	33 (53.2)
All TWs FT, n (%)	4 (5.6)	5 (6.8)	4 (10.0)	7 (17.1)	10 (4.8)	9 (5.1)	5 (8.1)
Mixed TWs, n (%)	10 (13.9)	16 (21.9)	6 (15.0)	12 (29.3)	89 (42.8)	87 (48.9)	24 (38.7)
% TBSA of All Wounds							
n	72	73	15	16	208	178	62
Mean (SD)	7.01 (4.879)	6.20 (4.777)	14.47 (6.198)	14.69 (6.797)	12.69 (6.973)	11.48 (6.311)	12.85 (7.560)
SE	-	-	1.600	1.699	0.483	0.473	0.960
Median (Min, Max)	5.75 (1.3, 23.5)	4.70 (1.0, 29.1)	13.50 (5.0, 30.0)	14.25 (6.0, 27.0)	11.50 (2.0, 30.0)	9.70 (3.0, 30.0)	11.63 (2.5, 30.0)
% TBSA Group of All Wounds, subject level							
≤15% n (%)	68 (94.4)	70 (95.9)	11 (73.3)	10 (62.5)	145 (69.7)	137 (77.0)	44 (71.0)
>15% n (%)	4 (5.6)	3 (4.1)	4 (26.7)	6 (37.5)	63 (30.3)	41 (23.0)	18 (29.0)

The mean (SD) % TBSA of all TWs treated was similar in the 2 treatment arms in the paediatric studies (5.85 [4.431] and 5.30 [4.273] for NexoBrid and SOC respectively in the CIDS study, and 12.8 [5.89] vs. 12.7 [5.80] for NexoBrid vs. SOC respectively in study MW2004-11-02). The majority of paediatric patients had total treated wound-area (all wounds) that was ≤15% TBSA (CIDS: 68/72 [94.4%] vs. 70/73 [95.9%] for NexoBrid vs. SOC respectively and MW2004-11-02: 11/15 [73.3%] vs. 10/16 [62.5%] for NexoBrid and SOC respectively). The majority of paediatric patients had treated TWs that were DPT (CIDS: 80.6% vs. 71.2% of TW NexoBrid vs. SOC, respectively and Study MW2004-11-02: 75.0% vs. 53.7% of TW NexoBrid vs. SOC, respectively).

Results - Time to Complete Eschar Removal

Side by side comparisons of time to complete ER in paediatric patients, together with a summary of results in adult patients, are presented in Table 29. Results of the ISE analysis were consistent with results in the CIDS study: the Kaplan-Meier estimated median time to complete ER per patient was statistical significantly shorter with NexoBrid compared with SOC (1 day vs. 5 days [Wilcoxon test p-value = 0.0126] in paediatric patients in study MW2004-11-02, and 1 day vs. 4 days [Wilcoxon test p-value <0.0001] in the adult patients in the pooled studies DETECT, MW2004-11-02, and MW2002-04-01).

Table 29: Time to Complete Eschar Removal (Days)

	Paediatric Patients				Adult Patients	
	CIDS (FAS)		MW2004-11-02 Paediatric Subgroup[a] (ITT)		Pooled Studies Adult Subgroup[b] (ITT)	
Statistics[c]	NexoBrid (N=72)	SOC (N=73)	NexoBrid (N=15)	SOC (N=16)	NexoBrid (N=208)	SOC (N=178)
N	72	73	15	16	223	178
Mean (SD)	1.28 (2.124)	8.60 (10.130)	0.8 (0.68)	6.2 (5.82)	1.7 (3.41)	6.1 (7.19)
SE	-	-	0.17	1.46	0.24	0.54
Median (Min, Max)	0.98 (0.0, 16.9)	5.74 (0.0, 46)	1.0 (0.0, 2.0)	4.5 (0.0, 19.0)	1.0 (0.0, 32)	3.0 (0.0, 38)
Number of Censored Observations	3	6	1	1	13	17
Median Time Estimate (Days)[d]	0.99	5.99	1.0	5.0	1.0	4.0
95% CI[d]	0.88 - 1.04	2.71 - 9.84	0.0 - 1.0	2.0 - 9.0	-	3.0 - 6.0
Wilcoxon Test Statistic[e,f]	77.0		9.00		931.00	
p-value[e,f]	0.0008		0.0126		<0.0001	

Percent Wound Area Surgically Excised for Eschar Removal

Side by side comparisons of percent wound area surgically excised for ER for all wounds in paediatric patients, together with a summary of results in adult patients, are presented in Table 30.

The results from the CIDS study are supported by results in the subgroup of paediatric patients in study MW2004-11-02, where mean (SD) of percent wound area surgically excised was lower for NexoBrid vs. SOC (9.5 [19.41] vs. 71.3 [38.68]). The estimated least square mean difference between NexoBrid and SOC in the paediatric subgroup of Study MW2004-11-02 was -61.80 (95% CI: -87.21 to -36.40). Results in paediatric patients were comparable to results in adult patients in the pooled analysis (studies: DETECT, MW2004-11-02, and MW2002-04-01).

Table 30: Percent Wound Area Surgically Excised - Per Patient

	Paediatric Patients				Adult Patients	
	CIDS (FAS)		MW2004-11-02 Paediatric Subgroup[a] (ITT)		Pooled Studies[b] Adult Subgroup (ITT)	
Statistics[c]	NexoBrid (N=72)	SOC (N=73)	NexoBrid (N=15)	SOC (N=16)	NexoBrid (N=208)	SOC (N=178)
n	68	68	14	16	205	167
Mean (SD)	1.5 (12.13)	48.1 (46.58)	9.5 (19.41)	71.3 (38.68)	11.6 (26.41)	53.5 (44.40)
SE	-	-	5.19	9.67	1.84	3.44
Median (Min, Max)	0.0 (0, 100)	40.0 (0, 160)	0.0 (0, 52.0)	88.4 (0, 100)	0.0 (0, 100)	61.6 (0, 175)
Number of Missing Observations	4	5	-	-	-	-
Treatment Difference Estimate[b]	-45.5		-		-	
SE of Treatment Difference Estimate[d]	6.83		-		-	
p-value[d]	<0.0001		-		-	
LS Mean Difference Estimate	-		-61.80		-41.25	
95% CI	-		-87.21 - -36.40		-48.57 - -33.93	

Cosmesis and Function (MVSS) at 12 Months

This was a primary efficacy endpoint in the paediatric CIDS study (2.76 points advantage over SOC; 95% CI -3.67 to -1.85, p-value <0.0001, see above). The DETECT study in adults included cosmesis at 12 months from wound closure as a safety endpoint. Results were comparable to results in the CIDS study. In the DETECT study, NexoBrid had a 1.36 MVSS point advantage over SOC (p-value = 0.0027). The 95% CI for this treatment effect was -2.24 to -0.48.

Other endpoints

Blood loss related to ER in paediatric patients in the CIDS study was numerically lower in the NexoBrid arm than in SOC arm (mean (SD): NexoBrid: 32.26mL (285) vs. SOC: 202.5mL (409)), however, the effect was not statistically significant due to the number of missing values. Blood loss data were consistent with results of acute blood loss and change in hemoglobin from before to after debridement in paediatric patients in study MW2004-11-02 (87.4 mL (400) vs. SOC: 959.6mL (1054)), and consistent with results in adult patients in both the ISE pooled analysis and the pivotal Phase 3 studies in adults (DETECT, MW2004-11-02, and MW2002-04-01; NExoBrid: 104.8mL (511) vs. SOC: 599.2mL (858)).

The incidence of autografted DPT TWs and the % wound area autografted per DPT TW in the CIDS study were numerically lower with NexoBrid arm vs. SOC (25.9% vs. 37.7%). This was supported by results of paediatric patients in study MW2004-11-02 NexoBrid: 21.7% vs. SOC: 31.8%). Results in paediatric patients are consistent with the positive trend towards fewer autografts and smaller area autografted observed in adult patients (DETECT, MW2004-11-02, and MW2002-04-01: NexoBrid: 26.8% vs. SOC: 33.1%).

Length of hospital stay (time to hospital discharge) was an exploratory endpoint in the CIDS study. The study didn't show a statistically significant difference between treatment arms. This was consistent with results in paediatric and adult patients in the ISE pooled analysis (DETECT, MW2004-11-02, and MW2002-04-01), where no notable differences in the length of stay for patients in the NexoBrid arm as compared with patients in the SOC arm or Gel Vehicle arms were observed.

Other clinical studies

Retrospective study 35-98-910

A total of 154 patients were included in the retrospective study 35-98-910. Of these, 75 patients (<16 years) were included in paediatric population.

In the NexoBrid arm, the mean age (SD) was lower in the study 35-98-910 compared to paediatric pooled population (4.3 [3.7] vs. 6.5 [5.03] years). The majority of paediatric patients were males in both pooled pediatric population (52/87 [59.8%]) and study 35-98-910 (30/46 [65.2%]). The majority of patients in both paediatric pooled populations and study 35-98-910 had total treated wounds (all wounds) of ≤ 15% TBSA (90.8% vs. 98.7%) in the NexoBrid arm.

Time to complete ER was not assessed in the retrospective study 35-98-910. The incidence of Surgical Excision for Eschar Removal was also not assessed. Debridement was achieved in 92.0% of the area that was in contact with NexoBrid. In the NexoBrid arm, percent of eschar removed per TW was similar in the paediatric pooled population and study 35-98-910 (96.7% vs. 92.0%).

The mean (SD) time to complete wound closure for NexoBrid and SOC on a TW level (clustered data of TWs in a patient), was 32.0 (16.29) days and 30.5 (16.96) days, respectively. The mean (SD) time to complete wound closure on a TW level was shorter in the Study 35-98-910 (21.4 [16.5] days) compared with the paediatric pooled population (32.0 [16.29] days).

Upon CHMP' request, the MAH has compared the paediatric efficacy data from the controlled studies (MW2012-01-01, CIDS, and MW2004-11-02) with the data from the open-label (MW2008-09-03) and retrospective (35- 98-910) studies. Efficacy results in paediatric patients from the retrospective study were generally consistent with the results in the pooled paediatric patients from controlled studies. Differences that were noted may be due to the differing methods of data collection between these studies. The results in the 3 paediatric patients from the open-label study (MW2008-09-03) were supportive of the overall conclusions. Overall, demographics of age, gender distribution, treated wound area, and burn depth were generally similar between pooled paediatric population and study 35-98-910. The sample size of MW2008-09-03 was not conducive to a meaningful comparison, but the data were within the range of what was reported for the pooled paediatric population and study 35- 98-910. Comparisons of key efficacy result data are summarized below:

Time to Complete Eschar Removal: In the NexoBrid arm, the results of time to ER are consistent across studies (1 day in the pooled data vs. 1 to 2 days in Study MW2008-09-03 [not analyzed in 35- 98-910]).

Incidence of Surgical Excision for Eschar Removal– Per Patient: In the NexoBrid arm, the incidence of excision performed for ER was 8.0% (7 out of 87 patients) and no patients required excision for ER in Study MW2008-09-03 [not analysed in 35-98-910]).

Percent Area of Autograft Performed per Target Wound: Overall, the mean of percent wound area autografted was low in both paediatric pooled population (14.2% for DPT TWs) and in the Study 35-98-910 (1.5% for TWs). In MW2008-09-031, 2 patients required (95% and 50%).

Time to Complete Wound Closure: In the NexoBrid arm, the mean [SD] time to complete wound closure was 32.0 [16.29] days in the paediatric pooled population and 21.4 [16.5] days in Study 35-98- 910. In MW2008-09-03, wound closure for all TWs was achieved after 29 days (n=2) and 61 days (n=1).

2.4.2. Discussion on clinical efficacy

The variation application is supported by interim results from study MW2012-01-01 (CIDS study), a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2 arm study aiming to

demonstrate the superiority of NexoBrid treatment over SOC treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA).

Design and conduct of clinical studies

The MAH received Protocol assistance at the CHMP on 11/11/2021 where it was indicated, with regards to study MW2012-01-01, that it could be acceptable for the CHMP to assess the 12 months interim data of the study for the intended extension to the paediatric population, given that the long-term follow-up data are likely to be supportive (and thus not considered pivotal for the determination of the benefit-risk balance of NexoBrid). Upon CHMP's request, the MAH committed to submit the long-term follow-up data for assessment post-approval, once available (by Q2 2024).

The present application thus includes the 12 months interim efficacy data derived from paediatric study MW2012-01-01 (CIDS study) to support the extension of the current indication of 'eschar removal for removal of eschar in adults with deep partial- and full-thickness thermal burns' to the paediatric population. At least 145 evaluable patients with the following age distribution: at least 75 patients from birth to less than 4 years; at least 30 patients from 4 years to less than 12 years of age; at least 20 patients from 12 years to less than 18 years of age were to be included in the study in line with the agreed PIP. The remaining 20 patients were to be enrolled to any of the above groups, per their age during enrolment. At least 70 evaluable patients were to be included for the long-term follow-up analyses.

A total of 153 patients were screened for enrolment, of which 145 patients were randomised and included in the full analysis set (FAS): NexoBrid 72 vs. SOC 73. Paediatric patients with thermal burn wounds defined as DPT and/or FT requiring hospitalisation and who meet the entrance criteria were enrolled in the study. The study was conducted in 3 stages; with only children ages 4 to 18 years, hospitalised in burn units, enrolled in Stage 1. After the DSMB did not have any safety concerns Stage 2 commenced, enrolling children between the ages of 1 to 18 years. Since no safety concerns were raised by the DSMB after stage 2, Stage 3 commenced, this time enrolling children ages 0 to 18 according to study procedures.

The numbers analysed in the pivotal CIDS study and the age distribution (45 patients ≥0 months and ≤23 months, 30 patients ≥24 months and ≤3 years, 50 patients ≥4 years and ≤11 years and 20 patients ≥12 years and <18 years) are considered adequate and meet the requirements of the PIP.

Methods with endpoints, recruitment with inclusion/exclusion criteria, dropout distribution and study conduct are also considered adequate.

Baseline data comparison showed good comparability between the two treatment groups (NexoBrid vs. SOC). Mean treated wound area (% TBSA) per age group was: 0-23 Months: 6.7% TBSA, 2-3 Years: 7.0% TBSA, 4-11 Years: 8.5% TBSA and 12-18 Years: 10% TBSA.

Efficacy data and additional analyses

The main analysis of the first co-primary endpoint, the 'time to complete eschar removal' (FAS population) demonstrated superiority of NexoBrid treatment over SOC, with a statistically significant shorter time to complete eschar removal for NexoBrid vs. SOC. The estimated median time to complete eschar removal (using the Kaplan-Meier method) was 0.99 days for NexoBrid vs. 5.99 days for SOC. The main analysis result was confirmed in sensitivity analyses that investigated the robustness of the results (missing data). Additionally, a subgroup analysis by age group (0 to 23 months, 24 months to 3 years, 0 to 3 years, 4 to 11 years, and 12 to 18 years) consistently demonstrated superiority of NexoBrid over SOC in each age group evaluated.

The main analysis of the second co-primary endpoint, the '% wound area surgically excised for eschar removal' (FAS population) resulted in a significantly smaller mean % wound area surgically excised with NexoBrid vs. SOC (1.5% vs. 48.1%). The main analysis result was confirmed in sensitivity analyses using a different population (PPS) and an additional analysis on a TW level. In a subgroup analysis by age group, superiority of NexoBrid over SOC was consistently demonstrated in each age group. These results demonstrate that NexoBrid reduces the surgical burden in paediatric patients.

The descriptive statistics for the third co-primary endpoint, 'cosmesis and function measured by MVSS at 12 months' post wound closure (FAS) demonstrated a lower mean MVSS score for NexoBrid (3.83 [SD 2.876] vs. SOC (4.86 [SD 3.256]). The main analysis demonstrated NI of NexoBrid vs. SOC, using a NI margin of 1.9. The effect was statistically significant (p-value <0.0001) at the significance level of one sided 0.025. All sensitivity analyses of this endpoint using best- and worst-case imputations confirmed NI of NexoBrid. Additionally, descriptive statistics of MVSS scores by age groups demonstrated lower mean MVSS scores for NexoBrid compared with SOC in all age subgroups.

In the main analysis of the first secondary endpoint, the 'proportion of patients who needed excision for eschar removal' (FAS), the odds ratio of requiring surgical excision of eschar for NexoBrid vs. SOC was estimated as 0.025 (95% CI: 0.007 to 0.090; p-value <0.0001) indicating a statistically significant advantage of NexoBrid over SOC. NexoBrid patients were less likely to require surgical excision than SOC-patients (NexoBrid: 8.33% (6/72 patients) vs. SOC: 64.38% (47/73)). Sensitivity analyses on a different population (PPS) as well as an additional analysis on the TW level, consistently supported the main result. Additional subgroup analysis by age group also supported the main analysis by demonstrating superiority of NexoBrid vs. SOC. Based on the hierarchical testing procedure, the main analysis of this endpoint can be considered as confirmatory.

The 'mean blood loss' in the NexoBrid arm (using the patient-oriented method) was numerically lower vs. SOC (32 mL vs 203 mL); however, the effect was not statistically significant (p-value = 0.3166 [FAS]); therefore, the hierarchical testing procedure stopped here.

There were multiple missing values in blood loss evaluation. Subgroup analysis by age group showed that blood loss was numerically lower for NexoBrid vs. SOC in 0 to 3 years, 4 to 11 years, and 12 to 18 years subgroups. In addition to the blood loss assessments based on ABL, blood related to eschar removal was also assessed by the change in haemoglobin measured before and after the debridement procedure as part of the safety assessments (see chapter 2.5,Laboratory findings: Blood transfusions, Change in haemoglobin).

In the main analysis of the third secondary endpoint, the 'proportion and number of DPT TWs that required autografting' was lower in the NexoBrid treatment arm (25.93% [21/81 TWs]) vs. SOC (37.68% [26/69 TWs]). The estimated odd ratio of NexoBrid vs. SOC was 0.414 (95% CI: 0.163 - 1.054) (p-value =0.0545). Results of all sensitivity and supportive analysis as well as the subgroup analysis by age consistently showed a lower proportion and number of DPT TWs requiring autografting for NexoBrid vs. SOC.

Descriptive statistics for the fourth secondary endpoint showed that the 'mean percent area of autograft in DPT wounds' with NexoBrid (15.9% [SD 38.57]) was smaller than with SOC (22.8% [SD 43.72]). The estimated treatment difference was not statistically significant (-3.7% [SE 7.60] (p-value =0.5045).

In the subgroup analysis by age group, the percent area of autograft was numerically lower with NexoBrid vs. SOC for patients aged 0 to 3 years and 12 to 18 years but was numerically higher than SOC for the subset of patients ages 4 to 11.

Exploratory analysis of POSAS (total, observer, and patient) of TWs at 6 weeks, 12 weeks, 6 months, and 12 months post wound closure demonstrated a consistent numerical advantage of NexoBrid over SOC.

In an exploratory analysis, no significant difference was observed in the incidence of reduction in interstitial compartmental pressure in circumferential extremity TWs in the NexoBrid and SOC treatment arms.

In an exploratory analysis, the % wound area surgically harvested was numerically lower for NexoBrid compared with SOC and the number of patients with at least 1 surgically harvested donor site wound was numerically lower with NexoBrid compared with SOC (difference ns).

Exploratory analyses of MVSS of TWs at 6 weeks, 12 weeks, and 6 months post wound closure were generally similar for the NexoBrid and SOC treatment arm.

Some endpoints with connection to the clinical efficacy [Time to reach complete wound closure; Lower Extremity Function Scale (LEFS); Disabilities of the Arm, Shoulder, and Hand (QuickDash); Range of Motion (ROM) and Quality of Life (EQ-5D)] were evaluated in the study as safety parameters; however the results are discussed below.

Time to Reach Complete Wound Closure

In the main Analysis (on the Target Wound Level) 'Median time to Reach Complete Wound Closure (>95%)' was 28 days for NexoBrid-patients vs. 24 days for SOC-patients (observed data only). This difference of 4 days can be considered as clinically not significant even though formal non-inferiority was only established in the main analysis (when incorporating a 7-day advantage for the SOC) which could not be confirmed in additional analyses (on a patient level). In the pooled studies (adult and paediatric patients), time to complete wound closure was (when estimated by the Kaplan-Meier method) median NexoBrid: 31.0 days vs. SOC: 27.0 days, or calculated (using actual data) NexoBrid vs. SOC: mean 32.5 days vs. 30.4 days, median 28.0 days vs. 24.0 days respectively).

Upon CHMP's request, the MAH provided an additional post hoc analysis comparing the observed only data on 'Time to complete wound closure' with the previously submitted main analysis. The new post hoc analysis corroborates the main analysis, since observed only data on 'median time to complete wound closure' for NexoBrid and SOC on a TW level was (NexoBrid vs. SOC): 28 days vs. 23.5 days, compared to the main analysis (NexoBrid vs. SOC): 28 days vs. 24 days, respectively. (The estimated median time to complete wound closure on a TW level - using the Kaplan Meier Method - was 32.00 days (95% CI: 28.00 – 42.00) for NexoBrid vs. 41.00 days (95% CI: 35.00 – 45.00) for SOC when including the NI margin of + 7 days for SOC.).

In the main analysis the hazard ratio of NexoBrid vs. SOC (estimated from the parametric frailty model) was 2.86 (95% CI: 1.23 - 6.67; p-value = 0.0149), indicating NI of NexoBrid to SOC.

In the new post hoc analysis the hazard ratio of NexoBrid vs. SOC (estimated from the parametric frailty model) was 4.89 (95% CI: 1.32 -18.11; p-value = 0.0176), supporting NI of NexoBrid to SOC (NI margin of 7 days in both analyses).

The results of the analysis on the basis of observed data only were incorporated in the SmPC section 5.1.

Functionality and QoL life measurements at 12 months were generally similar in the NexoBrid and SOC treatment arms. However, the number of patients included in the analyses was low, which precludes firm conclusions. No meaningful conclusions can be drawn from the BOQ results due to the low patient numbers.

The results of ROM evaluations were generally similar for NexoBrid and SOC treatment arms.

Analysis of pooled data

The efficacy results in the paediatric study CIDS for the co-primary endpoints were supported by efficacy data from paediatric patients in study MW2004-11-02. They were also consistent with results in adult

patients in the pooled analysis of the pivotal Phase 3 studies in adults (DETECT, MW2004-11-02, and MW2002-04-01).

The time to complete ER, % wound area surgically excised and incidence of surgical excision in paediatric patients in the CIDS study were lower for NexoBrid vs. SOC. These results are supported by results of paediatric patients in study MW2004-11-02. The results are also consistent with results in adult patients in the pooled pivotal Phase 3 studies (DETECT, MW2004-11-02, and MW2002-04-01).

Time to complete wound closure at the patient level in NexoBrid treated patients was comparable between the CIDS study and pooled adult population. In the adult pooled population, the time to reach complete (>95%) wound closure on a TW level was comparable in the NexoBrid and SOC treatment arms. The Kaplan-Meier estimated median time to complete wound closure for NexoBrid and SOC on a TW level (clustered data of TWs in a patient), was 32 (95% CI: 29.0 - 34.0) days and 28 (95% CI: 24.0 - 29.0) days, respectively. The coefficient for treatment effect for NexoBrid vs SOC arm was -1.44 (95% CI: -2.30 to -0.58).

Time to complete wound closure at the patient level in NexoBrid treated patients was comparable between the CIDS study (FAS population) and pooled paediatric population (safety population). In the paediatric pooled population, the time to reach complete (>95%) wound closure on a TW level was comparable in the NexoBrid and SOC treatment arms. The Kaplan-Meier estimated median time to complete wound closure for NexoBrid and SOC on a TW level (clustered data of TWs in a patient), was 31 (95% CI: 27.0 - 36.0) days and 31 (95% CI: 24.0 - 37.0) days, respectively. The coefficient for treatment effect for NexoBrid vs SOC arm was -2.20 (95% CI: -3.56 to -0.85).

Cosmesis and function (MVSS) at 12 months from wound closure was an efficacy endpoint in the paediatric CIDS study. Supporting these results, MVSS score was evaluated as a safety endpoint in adult patients in the adult DETECT study. NexoBrid showed advantage over SOC in both studies.

Retrospective study 35-98-910

A total of 154 patients were included in the retrospective study 35-98-910. Of these, 75 patients (<16 years) were included in paediatric population. In Study MW2008-09-03 three (3) were paediatric patients.

In the NexoBrid arm, the mean age (SD) was lower in the study 35-98-910 compared to paediatric pooled population (4.3 [3.7] vs. 6.5 [5.03] years). The majority of paediatric patients were males in both pooled pediatric population (52/87 [59.8%]) and study 35-98-910 (30/46 [65.2%]). The majority of patients in both paediatric pooled populations and study 35-98-910 had total treated wounds (all wounds) of ≤ 15% TBSA (90.8% vs. 98.7%) in the NexoBrid arm.

In study 35-98-910, debridement was achieved in 92.0% of the area that was in contact with NexoBrid. In the NexoBrid arm, percent of eschar removed per TW was similar in the paediatric pooled population and study 35-98-910 (96.7% vs. 92.0%).

The mean (SD) time to complete wound closure for NexoBrid and SOC on a TW level (clustered data of TWs in a patient), was 32.0 (16.29) days and 30.5 (16.96) days, respectively. The mean (SD) time to complete wound closure on a TW level was shorter in the Study 35-98-910 (21.4 [16.5] days) compared with the paediatric pooled population (32.0 [16.29] days). In Study MW2008-09-03, wound closure for all TWs was achieved after 29 days for 2 paediatric patients and after 61 days for 1 paediatric patient.

Efficacy results were consistent in the paediatric populations of the controlled, open-label, and retrospective studies.

Given the scarce PK data in the younger age group (0-3 years), the MAH proposed to revise SmPC section 4.2 to reflect that for paediatric patients aged 0-3 years old, NexoBrid should not be applied to more than 10% TBSA. This was agreed by CHMP. In addition, the results from the pivotal paediatric phase 3 study

(CIDS) supporting the paediatric extension of indication were adequately added to SmPC section 5.1. The patient leaflet was updated accordingly.

2.4.3. Conclusions on the clinical efficacy

The clinical data from the pivotal CIDS demonstrated clear superiority of NexoBrid over SOC in all three Co-Primary endpoints ('median time to complete eschar removal', 'Percent wound area surgically excised for eschar removal'' and Scar score MVSS at 12 months') as well as the first secondary endpoint 'Incidence of surgical excision'.

NexoBrid significantly reduces the amount of surgical excision of eschar required by burn wounds in paediatric patients in a significantly shorter period of time compared to SOC treatment.

A subgroup analysis by age group (0 to 23 months, 24 months to 3 years, 0 to 3 years, 4 to 11 years, and 12 to 18 years) consistently demonstrated superiority of NexoBrid over SOC in each age group. The results demonstrate that NexoBrid effectively removes the eschar earlier than the SOC in all paediatric age groups.

Furthermore, treatment with NexoBrid showed no deleterious effect on cosmesis and function at 12 months post wound closure in paediatric patients. These results were consistently observed across all age groups studied.

The analysis across studies (CIDS data vs. paediatric data from MW 2004-11-02) confirmed the clinical efficacy in the paediatric population and the comparison with clinical study data in adults (pooled data from DETECT, MW2004-11-02 and MW2002-04-01) showed comparable efficacy results of the CIDS data with the results in adults.

The CHMP concluded that the efficacy data available supports the following indication:

NexoBrid is indicated in all age groups for removal of eschar in patients with deep partial- and full-thickness thermal burns.

2.5. Clinical safety

Introduction

The main safety data in support of the extension of indication of NexoBrid in the paediatric population comes from the pivotal phase 3 CIDS study. The results from the CIDS study are supported by the safety data from pooled paediatric studies with pooled adult study data from the (phase 2 and 3) studies: MW2001-10-03, MW2002-04-01, MW2005-10-05, MW2008-09-03, MW2004-11-02, and DETECT study (MW2010-03-02); and by the results of the retrospective study (35-98-910).

Patient exposure

Study MW2012-01-01 (CIDS) assessed the safety (and efficacy) of NexoBrid vs. SOC in paediatric patients 0 to 17 years of age. Of the 145 patients randomised, 139 (95.9%) patients were treated and included in the SAS: 69 (95.8%) in the NexoBrid arm and 70 (95.9%) in the SOC treatment arm.

Of the patients randomised in the study, 132 patients (66 [91.7%] patients in the NexoBrid and 66 [90.4%] in the SOC treatment arm) completed the 12 weeks post wound closure FU period (12W FU Period) and 129 patients (66 [91.7%] patients in the NexoBrid and 63 [86.3%] in the SOC treatment

arms) completed the 12M FU Period. The most common reasons for discontinuation from the study were "lost to follow-up" and "patient withdrew consent to continue in the study".

The distribution of the SAS to the age groups was for 0 - 23 Months: N=42 (NexoBrid: 20 vs. SOC: 22), for 24 Months – 3 Years: N=30 (NexoBrid: 15 vs. SOC: 15), for 4 – 11 Years: N=47 (NexoBrid: 25 vs. SOC: 22) and for 12 – 18 Years: N= 20 (NexoBrid: 9 vs. SOC: 11).

The mean amount of NexoBrid administered in the CIDS study was 5.108 g (min.: 0.6 g – max.: 26.8 g). In the CIDS study, only 1 patient received 2 applications of NexoBrid (dose 16.8 g). Mean %TBSA of all TWs was similar for NexoBrid-patients (7.01% [SD 4.879]) vs. SOC-patients (6.20% [SD 4.777]).

Adverse events

The analysis of AEs in the CIDS study was based on the SAS consisting of 69 patients treated with NexoBrid vs. 70 patients treated with SOC (0 - 23 Months: N=42 [NexoBrid: 20 vs. SOC: 22], 24 Months – 3 Years: N=30 [NexoBrid: 15 vs. SOC: 15], 4 – 11 Years: N=47 [NexoBrid: 25 vs. SOC: 22] 12 – 18 Years: N= 20 [NexoBrid: 9 vs. SOC: 11]).

TEAEs were analysed separately for 3 different sub-periods:

1. Until the 12 weeks follow-up (0-12W FU Period)

2. Between the 12 weeks follow-up and the 12 months follow-up (including AEs from the first sub-period that were still ongoing) (12W-12M FU Period)

3. In the cumulative period (0-12M FU Period).

TEAEs in 0-12weeks Follow up Period

In the 0-12W FU Period (up to the 12 weeks follow-up), 31/69 (44.9%) patients treated with NexoBrid, vs. 29/70 (41.4%) with SOC reported at least 1 TEAE. Most were mild to moderate; severe TEAEs were reported by 5 patients (4 for NexoBrid vs. 1 for SOC; Table 31).

Table 31: Summary of incidence of TEAEs in the pivotal CIDS study– 0-12W FU Period (SAS)

Number of Patients	NexoBrid (N=69)			SOC (N=70)		
	n	%	Events	n	%	Events
With at Least 1 TEAE	31	44.9	99	29	41.4	97
With at Least 1 Mild or Moderate TEAE	30	43.5	81	29	41.4	92
With at Least 1 Severe TEAE	4	5.8	18	1	1.4	5
With at Least 1 TESAE	2	2.9	4	5	7.1	6
With at Least 1 TEAE Possibly, Probably, or Related to Study Drug	9	13.0	14	NA[a]	NA	NA
With at Least 1 Local TW-related TEAE	15	21.7	21	17	24.3	33
With TEAE with Outcome of Death	0	0	0	0	0	0

0-12W FU = 0-12 weeks follow-up, % = 100*n/N, N = number of patients in the SAS, n = number of patients with a TEAE, NA = not applicable, SAS = safety analysis set, SOC = standard of care, TEAE = treatment-emergent adverse event, TESAE = treatment emergent serious adverse event, TW = target wound

[a] Relationship to study treatment was not assessed for the SOC arm.

AEs reported in the 0-12W FU Period were also summarised by age group (0 - 23 months, 1 to 3 years, 0 to 3 years, 4 to 11 years, and 12 - 18 years). There was a trend towards the incidence of AEs increasing with age in both treatment arms: ≥1 TEAE: 0 – 23 Months: NexoBrid: 5/20 (25%) vs. SOC: 5/22 (22.7%); 1 -3 years: NexoBrid: 6/15 (40%) vs. SOC: 7/15 (46.7%); 4 - 11 years (NexoBrid: 14/25 (56%) vs. SOC: 10/22 (45.5%); 12 - 18 years: NexoBrid: 6/9 (66.7%) vs. SOC: 7/11 (63.6%). In all age subgroups the incidence of AEs was similar for NexoBrid-patients vs. SOC-patients. There was no increase in the incidence of severe or serious TEAEs across age groups.

TEAEs reported for ≥2 patients for each treatment were as follows:

• NexoBrid: pruritus (13.0% patients); pyrexia (10.1% p.); vomiting and wound complication (7.2% p. each); pain (5.8% p.); constipation, nasopharyngitis, and nausea (4.3% p. each); diarrhoea, ear infection, haemoglobin decreased, rash, and rhinovirus infection (2.9% p. each).

• SOC: pruritus (10.0% p.); pain and wound complication (7.1% p. each); pyrexia (5.7% p.); anaemia, tachycardia, and vomiting (4.3% p. each); anxiety, blister, bromhidrosis, chills, diarrhoea, headache, nausea, and wound infection (2.9% p. each).

Among the patients treated with NexoBrid who reported wound complication in the 0-12W FU Period, the reported terms included: 'pseudo-eschar amount greater than expected', 'wound pain (during movement)' and 'itching around wound'.

Among patients treated with the SOC who reported wound complication in the 0-12W FU Period, the reported terms included: 'poor wound care requiring surgical intervention' and 'itching of target/burn wound'.

For the 2 patients (2.9%) treated with NexoBrid who experienced rash in the 0-12W FU Period, 1 event was assessed as treatment-related. Both rash TEAEs were local TW-related TEAEs.

In the age group 0 – 3 years, TEAES reported for ≥2 patients for each treatment were as follows:

- NexoBrid: pyrexia 2/35 (5.7%), Nasopharyngitis 2/35 (5.7%), Wound complication 3/35 (8.6%), Pruritus 3/35 (8.6%).
- SOC: Anaemia 2/37 (5.4), Nasopharyngitis 2/37 (5.4%), Vomiting 2/37 (5.4%), Diarrhoea 2/37 (5.4%), Cough 2/37 (5.4%).

In the age group 4 - 11 years, TEAES reported for ≥2 patients for each treatment were as follows:

- NexoBrid: Pain 4/25 (16%), Pyrexia 4/25 (16%), Pruritus 5/25 (20%), Rash 2/25 (8%), Wound complication 2/25 (8%), Vomiting 4/25 (16.0%), Constipation 3/25 (12%), Nausea 3/25 (12%), Ear infection 2/25 (8%).
- SOC: Pyrexia 2/22 (9.1%), Chills 2/22 (9.1%), Pruritus 4/22 (18.2%), Bromhidrosis 2/22 (9.1%).

In the age group 12 - 18 years, TEAES reported for ≥2 patients for each treatment were as follows:

- SOC: Pruritus 3/11 (27.3%), Tachycardia 2/11 (18.2%).

For NexoBrid severe grade of TEAEs were noted for: Tachycardia (1), Vomiting (1), Pyrexia (2), Pain (1), Sepsis (1), UTI (1), Hypoalbuminaemia (1), Seizure (1), Tardive dyskinesia (1), anxiety (1), Sleep disorder (1), Pleural effusion (1), Pruritus (1), Rash (1), Hyperhidrosis (1) and Hypertension (1).

For SOC severe grade TEAEs were noted for: Pyrexia (1), Chills (1), Vascular device infection (1), Pruritus (1) and Hyperhidrosis (1).

Table 32: Summary of TEAEs by System Organ Class, Preferred Term, and Maximum Intensity (Reported for ⩾2 Patients in Either Treatment Arm) – 0-12W FU Period (SAS)

System Organ Class Preferred Term	NexoBrid (N=69) n (%)				Standard of Care (N=70) n (%)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Blood and Lymphatic System Disorders								
Anaemia	0	0	0	0	3 (4.3)	0	0	3 (4.3)
Cardiac Disorders								
Tachycardia	0	0	1 (1.4)	1 (1.4)	2 (2.9)	1 (1.4)	0	3 (4.3)
Gastrointestinal Disorders								
Constipation	3 (4.3)	0	0	3 (4.3)	0	1 (1.4)	0	1 (1.4)
Diarrhoea	1 (1.4)	1 (1.4)	0	2 (2.9)	1 (1.4)	1 (1.4)	0	2 (2.9)
Nausea	1 (1.4)	2 (2.9)	0	3 (4.3)	1 (1.4)	1 (1.4)	0	2 (2.9)
Vomiting	1 (1.4)	3 (4.3)	1 (1.4)	5 (7.2)	2 (2.9)	1 (1.4)	0	3 (4.3)
General Disorders and Administration Site Conditions								
Pain	1 (1.4)	2 (2.9)	1 (1.4)	4 (5.8)	2 (2.9)	3 (4.3)	0	5 (7.1)
Pyrexia	2 (2.9)	3 (4.3)	2 (2.9)	7 (10.1)	2 (2.9)	1 (1.4)	1 (1.4)	4 (5.7)
Chills	0	0	0	0	0	1 (1.4)	1 (1.4)	2 (2.9)
Infections and Infestations								
Nasopharyngitis	1 (1.4)	2 (2.9)	0	3 (4.3)	1 (1.4)	0	0	1 (1.4)
Ear infection	1 (1.4)	1 (1.4)	0	2 (2.9)	0	0	0	0
Rhinovirus infection	2 (2.9)	0	0	2 (2.9)	0	0	0	0
Wound infection	0	0	0	0	1 (1.4)	1 (1.4)	0	2 (2.9)
Injury, Poisoning and Procedural Complications								
Wound complication	3 (4.3)	2 (2.9)	0	5 (7.2)	3 (4.3)	2 (2.9)	0	5 (7.1)
Investigations								
Haemoglobin decreased	1 (1.4)	1 (1.4)	0	2 (2.9)	0	0	0	0
Nervous System Disorders								
Headache	0	0	0	0	2 (2.9)	0	0	2 (2.9)
Psychiatric Disorders								
Anxiety	0	0	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)	0	2 (2.9)
Skin and Subcutaneous Tissue Disorders								
Pruritus	2 (2.9)	6 (8.7)	1 (1.4)	9 (13.0)	4 (5.7)	2 (2.9)	1 (1.4)	7 (10.0)
Rash	1 (1.4)	0	1 (1.4)	2 (2.9)	0	0	0	0
Blister	0	0	0	0	2 (2.9)	0	0	2 (2.9)
Bromhidrosis	0	0	0	0	0	2 (2.9)	0	2 (2.9)

0-12W FU = 0-12 weeks follow-up, % = 100*n/N, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the SAS, n = number of patients with a treatment-emergent adverse event, SAS = safety analysis set.
Notes: Patient is counted only once with the maximum intensity within a system organ class and only one within the maximum intensity within a preferred term. Adverse events are coded using the MedDRA Dictionary Version 24.0. Adverse events are presented in alphabetic order of system organ class and then descending frequency of patients reporting preferred term in the NexoBrid arm.

TEAEs in 12weeks-12months Follow up Period

In the 12W-12M FU Period (time between 12 weeks and 12 months after wound closure), 7/69 (10.1%) NexoBrid-patients vs. 8/70 (11.4%) SOC-patients reported at least 1 TEAE. These included new events (starting during the 12W-12M FU Period) as well as continuing TEAEs from the 12W FU period. Most of the TEAEs were mild to moderate; 1 NexoBrid-patient reported a severe TEAE (Clavicle fracture; 4 to 11 years). A serious TEAE was reported by 1 SOC-patient (concussion; 12 to 18 years). No patients with NexoBrid had a TEAE reported as related to the study drug (the investigator-assigned relationship was not collected for TEAEs for patients treated with the SOC).

AEs reported in the 12W-12M FU Period were further summarised by age group:0 to 23 months (NexoBrid: 1/20 (5%), SOC: 2/22 (9.1%)), 1 - 3 years (NexoBrid: 2/15 (13.3%), SOC: 1/15 (6.7%)), 0 - 3 years (NexoBrid: 3/35 (8.6%), SOC: 3/37 (8.1%)), 4 - 11 years (NexoBrid: 4/25 (16%), SOC: 1/22 (4.5%)), and 12 - 18 years (NexoBrid: 0/9, SOC: 4/11 (36.4%)). There was no clear trend towards the incidence of AEs with age in both treatment arms.

The only TEAE reported by ≥2 patients treated with NexoBrid was wound complication (reported terms of 'itching of target wound' [mild] and 'itching of target wounds' [moderate] each reported by 1 patient).

The only TEAE reported by ≥2 patients treated with the SOC was nasopharyngitis (reported by 3 patients).

TEAEs in 0-12M FU Period

The most frequent TEAEs during the 0-12M FU Period (reported for ≥5% patients in either treatment arm) were:

• pruritus (9 patients (13%) with NexoBrid vs. 7 patients (10%) with SOC),

• pyrexia (7 patients (10.1%) with NexoBrid vs. 4 patients (5.7%) with SOC),

• wound complication:

- 6 patients (8.7%) with NexoBrid (reported terms included: 'pseudo eschar amount greater than expected', 'itching of target wounds', 'wound pain [during movement]') and

- 5 patients (7.1%) with SOC (reported terms included: 'poor wound care requiring surgical intervention' and 'itching of target/burn wound),

• pain (4 patients (5.8%) with NexoBrid vs. 5 patients (7.1%) with SOC) and

• vomiting (5 patients (7.1%) with NexoBrid vs.4 patients (5.7%) with SOC).

Treatment-related TEAEs in the 0-12weeks Follow up Period

Relationship to treatment was not assessed for the SOC treatment arm. The only treatment related TEAEs reported by more than 1 NexoBrid-patient were pyrexia (4/69 patients, 5.8%) and wound complication (2/69 patients, 2.9%).

There were no TEAEs considered to be related to NexoBrid during the 12W-12M FU Period. Therefore, the treatment-related TEAEs reported during the 0-12M FU Period were the same as those presented in Table 32.

Severe TEAEs of pyrexia and tachycardia were each reported by 1 (1.4%) NexoBrid-patient. The severe events of pyrexia and tachycardia were reported in the same patient in the 0-12W FU Period (Table 33).

Table 33: Summary of Treatment-related TEAEs by System Organ Class, Preferred Term, and Maximum Intensity – 0-12W FU Period (SAS)

System Organ Class Preferred Term	NexoBrid (N=69) n (%)			
	Mild	Moderate	Severe	Total
Cardiac Disorders				
Tachycardia	0	0	1 (1.4)	1 (1.4)
General Disorders and Administration Site Conditions				
Pyrexia	2 (2.9)	1 (1.4)	1 (1.4)	4 (5.8)
Pain	0	1 (1.4)	0	1 (1.4)
Infections and Infestations				
Cellulitis	1 (1.4)	0	0	1 (1.4)
Injury, Poisoning and Procedural Complications				
Wound Complication	1 (1.4)[a]	1 (1.4)[b]	0	2 (2.9)
Investigations				
Glucose Urine Present	1 (1.4)	0	0	1 (1.4)
Skin and Subcutaneous Tissue Disorders				
Petechiae	1 (1.4)	0	0	1 (1.4)
Pruritus	1 (1.4)	0	0	1 (1.4)
Rash	1 (1.4)	0	0	1 (1.4)
Skin Exfoliation	0	1 (1.4)	0	1 (1.4)

0-12 W FU = 0-12 weeks follow-up, % = 100*n/N, FU = follow-up, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the SAS, n = number of patients with a treatment-related treatment-emergent adverse event, SAS = safety analysis set.

Local TW-related TEAEs in the 0-12W FU Period

The most frequently reported TW-related TEAEs for each treatment were as follows:

• NexoBrid: wound complication (5/69 patients, 7.2%) and pruritus (3/69 patients, 4.3%)

• SOC: wound complication and pruritus (5/70 patients, 7.1% each)

Wound complications reported terms during the 0-12W FU Period included: NexoBrid: 'wound pain', 'itching target/burn wounds', and 'pseudo eschar amount greater than expected' and SOC: 'poor wound care requiring surgical intervention' and 'itching target/burn wound'.

Local TW-related TEAEs in the 12W-12M FU Period

Two patients in each treatment arm experienced local TW-related TEAEs during the 12W-12M FU Period; wound complication (reported terms of wound pain and pseudo eschar amount greater than expected) was reported for 2 patients treated with NexoBrid, and temperature intolerance and joint contracture were each reported by 1 patient treated with the SOC (Table 34).

Table 34: Summary of Local TW-related TEAEs by System Organ Class and Preferred Term – 0-12W FU Period (SAS)

System Organ Class Preferred Term	NexoBrid (N=69) n (%)	Standard of Care (N=70) n (%)
General Disorders and Administration Site Conditions		
Pain	1 (1.4)	2 (2.9)
Temperature Intolerance	0	1 (1.4)
Infections and Infestations		
Cellulitis	1 (1.4)	1 (1.4)
Wound Infection	0	2 (2.9)
Injury, Poisoning and Procedural Complications		
Wound Complication	5 (7.2)	5 (7.1)
Contusion	1 (1.4)	0
Skin Abrasion	1 (1.4)	0
Graft Loss	0	1 (1.4)
Injury	0	1 (1.4)
Post Procedural Haematoma	0	1 (1.4)
Wound	0	1 (1.4)
Wound Dehiscence	0	1 (1.4)
Wound Haemorrhage	0	1 (1.4)
Investigations		
Culture Wound Positive	1 (1.4)	1 (1.4)
Musculoskeletal and Connective Tissue Disorders		
Joint Contracture	1 (1.4)	1 (1.4)
Limb Discomfort	0	1 (1.4)
Myalgia	0	1 (1.4)
Pain in Extremity	0	1 (1.4)
Skin and Subcutaneous Tissue Disorders		
Pruritus	3 (4.3)	5 (7.1)
Erythema	1 (1.4)	0
Petechiae	1 (1.4)	0
Rash	1 (1.4)	0
Rash Maculo-papular	1 (1.4)	0
Blister	0	2 (2.9)
Skin Irritation	0	1 (1.4)
Skin Odour Abnormal	0	1 (1.4)

0-12W FU = 0-12 weeks follow-up, % = 100*n/N, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the SAS, n = number of patients with TW-related treatment-emergent adverse events, SAS = safety analysis set, TW = target wound.

Local TW-related TEAEs in the 012M FU Period

TW-related TEAEs that occurred during the 0-12M FU Period (cumulative period). The TW-related TEAEs reported by the most patients for each treatment were as follows:

- NexoBrid: wound complication (6/69 patients, 8.7%) and pruritus (3/69 patients, 4.3%)
- SOC: wound complication and pruritus (5/70 patients, 7.1% each).

Serious adverse event/deaths/other significant events

There were no deaths during the study.

SAEs

Two NexoBrid-patients and 5 SOC-patients had SAEs during the 0-12W FU Period (Table 35). These were mild to moderate, except 1 patient treated with NexoBrid (female, 14-months) who had severe tachycardia, pyrexia, and systemic inflammatory response (Sepsis). This event (reported within 24 hours after treatment) was assessed by the investigator as remotely related, and tachycardia and pyrexia were assessed as possibly related to NexoBrid. This SAE was later assessed by the DSMB to be not related to NexoBrid, but to a pre-existing respiratory infection and tachycardia. SAEs of pyrexia and tachycardia (both considered to be of severe intensity and possibly related to study treatment by the investigator) were also reported for this patient. The other SAE (Contracture of left axilla, 4-year-old male) was considered as not related to NexoBrid. Relationship to treatment was not assessed for the SOC treatment arm.

Table 35: Summary of SAEs by System Organ Class, Preferred Term, and Maximum Intensity– 0-12W FU Period (SAS)

System Organ Class Preferred Term	NexoBrid (N=69) n (%)				Standard of Care (N=70) n (%)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Cardiac Disorders								
Tachycardia	0	0	1 (1.4)	1 (1.4)	0	0	0	0
General Disorders and Administration Site Conditions								
Pyrexia	0	0	1 (1.4)	1 (1.4)	0	0	0	0
Systemic Inflammatory Response Syndrome	0	0	1 (1.4)	1 (1.4)	0	0	0	0
Withdrawal Syndrome	0	0	0	0	0	1 (1.4)	0	1 (1.4)
Infections and Infestations								
Viral Infection	0	0	0	0	1 (1.4)	0	0	1 (1.4)
Injury, Poisoning and Procedural Complications								
Injury	0	0	0	0	1 (1.4)	0	0	1 (1.4)
Procedural Pain	0	0	0	0	1 (1.4)	0	0	1 (1.4)
Wound Complication	0	0	0	0	0	1 (1.4)	0	1 (1.4)
Musculoskeletal and Connective Tissue Disorders								
Joint Contracture	0	1 (1.4)	0	1 (1.4)	0		0	0
Respiratory, Thoracic and Mediastinal Disorders								
Laryngospasm	0	0	0	0	1 (1.4)	0	0	1 (1.4)

0-12W FU = 0-12 weeks follow-up, % = 100*n/N, MedDRA = Medical Dictionary for Regulatory Activities, N = number of patients in the SAS, n = number of patients with a serious treatment-emergent adverse event, SAS = safety analysis set.

Only 1 SOC-patient experienced SAEs during the 12W-12M FU Period, an injury and concussion, which were of moderate severity.

Laboratory findings

The most common shift in a biochemistry laboratory value was from a normal baseline to an abnormal high glucose level, which occurred in 13 (25.0%) NexoBrid-patients vs. 6 (13.3%) SOC-patients. When evaluated by type of eschar removal procedure, the % of patients with a shift from normal baseline to abnormal post baseline high glucose was lower with NexoBrid (46.4%) compared with first surgical SOC (55.6%) treatment.

For electrolytes, the most common shift was from a normal baseline to abnormal low calcium levels, which occurred in 6 (11.5%) NexoBrid-patients vs. 0 SOC-patient.

The following potentially clinically significant (PCS) shifts from normal baseline were observed:

- Shift from normal to PCS low calcium (defined as <2 mmol/L and decrease ≥10%) for 1 (1.9%) NexoBrid-patients; No PCS shift in corrected calcium were observed.

- Shift from normal to PCS high glucose (defined as >11.10 mmol/L and increase ≥2.78 mmol/L) for 1 (1.9%) NexoBrid-patients (observed in a patient who received a glucose infusion prior to the laboratory assessment).

The following PCS in haematology shifts from normal baseline were observed:

- Shift from normal to PCS high neutrophils (defined as ≥20% upper limit of normal WBC upon age group and increase ≥ 10% from baseline) were observed for 4 (8.9%) NexoBrid-patients vs. 7 (17.5%) SOC-patients.

- Shift from normal baseline to PCS high leukocytes (defined as ≥20% age related threshold) reported for 1 (2.1%) NexoBrid-patients vs. 2 (4.7%) SOC-patients.

- Shift from normal baseline to PCS low leukocytes (defined as ≤20% age related lower threshold) reported for 1 (2.1%) NexoBrid-patients.

- Shift from normal baseline to PCS high platelets (defined as >600 and increase >10%) reported for 1 (2.6%) patient treated with SOC.

There were no PCS shifts (as defined by the criteria in the SAP) in coagulation parameter values.

Abnormal CS results for vital signs (Blood Pressure, Pulse, Respiratory Rate, and Body Temperature, as assessed by the investigator) were reported post baseline for 1 NexoBrid-patient at 4 days post dose (elevated temperature), and 1 SOC-patient (elevated temperature) at 5- and 7-days post dose.

Overall, no NexoBrid-patients in either age group had a shift from normal to a CS abnormal pain assessment post-treatment. One SOC-patient >4 years of age had a shift from normal to a CS abnormal pain assessment post treatment, and 1 SOC-patient <4 years had a shift from an abnormal NCS to abnormal CS pain assessment post-treatment. Similar results were observed when excluding patients with hospital discharge before Day 7.

Concomitant medication

During the 0-12W FU Period, 100% (69/69) of NexoBrid-patients and 98.6% (69/70) of SOC-patients received at least 1 concomitant medication. The most commonly used (ATC Level 2) concomitant medications were analgesics used by 62/69 (89.9%) of NexoBrid-patients vs. 61/70 (87.1%) of SOC-patients. There was a similar incidence rate for antibacterials for systemic use (41/69 [59.4%] in NexoBrid-patients vs. 39/70 [55.7%] treated with SOC).

The mean overall (SD) systemic antibiotic use was 5.89 (7.34) days for NexoBrid-patients vs. 4.94 (7.04) days for SOC-patients. The mean (SD) prophylactic antibiotic use was 4.38 (6.33) days for NexoBrid-patients vs. 4.31 (6.52) days for SOC-patients. The mean antibiotic use due to AE involvement was 1.80 (4.90) days for NexoBrid vs. 0.52 (2.82) days for SOC. TEAEs in the infections and infestations system organ class were reported for 13 (18.8%) NexoBrid-patients vs. 6 (8.6%) SOC-patients during the 0-12W FU Period, and for 14 (20.3%) NexoBrid-patients vs. 9 (12.9%) SOC-patients during the 0-12M FU Period. Treatment-related infections and infestations were reported for 1 (1.4%) NexoBrid-patient and 0 SOC-patient during the 0-12W and 0-12M FU period.

Blood Transfusions

Overall, 7 NexoBrid-patients vs. 8 SOC-patients received blood transfusions during hospitalisation. Among these 15 patients, 0 NexoBrid-patient vs. 5 SOC-patients received blood transfusion during eschar removal; 3 NexoBrid-patients vs. 1 SOC-patient received a blood transfusion within 1 week after eschar removal, and 4 NexoBrid-patients vs. 2 SOC-patients received a blood transfusion later than 1 week after the eschar removal.

Change in haemoglobin

On a patient level the mean (SD) change in haemoglobin following eschar removal procedures was 0.21 (8.714) g/L for NexoBrid-patients vs. 6.71 (13.415) g/dL for SOC-patients (p-value = 0.0201). On a procedure level, the mean (SD) blood loss using Hgb-change following eschar removal procedures was -0.35 (8.135) g/dL for NexoBrid-patients vs. 5.05 (12.773) g/dL for SOC-patients (p-value = 0.0487).

Rate of Hospital Readmission

At least one hospital readmission was reported for 8 patients (11.6%) in both treatment arms. Unplanned hospital readmissions were reported for 2 patients (2.9%) each in both treatment arms.

Discontinuation due to adverse events

No patient discontinued during or after treatment due to TEAEs (1 NexoBrid-patient withdrew due to an AE prior to treatment, according to Investigator decision and 1 NexoBrid-patient had fever and possible wound infection after randomisation; the PI decided not to treat according to the randomisation).

Analysis performed across trials (pooled analyses)

The MAH compared TEAEs from the pooled paediatric studies with pooled adult study data from the (phase 2 and 3) studies: MW2001-10-03, MW2002-04-01, MW2005-10-05, MW2008-09-03, MW2004-11-02, and DETECT study (MW2010-03-02).

In the pooled studies (adult and paediatric patients, Table 36), most patients in all the arms had mild or moderate TAEs. One patient in the NexoBrid arm discontinued due to a TEAE.

Seven patients died in the acute post wound closure phase (6 [2.0%] NexoBrid and 1 [0.5%] SOC). There were no TEAEs leading to death during the CIDS study (or in the pooled paediatric study data).

The frequency of TEAEs in NexoBrid treated patients was lower in the CIDS study than in the pooled studies (adult and paediatric patients), 44.9% vs. 64.3%, respectively. The frequency of severe and serious TEAEs was lower in the CIDS study than in the pooled studies (5.8% vs. 11% of patients had severe TEAEs, and 2.9% vs. 8.3% of patients had serious TEAEs, respectively). Frequency of related TEAEs was higher in the CIDS study than in the pooled studies (13% vs. 9.7%).

Table 36: Overview of Adverse Events – Pooled Studies (Adult and Paediatric Population)

	NexoBrid (N=300) n (%)	SOC (N=195) n (%)	Placebo Control (Gel Vehicle) (N=68) n (%)
Any TEAEs	193 (64.3)	107 (54.9)	50 (73.5)
Mild	93 (31.0)	64 (32.8)	29 (42.6)
Moderate	66 (22.0)	31 (15.9)	16 (23.5)
Severe	33 (11.0)	12 (6.2)	5 (7.4)
Serious TEAEs (SAEs)	25 (8.3)	12 (6.2)	7 (10.3)
Treatment-related TEAEs	29 (9.7)	NA	1 (1.5)
TEAEs leading to early discontinuation	1 (0.3)	0	0
TEAEs leading to death	6 (2.0)	1 (0.5)	0

N = number of patients in the SAS, n = number of patients with a TEAE, NA = not assessed, SAE = serious adverse event; SOC = standard of care; TEAE = treatment-emergent adverse event

Note: A total of 6 studies contributed to the data presented for pooled studies (MW2001-10-03, MW2002 04-01, MW2005-10-05, MW2008-09-03, MW2004-11-02, and MW2010-03-02).

The frequency of TEAEs in NexoBrid treated patients was also lower in the CIDS study than in the pooled paediatric studies, 44.9% vs. 65%. The frequency of severe TEAEs was comparable between CIDS and the pooled studies (5.8% vs. 5%). The frequency of serious TEAEs was again lower in the CIDS study than in the pooled studies (2.9% vs. 5%). Frequency of related TEAEs in NexoBrid treated paediatric patients was higher in the CIDS study than in the pooled studies (13% vs. 5.0%).

In the pooled studies the percentage of patients experiencing any TEAEs was similar in both treatment arms (NexoBrid: 13 [65.0%] vs. SOC: 9 [56.3%]).

Table 37: Overall Summary of AEs, Subset of Pooled Studies from Cohort 1 (Paediatric Population Only)

System Organ Class Preferred Term	NexoBrid (N=20, PY=6.53) n (%)	SOC (N=16, PY=5.62) n (%)
Any AEs	13 (65.0)	9 (56.3)
Any TEAEs	13 (65.0)	9 (56.3)
Serious TEAEs	1 (5.0)	2 (12.5)
Treatment-Related TEAEs[a]	1 (5.0)	0
Severe TEAEs	1 (5.0)	3 (18.8)
TEAEs leading to early discontinuation	0	0
TEAEs leading to death	0	0

AE = adverse event, SOC = standard of care, PY = total patient years = total number of days in the study of all patients in a specific treatment arm divided by 365.25, TEAEs = treatment emergent adverse events.
Percentages are calculated based on column N.
[a] AE is defined as related if causality is possibly related, probably related or related.

Cohort 1 (MW2008-09-03 and MW2004-11-02)

Common Adverse Events

In the CIDS study the most frequent TEAEs for each treatment were as follows:

• NexoBrid: pruritus (13.0% patients); pyrexia (10.1% patients); vomiting and wound complication (7.2% patients each); pain (5.8% patients); constipation, nasopharyngitis, and nausea (4.3% patients each); diarrhoea, ear infection, haemoglobin decreased, rash, and rhinovirus infection (2.9% patients each).

• SOC: pruritus (10.0% patients); pain and wound complication (7.1% patients each); pyrexia (5.7% patients); anaemia, tachycardia, and vomiting (4.3% patients each);

In the pooled paediatric only data, the most frequent TEAEs (reported for ≥10% of NexoBrid-patients) were pruritus (30%), pyrexia (20%), vomiting (10%), anaemia (15%), nausea (15%), hyperthermia (15%), infection (10%), hypoalbuminaemia (10%), and rash (10%).

Treatment-related Adverse Events

In the CIDS study the only treatment related TEAEs reported by more than 1 patient treated with NexoBrid were pyrexia (4/69 patients, 5.8%) and wound complication (2/69 patients, 2.9%; reported terms of 'pseudo eschar amount greater than expected' [possibly related] and 'wound complication' [related] reported for 1 patient each).

In the pooled adult and paediatric data related TEAEs were most frequently reported within the system organ class of General Disorders and Administration Site Conditions in the NexoBrid group (7.3%). By PT, related TEAEs reported by 3 or more patients in the NexoBrid group were pain (18/300, 6%), pyrexia (6/300, 2%), and tachycardia (3/300, 1%).

Local Treatment-emergent Adverse Events

In the CIDS study, the most frequently reported TW-related TEAEs for each treatment were as follows:

• NexoBrid: wound complication (5/69 patients, 7.2%) and pruritus (3/69 patients, 4.3%)

• SOC: wound complication and pruritus (5/70 patients, 7.1% each)

Wound complications reported terms during the 0-12W FU Period included 'wound pain', 'itching target wounds' and 'pseudo eschar amount greater than expected' for patients treated with NexoBrid, and poor 'wound care requiring surgical intervention' and 'itching wound/target wound' in patients treated with SOC.

In the pooled paediatric studies the most frequent TEAEs (reported for >5% patients in either treatment arm) were pruritus (30.0% NexoBrid and 6.3% SOC), wound infection (0 in NexoBrid and 18.8% SOC), skin graft failure (5.0% NexoBrid and 6.3% SOC), staphylococcal infection and wound decomposition (0 in NexoBrid and 6.3% SOC each).

SAEs

In the CIDS study two patients treated with NexoBrid, and 5 patients treated with the SOC experienced SAEs during the 0-12W FU Period (NexoBrid: Tachycardia, Pyrexia, Systemic Inflammatory Response Syndrome (Sepsis; all in one patient) and Joint Contracture; SOC: Withdrawal Syndrome, Viral Infection, Injury, Procedural Pain, Wound Complication, Laryngospasm).

In the pooled studies (adult and paediatric patients), the percentages of patients who experienced serious TEAEs were for NexoBrid: (8.3%; 25/300) and for SOC (6.2%; 12/195). SAEs were most frequently reported within the system organ class of Infections and Infestations for: NexoBrid (2.3%) vs. SOC (2.1%). 3 TEAEs were reported in more than 1 patient (5 patients with sepsis, 2 patients with wound infection, and 2 patients with deep vein thrombosis [NexoBrid group]); all other serious TEAEs by PT occurred in a single patient. By PT, there were no overlapping SAEs between NexoBrid treated patients in the CIDS study and in the pooled studies.

In the pooled paediatric studies one patient (5.0%) treated with NexoBrid (Wound complications) and 2 patients (12.5%) treated with the SOC (Wound infection, Wound decomposition) experienced SAEs.

Pain

In the CIDS study, the incidence of TEAEs associated with pain related to TW occurring during the 0-12W FU period was 4.3% in both the NexoBrid and SOC treatment arms.

In the pooled studies (adult and paediatric patients), in the NexoBrid group, the frequency of overall pain events by combined PTs after implementation of preventive measures was similar with NexoBrid (4%), vs. SOC (3.8%).

Pyrexia

The incidence of TEAEs associated with fever by PT (pyrexia, hyperthermia, and body temperature increased) during the 0-12W FU period in the CIDS study was 11.6% in the NexoBrid arm vs. 5.7% with SOC.

In the pooled studies (adult and paediatric patients) after implementation of preventive measures the frequency of pyrexia was for NexoBrid (12.1%) vs. SOC (8.1%).

Wound Infection

In the CIDS study, the frequency of 'any TW associated with TW infection' was 1.4% in the NexoBrid arm vs. 4.3% for SOC.

Post-implementation of preventive measures, in pooled studies (adult and paediatric population) the frequencies of patients with infection were similar in the NexoBrid and SOC groups (Infection: 5.4% vs. 8.1%, respectively; Fungal Infection: 1.3% vs. 0%, respectively).

Sepsis

In the CIDS study, 1 NexoBrid-patient had SAEs with signs of sepsis (considered to be of severe intensity and remotely related to study treatment by the investigator). This SAE was assessed by the DSMB to be not related to NexoBrid, but to a pre-existing respiratory infection and tachycardia.

In the pooled Phase 3 studies post-implementation of preventive measures, the frequencies for any sepsis TEAE were: NexoBrid (2.8%) vs. SOC (2.0%).

Upon CHMP's request, the MAH has provided a detailed comparison with pooled adult and paediatric data. The incidence of TEAEs in the paediatric NexoBrid-pool was lower compared to the adult NexoBrid-pool (paediatric p. 49.4% vs. adults 64.3%). Also, SAEs in the paediatric NexoBrid-pool was lower vs. the adult NexoBrid-pool (paediatric p. 3.4% vs. adults 8.6%). The same applies for severe TEAEs (paediatric p. 5.6% vs. adults 11.4%). Sepsis related SAEs were recorded for 3 (3.4%) in pooled paediatric NexoBrid-p. (vs. 1 p. (1.2%) with SOC) compared to 12 (4.3%) in pooled adult NexoBrid-p. (vs. 4 p. (1.5%) with SOC-p. vs. 2 p. (2.9%) with Gel-p.).

The number of related TEAEs was similar between the paediatric vs. the adult NexoBrid-population (11.2% vs. 10.0%). Frequency of local TW-related TEAEs was lower in the pooled paediatric NexoBrid group vs. paediatric SOC group (24.7% vs. 27.9% in SOC). Local pain incidence was equal to SOC (2.2% vs. 2.3%) as was incidence of wound complications (5.6% vs. 5.8% in SOC). Only 1 wound infection was reported in NexoBrid paediatric patients (1.1 vs. 8.1% in SOC). Pruritus was reported slightly more often with NexoBrid vs. SOC (10.1% vs. 7.0%).

There were some differences in frequencies of AEs of special interest between the paediatric and the adult pool. Lower frequencies in the paediatric population were noted for: tachycardia, pain and wound infection. Higher frequencies were noted for hyperthermia/fever (when compared to adults after implementation of local antibiotic measures), hypalbuminaemia and rash. Equal frequency was presented for anaemia. There were no new safety signals in the paediatric population.

TEAE Analysis per age group and dose

Upon CHMP's request, t MAH provided additional pooled analyses (including CIDS data) of TEAEs (up to 12 weeks after wound closure) per age group and dose (dose ≤Median vs. dose >Median):

Incidence of 'Any TEAE' per age group and dose (dose ≤Median vs. dose >Median):

Age group: 0 to 3 Years: dose ≤Median: 4 of 18 (22.2%) vs. dose >Median 7 of 16 (43.8%) (factor 3);

Age group: 4 to 11 Years: dose ≤Median: 7 of 13 (53.8%) vs. dose >Median 7 of 11 (63.6%) (factor 3);

Age group: 12 to 18 Years: dose ≤Median: 3 of 5 (60.0%) vs. dose >Median 3 of 5 (60.0%).

This comparison shows an imbalance in incidence of any TEAE with dose in the younger two age groups (factor 3) as compared to the age group of 12–18-year-olds, where dose did not influence the incidence rate (although the number of subjects was very low in the oldest age group, limiting the interpretability).

Comparison for 'Any SAE':

Age group: 0 to 3 Years: dose ≤Median: 0 vs. dose >Median: 1;

Age group: 4 to 11 Years: dose ≤Median: 0 vs. dose >Median: 1;

Age group: 12 to 18 Years: dose ≤Median: 0 vs. dose >Median: 0;

Numbers per age group are too small to draw any conclusion with regards to SEAs, but results do not oppose the finding above with 'Any TEAE' (or with the other categories below) either.

Comparison for 'Related TEAEs':

Age group: 0 to 3 Years: dose ≤Median: 0 vs. dose >Median: 6 (17.6%) (factor >3);

Age group: 4 to 11 Years: dose ≤Median: 2 of 13 (15.4%) vs. dose >Median: 2 of 12 (16.7%);

Age group: 12 to 18 Years: dose ≤Median: 1 vs. dose >Median: 0;

For the youngest age group 0 to 3 years, the trend to a higher incidence with dose > median is corroborated here, but not so for the older age group 4-11 years (nor for the oldest age group).

Comparison for 'Special TEAEs' (Pain, Fever, Target Wound Infection):

Age group: 0 to 3 Years: dose ≤Median: 1 (5.6%) vs. dose >Median 2 (11.8%); (factor 2.1)

Age group: 4 to 11 Years: dose ≤Median: 4 (30.8%) vs. dose >Median 4 (33.3%);

Age group: 12 to 18 Years: dose ≤Median: 2 (40.0%) vs. dose >Median 0.

For the youngest age group 0 to 3 years, the trend to a higher incidence with dose > median is again corroborated here.

Comparison for 'General TEAEs':

Age group: 0 to 3 Years: dose ≤Median: 2 (11.1%) vs. dose >Median 5 (29.4%) (factor 2.6);

Age group: 4 to 11 Years: dose ≤Median: 4 (30.8%) vs. dose >Median 7 (58.3%);

Age group: 12 to 18 Years: dose ≤Median: 3 (60.0%) vs. dose >Median 2 (40%).

For the youngest age group 0 to 3 years, the trend to a higher incidence with dose > median is corroborated here again.

Supportive clinical safety study

Retrospective study 35-98-910

The results from the CIDS study are supported by the results of the retrospective study (35-98-910) which included 13 patients in the age of 0-12 months treated over 0.5% -12% TBSA. The incidence of any TEAE in this age group was 76.9% (10/13), slightly higher than in the 0-23 months (69.2%) and 2-3 years age groups (66.7%), but lower than in the older paediatric age groups (92% for 4-11years and 87.5% for 12-18 years) and in the pooled paediatric (77.5%) and adult patients (83.8%) that participated in the retrospective study.

Adverse Events (AEs) in the retrospective study assessed as possibly/probably related to NexoBrid in the 0-12 months age group were fever in 4 patients and pain in one patient. These AEs with reasonable possibility to NexoBrid of fever and pain are similar to the known Adverse Drug Reactions (ADRs) in the other age groups in the pooled paediatric population as well as in adults and are included in Section 4.8 of the SmPC. The retrospective study was performed before preventive measures for pain and pyrexia (preventive analgesia and soaking) were implemented. Severe AEs were reported in only one patient: Sepsis and Acute respiratory distress syndrome in the 0-12 months age group. Both were assessed as not related to the study drug.

Serious AEs were reported in 2 patients aged of 0-12 months, both assessed as not related to the study drug: one patient had fever and the second patient had acute respiratory distress syndrome (ARDS) and

sepsis, that started between 24-72 hours following eschar removal treatment and was assessed as not related to the study drug. In total, serious AEs were reported in 4/80 (5%) of paediatric patients in the retrospective study (2 patients in the 0-12 months (15.4%) and 2 patients in the 4-11 years age group), and in 6/74 (8.1%) of adult patients. The common TEAEs in the age group 0-12 months were:

Anaemia: this was reported with a higher percentage in the 0-12 months age group, reported in 3/13 treated subjects (23.1%). All AEs of anaemia were assessed as not related to study drug.

Pain and pyrexia: incidence rates were reported with higher percentage in the 0-12 months age group compared to the 0-23 months and 2-3years age groups, but lower or similar to the older paediatric age groups, and in adults.

Diarrhea and Upper respiratory tract infection: these common occurrences in the young paediatric population were reported with higher incidence in the 0-12 months age group, but no conclusions can be drawn due to the small numbers of patients.

No new safety concern associated with the 0-3 years age group was observed.

Post marketing experience

There is also 'off-label' data available for paediatric patients.

Using the MedDRA PT off label use as a search criterion, 49 case reports from the post marketing sources for the paediatric population were retrieved from MediWound's global safety database until 17 December 2021.

These case reports described the following types of off label use: Use in paediatric patients (40 case reports), Use in paediatric patients on more than 15% TBSA (5 case reports), Use in paediatric patients with chemical burns (2 case reports), Use in paediatric patients with electrical burns (2 case reports).

Two case reports of use of NexoBrid in paediatric patients also reported ADRs of 'drug ineffective', 'pain', 'muscle twitching' and 'therapeutic response decreased'.

In general, the AE profile of adult and paediatric patients seen in the published literature was similar to that seen in clinical studies.

2.5.1. Discussion on clinical safety

Based on the safety data submitted to support this extension of indication to the paediatric population, 166 children were treated with NexoBrid during the paediatric development programme:

- CIDS study: 69 children from birth to < 18 years
- Study MW2012-01-02 = extension study of Study MW2004-11-02: 17 children from 4 to < 18 years
- Phase 1/2 retrospective Study 35-98-910 (which was not a part of the PIP): 77 children, age range not specified
- Phase 2 MW2008-09-03 study, 3 children, age range not specified.

In the CIDS study, the number of exposed subjects in the safety analysis set (SAS) was small in the two treatment arms (NexoBrid vs. SOC: N=69 vs. N=70). The numbers in the age groups were even smaller: 0 - 23 months: N=42 (NexoBrid: 20 vs. SOC: 22); 24 months – 3 years: N=30 (NexoBrid: 15 vs. SOC: 15); 4 – 11 Years: N=47 (NexoBrid: 25 vs. SOC: 22) and 12 – 18 years: N= 20 (NexoBrid: 9 vs. SOC: 11). However, the numbers of patients as agreed in the PIP were met.

TEAEs in the 0-12 Week Follow-Up Period

As expected, more patients experienced TEAEs within 0 to 12 weeks following wound closure compared with the FU period between 12 weeks and 12 months, with incidences that were generally similar between the NexoBrid and SOC treatment arms (at least 1 TEAE NexoBrid: 44.9% vs. SOC: 41.4%). Overall, the number of patients who experienced SAEs was low in both the NexoBrid and SOC treatment arms (NexoBrid: 2/69, 2.9% vs. SOC: 5/70, 7.1%) and the majority were of mild to moderate severity.

Upon CHMP's request, the MAH has provided a discussion on severe AEs. Eighteen severe AEs in the first 3 months were reported in 4 NexoBrid-patients vs. 5 severe AEs were reported in 1 SOC-patient (CIDS study).

Analysis of the case narratives revealed that most AEs graded as severe were reported in one study site. No relation to age of the patients was connected to the severity classification. Most severe AEs were not related to treatment, excluding fever and tachycardia (reported in 1 patient) which are already included in section 4.8 of the SmPC as ADR. These are no new safety signals.

One patient in the NexoBrid treatment arm had SAEs that were considered as remotely related by the investigator (severe systemic inflammatory response, Sepsis) and possibly related to NexoBrid (severe tachycardia and severe pyrexia). The SAE of sepsis was assessed again by the DSMB and found to be not related to NexoBrid, but to a pre-existing respiratory infection and tachycardia.

The incidence of TW-related TEAEs was similar in the NexoBrid and SOC treatment arms during this period NexoBrid: 21.7%. vs. SOC: 24.3%.

The most frequent TEAEs in the NexoBrid treatment arm included pruritus (not TW-related TEAEs [6 patients] and local TW-related TEAEs [3 patients]), pyrexia, vomiting, wound complication (including terms of 'pseudo eschar amount greater than expected', 'itching target wounds', 'wound pain'), and pain.

The most frequent TEAEs in the SOC treatment arm included pruritus (not TW-related TEAEs [3 patients] and local TW-related TEAEs [4 patients]), pain, wound complication (including 'poor wound care requiring surgical intervention', 'intermittent itching wound'), and pyrexia.

The most frequently reported treatment related TEAEs in NexoBrid-patients during the 0-12W FU Period were pyrexia and wound complications (including reported terms of 'pseudo eschar amount greater than expected' and 'wound pain' in 1 patient each).

The most frequently reported TW related TEAEs in both the NexoBrid and SOC treatment arms were wound complications ('wound pain', 'wound itching' and 'pseudo eschar amount greater than expected' for patients treated with NexoBrid, and 'wound itching', and 'poor wound care requiring surgical intervention' in patients treated with the SOC) and local TW-related pruritus.

The incidence of (preferred term) pain in the 0-12W FU period was similar in the NexoBrid and SOC treatment arms during the 0-12W FU Period (4.3% for both groups).

Fever was evaluated as an AESI during the study and included the PTs of pyrexia, hyperthermia, and body temperature increased. The incidence of 'any fever TEAEs' was (NexoBrid vs. SOC) 11.6% vs. 5.7% respectively.

The incidence of TEAEs associated with TW infections were evaluated as an AESI in the study and included the PTs of TW infections, wound infection, or culture wound positive. The frequency of 'any TW-associated TEAE' was (NexoBrid vs. SOC) 1.4% vs. 4.3%.

In the CIDS-study there was an imbalance between treatment groups for pyrexia-related TEAEs and infections. In the pooled paediatric population, the incidence of TEAEs related to fever was 15 (16.9%) with NexoBrid vs. 8 (9.3%) with SOC. In 12/15 NexoBrid-p. the fever onset was by Day 3 (vs. 6/8 in

SOC-p.). Pyrexia/hyperthermia is already included as an ADR in SmPC section 4.8 with a frequency 'very common'. Also, there is nodditional risk for the paediatric (sub) populations. In the paediatric population occurrence of fever was lower compared to the pooled adult population (16.9% vs. 19.3%).

In the paediatric pooled analysis, there was a lower incidence of local target wound related infections with NexoBrid compared to SOC (1 [1.1%] vs. 7 [8.1] with SOC). In the CIDS–study it was 1 vs. 3 in SOC.

Other, not TW related infections were recorded with similar frequencies in the NexoBrid and SPC-groups and occurred mostly at time points well beyond the period of time where NexoBrid could have an influence (NexoBrid vs. SOC: 18 (20.2%) vs. 13 (15.1%)).

TEAEs in in the 12W-12M FU Period

For this period, the incidence of TEAEs was low and was similar for the NexoBrid and SOC treatment arms (10.1% vs. 11.4%). Most TEAEs were mild to moderate, with severe AEs reported in 1 patient treated with NexoBrid (Clavicle fracture). TEAE PTs reported for more than 1 patient included 'wound complication' reported for 2 patients treated with NexoBrid and 'nasopharyngitis' reported for 3 patients treated with the SOC.

No patient treated with NexoBrid, and 1 SOC-patient (injury and concussion) had SAEs during the 12W-12M FU Period. Two patients in each treatment arm had local TW-related AEs during this period. These included wound complication ('wound pain' and 'pseudo eschar amount greater than expected') reported for 2 NexoBrid-patients, and 'temperature intolerance' and 'joint contracture' for 1 patient each treated with SOC.

In the clinical study MW2012-01-01 (CIDS), one patient experienced an epileptic seizure in the NexoBrid treatment arm (1/69, 1.45%) 24-72 hours after NexoBrid treatment (as was observed in pre-clinical studies, see discussion on non-clinical aspects).

Upon CHMP's request, the MAH submitted a concise analysis of the case. In the pooled paediatric and adult studies, 5 adult NexoBrid-patients and 1 paediatric patient had AEs of PT 'Seizure or Epilepsy' vs. 1 adult patient in the placebo group. In 4 out of the 5 NexoBrid-patients the AEs occurred between 14 to 79 days after NexoBrid application, well beyond the elimination time for the drug. In the paediatric patient, the seizure occurred 56 hours after NexoBrid application. Three of the patients had two episodes of seizures long after NexoBrid treatment, which implies a relationship other than the drug exposure.

One seizure was a pseudo convulsion implying psychogenic etiology; 1 was a very short unclear neural episode (with possible relationships to Methamphetamine withdrawal); 2 of the NexoBrid-patients had a medical history of epilepsy.

Therefore, the MAH concluded that there is no reasonable relationship between NexoBrid treatment and the convulsions in both paediatric and adults, this was accepted by the CHMP.

Systemic Antibiotic Use

The mean number of days of systemic antibiotic use (including for prevention, pre-treatment conditions, and treatment of TEAEs) was similar for both groups (NexoBrid vs. SOC): 5.89 days vs. 4.94 days.

Blood transfusions

Overall, only 7 patients (NexoBrid) vs. 8 patients (SOC) received blood transfusions during hospitalisation. No NexoBrid-patient vs. 5 SOC-patients received blood transfusion during the eschar removal period. Three NexoBrid-patients vs. 1 SOC-patient received a blood transfusion within 1 week after eschar removal period, and 4 NexoBrid-patients vs. 2 SOC-patients received a blood transfusion later than 1 week after the eschar removal period.

Hospital readmissions

The rates of hospital readmission were low in both the NexoBrid and SOC treatment arms, reported for 8 patients in both treatment arms. Unplanned hospital readmissions were reported for 2 patients in both treatment arms.

Analyses performed across trials (pooled analyses)

The comparisons presented cover the CIDS study data vs. pooled adult plus paediatric data and vs. pooled paediatric data from (MW2008-09-03 and MW2004-11-02).

Upon CHMP's request, the MAH has provided a pooled analysis of paediatric safety data vs. pooled adult safety data from controlled studies. This comprised 89 paediatric NexoBrid-patients vs. 86 SOC-patients and 280 adult NexoBrid-patients vs. 179 adult SOC-patients (and 58 adult Gel vehicle patients). The mean exposure was much lower in the pooled paediatric population (5.6g [±5.93g]; median 3.7g, min–max: 1–27g) compared to the pooled adult population (15.7g [±10.4g]; median 12.0g, min–max: 2–60g). Mean total TBSA-area of TWs in the paediatric pool was also much lower (7.2 % [±4.83]; median 6.0%, min–max: 0.24–24%) compared to the adult pool (12.8 % [±7.22]; median 11.0%, min–max: 1–39%).

Pooled analysis showed that no deaths occurred in the paediatric study population (vs. 6 in the adult NexoBrid-population). The incidence of TEAEs in the paediatric NexoBrid-pool was lower compared to the adult NexoBrid-pool (paediatric patients 49.4% vs. adults 64.3%).

In addition, SAEs in the paediatric NexoBrid-pool was lower compared to the adult NexoBrid-pool (paediatric patients 3.4% of p. vs. adults 8.6% of p.). The same applies for severe TEAEs (kids 5.6% of p. vs. adults 11.4% of p.). The number of patients with related TEAEs was similar in the paediatric NexoBrid-population (11.2% of p.) vs. the adult NexoBrid-population (10.0% of p.). Treatment relation was not established for any TEAE in the SOC arm.

There was one serious case of sepsis related TEAE in the NexoBrid group.

Sepsis related SAEs were recorded for 3 (3.4% ['common']) of pooled paediatric NexoBrid-p. (vs. 1 p. (1.2%) with SOC) compared to 12 (4.3%) ['common'] in pooled adult NexoBrid-p. (vs. 4 p. (1.5%) with SOC-p. vs. 2 p. (2.9%) with Gel-p.). The MAH considered that for sepsis related SAEs the difference in numbers in the paediatric population is small (Any Sepsis TEAEs: NexoBrid: 3/89 (3.4%) vs. SOC: 1/86 (1.2%)). In adults, frequencies were higher as compared to children (Any Sepsis TEAEs with NexoBrid: 12/280 (4.3%) vs. SOC 3/179 (1.7%) vs. Placebo 2/68 (2.9%). The difference between treatment groups were again small. Based on the available data, the CHMP agreed that sepsis should not be included in SmPC section 4.8 as an adverse drug reaction.

TEAEs considered related to NexoBrid treatment/local TW related TEAEs in the pooled paediatric population were: pruritus (9 [10.1%] 'very common'), wound complication (5 [5.6%] 'common'), pyrexia (4 [4.5%] 'common') and pain (5 [5.6%] 'common'). In the adult pool these were: pain (17 [6.1%] 'common'), wound infection/cellulitis (17 [6.3%] 'common'), pruritus (17 [6.2%] 'common'), wound complications (9 [3.3%] 'common'), pyrexia (6 [2.1%] 'common'), tachycardia (3 [1.1%] 'common') and rash (2 [0.7%] 'uncommon').

Compared to SOC, frequencies (in numbers of patients affected) in the pooled paediatric analysis of any TEAEs was slightly higher in NexoBrid-patients (54.3% vs.49.4 % of p. with SOC), but severe TEAEs occurred at similar frequencies (5.6% vs. 4.7% in SOC) and number of patients with serious TEAEs were lower with NexoBrid (3 [3.4%] vs. 7 [8.1%] in SOC.

Frequency of local TW-related TEAEs was lower in the pooled paediatric NexoBrid group vs. paediatric SOC group (24.7% vs. 27.9% in SOC). Local pain incidence was equal to SOC (2.2% vs. 2.3%) as was

incidence of wound complications (5.6% vs. 5.8% in SOC). Only 1 wound infection was reported in NexoBrid paediatric patients (1.1 vs. 8.1% in SOC). Pruritus was reported slightly more often with NexoBrid vs SOC (10.1% vs. 7.0%).

In the pooled paediatric population, there were 3 patients with TEAE hypoalbuminemia reported in the NexoBrid arm vs. none with SOC.

In addition, the following related shifts were presented by the MAH (shift from normal to low) for the CIDS study: Albumin: 3/46 (6.5%) in the SOC group, Globulin: 3/52 (5.8%) in the NexoBrid Group, Protein: 1/52(1.9%) in the NexoBrid group and 3/46 (6.5%) in the SOC group. No potentially clinical significant shift was observed in the NexoBrid arm in the pooled paediatric population, vs. one patient (3.6%) in the SOC arm. When comparing the Lab shift for the pooled paediatric population, frequencies for low albumin post treatment were similar for NexoBrid vs. SOC (20.9% in NexoBrid arm vs. 17.9% with SOC). Therefore, it was agreed that hypoalbuminemia should not be included in section 4.8 as an ADR.

TEAE Analysis per age group and dose

The analyses of incidences of TEAEs per age group and dose (dose ≤Median vs. >Median dose) show, that - especially in the youngest age group (of children 0-3 years of age) - incidences of 'Any TEAE', 'Related TEAEs', 'Special TEAEs' (Pain, Fever, Target Wound Infection) and 'General TEAEs' were distinctively higher in the >Median dose subgroup of patients 0-3 years of age, as compared to the ≤Median dose subgroup. This was not the case in the older age groups. Therefore, this imbalance cannot only be attributed to more severe disease (in the subgroup > Median dose).

In combination with the additional PK data analyses (correlation of age with C_{max}/dose and age with AUC_{0-4} / dose, see assessment of OCs 2-3 above), which suggest higher C_{max}/dose and higher AUC_{0-4}/dose values for the youngest children (0-3 years), the imbalance in TEAE-rates by dose and age group - especially for 'Related TEAEs' and Local TEAEs - cannot be ignored, even though the database is very small and given the scares PK data. Due to the overall small number of paediatric patients, conclusions cannot be drawn reliably.

Overall, based on the limited PK and safety data, the CHMP agreed with the MAH's proposal i.e. children 0-3 years of age can be safely treated up to 10% TBSA and children over 4 years of age can be safely treated up to 15% TBSA. The section 4.2 Posology of the SmPC (subsection 'Paediatric population') has been updated accordingly.

Retrospective study 35-98-910

The retrospective study was conducted between the years 1985 to 2000. After termination, preventive measures for pyrexia and pain were installed. In this study safety data are available for 80 children/adolescents in the following age groups: 0-23 months (N=26), 2-3 years (N=21), 0-3 years (N=47), 4-11 years (N=25), 12-18 years (N=8). In the Retrospective Study, the frequency of 'any TEAEs' was lower in the paediatric patients than in the adult patients (77.5% vs. 83.8%).

For the age groups 'any TEAE' was observed: 0-12months: 10 (76.9%), 0-23 months: 18 (69.2%), 2-3 years: 14 (66.7%), 0-3 years: 32 (68.1%), 4-11 years: 23 (92.0%) and 12-18 years: 7 (87.5%). The incidence of 'any TEAE' was higher in the older age groups > 3 years compared to the age group 0 to 3 years, however the youngest 0-1 year olds had a higher incidence compared to the children of 1-2 and 2-3 years of age.

Frequency of 'Any TEAEs' in NexoBrid-treated paediatric patients was lower in the pooled paediatric population than in the Retrospective Study (49.4% vs. 77.5%). By age groups, frequency of 'Any TEAEs' in NexoBrid-treated paediatric patients was (pooled paediatric population vs. Retrospective Study): 0 to 3 years: 31.4% vs. 68.1%; 4 to 11 years: 64.9% vs. 92.0%; and 12 to 18 years: 52.9% vs. 87.5%.

The most frequent TEAEs (reported for ≥5% NexoBrid-treated paediatric patients in either pooled aediatric population or Retrospective Study) were: pyrexia (pooled paediatric population: 12.4% vs. Retrospective Study: 68.8%); pain (5.6% vs. 22.5%); pruritus (16.9% vs. 6.3%); vomiting (7.9% vs. 10.0%); anaemia (3.4% vs. 8.8%); sepsis (1.1% vs. 8.8%); nausea (6.7% vs. 0%); diarrhoea (3.4% vs. 6.3%) and wound complication (5.6% vs. 0%).

By age groups of paediatric patients in the Retrospective Study (0 to 3 years, 4 to 11 years, and 12 to 18 years), there were few events by PT reported in ≥5 patients: pyrexia (57.4%), anaemia (12.8%), and pain (12.8%) in the age group 0 to 3 years; pyrexia (84.0%), pain (36.0%), and vomiting (20.0%) in the age group 4 to 11 years; and pyrexia (87.5%) in the age group 12 to 18 years.

Overall, the safety data from the retrospective study did not show any new safety concern. Higher frequencies in the retrospective study can be explained by the preventive measures for pyrexia and pain, which were installed only after the termination of the retrospective study.

Taking into consideration the methodological limitations related to the design of retrospective studies, safety results from study 35-98-910 are only considered to be supportive.

Based on information from MW-2012-01-01 paediatric CIDS study, the following changes to the SmPC section 4.8 of the SmPC were agreed:

- 'Wound infection' ADR was revised to include 'cellulitis'.
- Local pruritus related to TW was more frequent with NexoBrid in all age groups 0-11 years of age. Therefore, the frequency of the ADR 'local pruritus' was changed from uncommon to common.
- 'local rash' was added as a common ADR because the incidence of hypersensitivity reactions, including allergic reactions and cases of rash, was approximately 5% (4/69) of NexoBrid treated patients; 2/69 were considered related.
- 'intradermal hematoma' was added as a new ADR with a frequency uncommon.

In addition, the information on description of selective ARs and on paediatric were updated based on the data submitted as part of this application.

Exclusion (safety) criteria in clinical studies included exclusion of patients with history of allergy and/or known sensitivity to pineapples, *papaya*, Bromelain, or papain. Therefore, the SmPC section 4.3 was updated accordingly (as papain occurs also in papaya).

Upon CHMP's request, the following information *'the medicinal product should be used with caution in areas or varicose veins, to prevent erosion of the veins' wall and the risk of bleeding.'* was shifted from SmPC section 4.2 to SmPC section 4.4. as it relates to special warning and precaution.

The existing warning on systemic absorption in SmPC section 4.4. was updated to reflect that NexoBrid should not be applied to more than 10% or 15% TBSA in patients aged 0-3 years old and patients 4-18 years, respectively.

The patient leaflet was updated accordingly.

The MAH committed to submit the final CSR for the CIDS study for assessment, once available (by Q2 2024).

2.5.2. Conclusions on clinical safety

Based on the limited PK and safety results, children 0-3 years of age can be safely treated up to 10% TBSA and children over 4 years of age can be safely treated up to 15% TBSA. The section 4.2 Posology of the SmPC (subsection 'Paediatric population') has been updated accordingly.

Additional ADRs 'cellulitis', 'local rash', 'local pruritus' and 'intradermal haematoma' were added in section 4.8 of the SmPC based on information from MW2012-01-01 Paediatric study (CIDS).

Considering the limited safety data available, the MAH committed to submit the final results of the CIDS study for assessment once available (i.e., by Q2 2024). In addition, the PSUR cycle for NexoBrid was reduced to a yearly cycle to allow a closer safety follow-up of the paediatric patients in the post-approval setting.

2.5.3. PSUR cycle

Based on the limited safety data on the new paediatric indication, the CHMP is of the opinion that the already existing entry in the EURD list for concentrate of proteolytic enzymes enriched in bromelain needs to be amended as follows: the PSUR cycle for the medicinal product should follow a yearly cycle. The next data lock point will be 17 December 2024.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.4 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 9.4 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Pain Pyrexia/hyperthermia Wound complications (including wound infections) Allergic reactions (including anaphylactic reaction)
Important potential risks	Severe irritation Increased tendency to bleeding
Missing information	Use in pregnancy

Pharmacovigilance plan

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection:

- **Specific Adverse Reaction Follow-up Questionnaire**

The structured follow-up form is designed to optimise the collection of data needed for better understanding and characterisation of NexoBrid safety profile.

This form aims to collect detailed information about NexoBrid adverse event/reaction, respective patient and patient's relevant medical history including information about concomitant medication or laboratory testing.

There are no additional pharmacovigilance activities.

Risk minimisation measures

Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Pain	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.8, and 5.3 – PL sections 3 and 4 Recommendation for pain management in section 4.2 of the SmPC and section 3 of PL. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Pyrexia/hyperthermia	**Routine Risk Minimisation Measures:** – SmPC sections 4.4 and 4.8 – PL sections 2 and 4 Section 4.4 of the SmPC recommends additional monitoring of burn patients for rise in body temperature and signs of local and systemic inflammatory and infectious processes. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Wound complications (including wound infections)	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.4, and 4.8 – PL sections 2, 3, and 4 Detailed description of wound management and instructions for preventive measures against development of	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	infection are included in sections 4.2 and 4.4 of the SmPC and section 3 of the PL. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	
Allergic reactions (including anaphylactic reaction)	**Routine Risk Minimisation Measures:** – SmPC section 4.3, 4.4, 4.8, and 6.6 – PL sections 2 and 4 Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Severe irritation	**Routine Risk Minimisation Measures:** – SmPC sections 4.2 and 5.3 Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None
Increased tendency to bleeding	**Routine Risk Minimisation Measures:** – SmPC sections 4.2, 4.4, and 4.5 – PL section 2 Section 4.4 of the SmPC recommendation for monitoring of signs of coagulation abnormalities in patients with coagulation disorders, low platelet counts, and increased risk of bleeding. Restricted medical prescription **Additional Risk Minimisation Measures:** – Healthcare Professional Information Pack – Training	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy	**Routine Risk Minimisation Measures:** – SmPC section 4.6 – PL section 2 Restricted medical prescription	**Routine Pharmacovigilance Activities beyond Signal Detection and Adverse Reactions Reporting:** – Follow-up questionnaire **Additional Pharmacovigilance Activities:** – None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8., 5.1, 5.2 and 5.3 of the SmPC have been updated. The Annex II and the Package Leaflet have been updated accordingly.

In addition, the MAH took the opportunity to combine the two SmPCs (i.e. NexoBrid 2 g and NexoBrid 5 g), to remove the black triangle from the SmPC and the PL; and to introduce minor editorial corrections in the product information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to NexoBrid. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is seeking an extension of indication for Nexobrid, a mixture of enzymes from the stem of Ananas comosus (pineapple plant) to paediatrics (0-17 years). The proposed indication is "NexoBrid is indicated in all age groups for removal of eschar in patients with deep partial- and full-thickness thermal burns."

Burned and traumatised tissue is known as an eschar, and can include part of, or the entire, thickness of the skin and may even include deeper tissues. Eschar removal, "debridement", is considered a critical initial stage of the comprehensive wound care process. Early (i.e., within 1 to 2 days/before the onset of inflammation) and rapid debridement of eschar is essential to initiate body's own wound healing process, to allow clinical visual evaluation of burn severity and depth, preserve viable tissue, and prevent further complications.

Children are more prone to accidents, including thermal injury, than healthy adults, and in many countries, children constitute the majority of the burn victim population. This is a debilitating condition accompanied by intense pain and often by longer-term illness that creates suffering not only for the child but for the wider family and community.

3.1.2. Available therapies and unmet medical need

Current treatment guideline (e.g. European practice guideline) recommends that debridement may be done by applying dressings, surgical debridement of eschar or by applying enzymatic debridement by NexoBrid. Surgical debridement is considered effective, but it is traumatic, requires general anesthesia, and is resource-intensive and time consuming. Concerns for surgical and postsurgical complications including blood and heat loss, often dictate that only a limited percentage of the affected areas (~15% TBSA) will be surgically debrided and autografted at one time in order to limit inflicting excessive stress on the patient. Surgical debridement is also considered non-selective, resulting in the loss of healthy viable tissue while non-viable eschar may still remain.

Although less invasive than surgical methods, currently available conservative non-surgical ER procedures (e.g. collagenase ointment (Santyl, Iruxol), antimicrobial agents such as SSD, or various hydrogels) are generally considered inefficient, can result in maceration and a lengthy sloughing period, and have the potential for development of granulation tissue and increased infection and scarring.

Therefore, NexoBrid is considered to be a more viable alternative to surgical excision.

Overall, it is agreed that there is an unmet need for non-surgical treatment of paediatric burns.

3.1.3. Main clinical studies

To demonstrate clinical efficacy in the paediatric population the MAH submitted one pivotal clinical study MW2012-01-01 (CIDS)).

Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2-arm study aimed at demonstrating the superiority of NexoBrid treatment over SOC in patients with deep partial thickness (DPT) and full thickness (FT) thermal burns of ≥1% TBSA.

The co-primary endpoints in the CIDS study were 'time to complete ER compared to SOC', 'the % wound area surgically excised for ER' and 'cosmesis and function using MVSS at 12 months from wound closure'.

This application was based on interim results from the CIDS study. The final results will be submitted for assessment post-approval, once available.

3.2. Favourable effects

The CIDS study demonstrated clinical superiority of NexoBrid over SOC in all 3 Co-Primary endpoints:

- 'Time to complete eschar removal' (NexoBrid vs. SOC: 0.99 days (95% CI: 0.88 to 1.04) vs. 5.99 days (95% CI: 2.71 to 9.84),
- 'Mean % wound area surgically excised for eschar removal' (NexoBrid vs. SOC: 1.5 [12.13]) vs. 48.1 [46.58] (p-value <0.0001),
- 'Scar score MVSS at 12 months' (NexoBrid vs. SOC: 3.83 [SD 2.876]) vs. 4.86 [SD 3.256], p-value<0.0001),

and additionally for the first secondary endpoint:

- 'Incidence of surgical excision' (NexoBrid vs. SOC: 8.33% (6/72 patients) vs. 64.38% (47/73 patients; p-value<0.0001)

  in a hierarchal test procedure.

It was demonstrated in the CIDS study that NexoBrid is a fast and effective topical eschar removal agent while significantly reducing the need for surgical excision of eschar compared with SOC.

A subgroup analysis by age group (0 to 23 months, 24 months to 3 years, 0 to 3 years, 4 to 11 years, and 12 to 18 years) consistently demonstrated superiority of NexoBrid over SOC in each age group. NexoBrid effectively removed the eschar earlier than the SOC in all paediatric age groups.

There was no deleterious effect on cosmesis and function at 12 months post wound closure in the paediatric patients. These results were consistently observed across all age groups in the CIDS study.

In addition, the endpoint 'Time to reach complete wound closure' (>95% without drainage or dressing requirements confirmed at 2 consecutive study visits, 2 weeks apart) was compared at a TW level (using the Kaplan Meier Method). For this safety endpoint results were as follows:

- 'Time to reach complete wound closure' (NexoBrid vs. SOC, median: 31 days vs. 31 days).

3.3. Uncertainties and limitations about favourable effects

Despite an overall statistically significant superior result in the NexoBrid treatment arm, the numerical difference between groups was small. Nevertheless, the CHMP ultimately considered the difference to be of clinical relevance.

3.4. Unfavourable effects

Clinical study experience in paediatric patients (newborn up to 18 years of age) includes use of NexoBrid in a dedicated SOC-controlled study (MW2012), in which 69 patients were exposed to NexoBrid (age range new born-18 years) and use in paediatric patients from studies MW2004 and MW2008, which included 17 and 3 paediatric patients, respectively (age range 4-17 years). The data demonstrates that the overall safety profile in children newborn and older and in adolescents, is similar to the profile in adults.

The most commonly reported adverse reactions of the use of NexoBrid in the paediatric population were pyrexia and pain (incidence of 16.9% and 7.9%, respectively). The data from the clinical development in adults 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.

- No patient died during study MW2012-01-01 (CIDS),
- SAEs (0-12weeks follow-up): NexoBrid (tachycardia, fever, sepsis, joint contracture) vs. SOC (withdrawal syndrome, viral infection, lyrangospasm, wound complication, injury, procedural pain): 2 patients vs. 5 patients,
- Severe AEs (0-12weeks follow-up): NexoBrid vs. SOC: 4 patients vs. 1 patient, (related to NexoBrid are fever and tachycardia),
- Local, TW related AE (0-12weeks follow-up): NexoBrid vs. SOC: 21.7% vs. 24.3% of patients,
- RMP identified risks (0-12weeks follow-up):

- Pain: NexoBrid vs. SOC: 4.3% vs. 4.3% of patients,
- Pyrexia: NexoBrid vs. SOC: 11.6% vs. 5.7% (imbalance noted, see LoQ in Annex 1 below),
- Wound Complications: NexoBrid vs. SOC: 7.2% vs. 7.1%,
- Wound Infections: NexoBrid vs. SOC: 1.4% vs. 4.3%,
- Allergic reactions: related TEAEs NexoBrid: 2/69 (2.9%),

- Additional analyses comparing pooled paediatric safety data with pooled adult data showed that incidences of TEAEs per age group differ between the subgroups ≤median dose vs. >median dose in the age group 0-3 years of age. This imbalance was seen in incidences for: 'Any TEAE', 'Related TEAEs', 'Special TEAEs' (Pain, Fever, Target Wound Infection) and 'General TEAEs'. Frequencies were distinctively higher in the >Median dose subgroup (for patients 0-3 years of age), as compared to the ≤Median dose subgroup.

Based on the data available, the following changes to the SmPC section 4.8 of the SmPC were implemented:

- The ADR 'Wound infection' was updated to include 'cellulitis'.
- 'Local pruritus' related to TW was more frequent with NexoBrid in all age groups 0-11 years of age. Therefore, the frequency of this ADR was changed from uncommon to common.
- 'local rash' was added as a common ADR as the incidence of hypersensitivity reactions, including allergic reactions and cases of rash, was approximately 5% (4/69) of NexoBrid treated patients; 2/69 were considered related.
- 'intradermal hematoma' was added as a new ADR with a frequency uncommon.

Exclusion (safety) criteria in clinical studies included exclusion of patients with history of allergy and/or known sensitivity to pineapples, *papaya*, Bromelain, or papain. Therefore, the SmPC section 4.3 was updated accordingly (as papain occurs also in papaya).

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties arise mainly from the small numbers of exposed paediatric patients in the submitted CIDS study (SAS NexoBrid vs. SOC: 69 vs. 70 patients) and in the pooled paediatric studies (pooled paediatric population: NexoBrid N=89 vs. SOC N=86). Due to the low numbers of adverse reactions reported in each age group, it is not possible to draw valid conclusions regarding potential age-related differences in the safety profile.

As the application was based on the 12 months interim data of the CIDS study, the CHMP has recommended the MAH to submit the final results of the CIDS study to provide long-term follow up data on NexoBrid.

Overall, based on the limited PK and safety results, children 0-3 years of age can be safely treated up to 10% TBSA and children over 4 years of age can be safely treated up to 15% TBSA. Taking into account the limited safety data available thus far in the new paediatric indication, the PSUR cycle for the medicinal product was shortened to follow a yearly cycle, allowing to closely monitor the safety profile NexoBrid in paediatric patients' post-approval.

3.6. Effects Table

Table 38: Effects Table for NexoBrid

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
1.	Median time to complete eschar removal	days	0.99 (95% CI: 0.88 to 1.04)	5.99 (95% CI: 2.71 to 9.84)	No uncertainty/co-Co-primary endpoint	CIDS study
2.	Wound area surgically excised	%	1.5 [±12.13]	48.1 [±46.58]	No uncertainty/co-primary endpoint	CIDS study
3.	MVSS at 12 months		3.83 [SD 2.876])	4.86 [SD 3.256]	No uncertainty/co-primary endpoint Interim result	CIDS study
4.	Incidence of surgical excision	%	8.33 (6/72 p.)	64.38 (47/73 of p.)	No uncertainty/main secondary endpoint Hierarchichal testing	CIDS study
Unfavourable Effects						
1.	SAEs		2 p.	5 p.		CIDS study
2.	Severe TEAEs		4 p.	1 p.		CIDS study
3.	TW related TEAEs	% of p.	21.7	24.3		CIDS study
4.	Pain	% of p.	4.3	4.3		CIDS study
5.	Pyrexia	% of p.	11.6	5.7		CIDS study
6.	Wound Complications	% of p.	7.2	7.1		CIDS study
7.	Wound Infections	% of p.	1.4	4.3		CIDS study
8.	Allergic reactions	% of p.	2.9			CIDS study

Abbreviations: MVSS: Modified Vancouver Scar Scale, SAEs: serious adverse events, TEAEs: treatment emergent adverse events, TW: target wound .

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy data from the submitted pivotal paediatric study clearly demonstrate efficacy in the paediatric population overall and for the age groups separately.

There were no new safety concerns in the paediatric population and comparison of TEAE incidences in the pooled populations overall show lower incidences in the paediatric patients for 'Any TEAE', 'Serious TEAEs' and 'Severe TEAEs' when compared to adults.

Although the number of exposed paediatric patients per age–group is very low, it can be concluded that the safety profile of NexoBrid in paediatric patients has been established. Long-term safety data (final results from CIDS study) will be submitted post approval, once available.

3.7.2. Balance of benefits and risks

The efficacy of NexoBrid in the paediatric population overall and for the age groups separately has been demonstrated. There is evidence that NexoBrid significantly reduces the amount of surgical excision of eschar required by burn wounds in paediatric patients in a significantly shorter period of time compared to SOC treatment. This is considered to be clinically relevant. The safety profile, albeit limited, is in line with the favourable profile observed in adults. Long-term safety data from the CIDS study will be submitted for assessment post-approval, once available.

Given the limited PK and safety data available in the younger age group (0-3 years), the CHMP agreed with the MAH's proposal to limit the use of NexoBrid to maximum 10% TBSA for paediatric patients aged 0-3 years old.

NexoBrid should only be applied by trained healthcare professionals in specialist burn centres. This is already 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.

3.8. Conclusions

The overall B/R of NexoBrid is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of current indication for removal of eschar in adults with deep partial- and full-thickness thermal burns to the paediatric population for NexoBrid based on interim results from study MW2012-01-01 (CIDS study), listed as Study MW2012-01-01 is a 3-stage, multi-centre, multi-national, randomised, controlled, open label, 2 arm study aiming to demonstrate the superiority of NexoBrid treatment over SOC treatment in paediatric patients (aged 0 to 18 years) with deep partial thickness (DPT) and full thickness (FT) thermal burns of 1% to 30% of total body surface area (TBSA).
As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Annex II and Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to remove the black triangle from the SmPC and the package leaflet, combine the SmPCs and introduce minor editorial corrections to the product information. Version 9.4 of the RMP is acceptable.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0189/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Product Name-H-C-Product Number-II-Var.0058'

Attachments

1. Product information as adopted by the CHMP on 9 November 2023.