Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Nexobrid

Active ingredient: anacaulase-bcdb

Sponsor: Nexo Pharmaceuticals Pty Ltd

November 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
CI	Confidence interval
CMI	Consumer Medicines Information
DPT	Deep partial thickness
FAS	Full analysis set
FT	Full thickness
OR	Odds ratio
PI	Product Information
PK	pharmacokinetic
PPS	per protocol set
PSUR	Periodic safety update report
RMP	Risk management plan
SAS	Safety analysis set
SAE	Serious adverse events
SOC	Standard of care
TBSA	total body surface area
TGA	Therapeutic Goods Administration

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Nexobrid
Active ingredient:	Anacaulase-bcdb
Decision:	Approved
Date of decision:	8 September 2025
Date of entry onto ARTG:	15 September 2025
ARTG number:	450205
▼*Black Triangle Scheme*	Yes
Sponsor's name and address:	Nexo Pharmaceuticals Pty Ltd
Dose form:	Powder
Strength:	One vial of 5 g lyophilized powder (containing 4.85 grams of anacaulase-bcdb) and one bottle of 50 g gel vehicle per composite pack.
Containers:	5 g powder in a vial (glass type II) sealed with a rubber (bromobutyl), stopper and covered with a cap (aluminium), and 50 g gel in a bottle (borosilicate, glass type I), sealed with a rubber stopper and covered with a screw cap (tamper-proof polypropylene).
Pack size:	1 vial of powder and 1 bottle of gel per pack
Approved therapeutic use for the current submission:	Nexobrid is indicated for eschar removal in adults and paediatric patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.
Route of administration:	Topical
Dosage:	5 g lyophilized powder (containing 4.85 grams of anacaulase-bcdb) mixed in 50 g gel vehicle, per 2.5% adult BSA, or per 450 cm^2 of treated burn area. For further information regarding dosage refer to the Product Information.
Pregnancy category:	Category B1 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Nexo Pharmaceuticals Pty Ltd (the sponsor) to register Nexobrid (anacaulase-bcdb) for the proposed indication:

> *For use as a temporary debriding agent for the removal of eschar in partial deep dermal and full thickness burns in patients requiring hospitalization.*

Disease or condition

Burns represent a major global public health challenge characterised by significant morbidity and mortality, a disproportionate burden in low-and middle-income countries, and a need for specialised and resource-intensive treatment. An estimated 7 to 12 million people per year sustain a burn injury that requires medical care globally.[1] The World Health Organization estimates that 180,000 deaths each year are attributable to burns,[2] with over 90% occurring in low- and middle-income countries.[3] Long-lasting morbidity in the form of scarring, contractures and loss of function compounds the associated disease burden.[4] Established risk factors include age, with children and young people at highest risk of burn injury as well as higher incidence observed in older adults, male sex, and certain medical comorbidities including epilepsy and peripheral neuropathies.[5] Systems and infrastructure for burns prevention and coordinated multi-disciplinary emergency care of burn injuries are generally more advanced in high-income countries.

In Australia in 2021-22, there were 5,500 hospitalisations within the broad category of thermal injury, equating to 22 per 100,000 population, with 64% of hospitalisations for male patients, and children under 5 years having the highest rate of hospitalisation.[6] Between 2009 and 2015 there were 310 burn-related fatalities recorded in Australia and New Zealand, the majority due to fire and occurring at home.[7] Inequity in the burden due to burns is evident within Australia, with a recent publication showing that Aboriginal and Torres Strait Islander children <16 years old hospitalised due to burns had longer length of stay, higher rates of burn due to flame, higher

[1] Smolle C, Cambiaso-Daniel J, Forbes AA et al. Recent trends in burn epidemiology worldwide: A systematic review. Burns. 2017;43(2):249

[2] World Health Organization. Burns. Updated: 13 October 2023. Accessed: 17 December 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/burns.

[3] Peck M, Pressman MA. The correlation between burn mortality rates from fire and flame and economic status of countries. Burns. 2013;39(6):1054.

[4] Jeschke MG, van Baar ME, Choudry MA et al. Burn injury. Nature Reviews Disease Primers. 2020;6.

[5] Stewart BT, Jeschke MG, Collins KA. Epidemiology, risk factors, and prevention of burn injuries. UpToDate. Updated 26 Nov 2024

[6] Australian Institute of Health and Welfare. Injury in Australia: Thermal causes. Australian Government. Updated 6 July 2023.

[7] McInnes JA, Cleland HJ, Cameron PA et al. Epidemiology of burn-related fatalities in Australia and New Zealand, 2009-2015. Burns. 2019;45(7):1553-1561.

rates of wound infection, and when compared to non-Indigenous children were much more likely to live rurally and to be of lower socioeconomic status.[8]

Distinct mechanisms of burn include thermal burns, which are associated with flames, hot liquids, hot solid objects and steam, as well as electrical burns, friction burns, chemical burns and radiation burns.[9] Burns are typically classified according to the depth of tissue injury, designated as superficial, superficial partial-thickness, DPT and FT,[10] with key characteristics of each category summarised in Table 1. Burn wounds are not typically uniform in depth, and may comprise a mix of different burn categories, whilst assessment of a wound in the acute phase may be complicated by the dynamic nature of burn wounds which can progress and convert to deeper wounds over time.[11]

Table 1. Classification of burn wounds, and key characteristics[12]

Depth	Appearance	Sensation	Healing time
Superficial (epidermal)	Dry, red Blanches with pressure	Painful	3 to 6 days
Superficial partial-thickness	Blisters Red, moist, weeping Blanches with pressure	Painful to temperature, air and touch	7 to 21 days
Deep partial-thickness	Blisters (easily unroofed) Wet, or waxy dry Variable colour (patchy to cheesy white to red) Blanching with pressure may be sluggish	Painful to pressure only	>21 days, usually requires surgical treatment
Full thickness	Waxy white to leathery grey to charred and black Dry and inelastic No blanching with pressure	Deep pressure only	Rare, unless surgically treated

Burn wound eschar, which is specifically included in the proposed indication for Nexobrid, refers to ischaemic, necrotic tissue and dried secretions which collects in the wound bed. Complications resulting from the presence of eschar in the wound can include compression of

[8] Ryder C, Mackean T, Hunter K et al. Burn injuries in hospitalized Australian Children- An Epidemiological profile. J Burn Care Res. 2021;42(3):381-389.

[9] Rice PL, Jeschke MG, Collins KA. Assessment and classification of burn injury. UpToDate. Updated 10 December 2024.

[10] Rice, 2024.

[11] Rice, 2024.

[12] Adapted from Rice, 2024.

surrounding structures, infection, and delayed wound healing. Contemporary clinical practice favours early removal of eschar from a burn wound to prevent complications and promote wound healing; however, the natural history of eschar is of separation from the wound bed over time.

Current treatment options

Management of DPT/FT burns is typically undertaken by, or in close consultation with, a specialist burns surgeon working in concert with a broader multi-disciplinary burns team.[13] Particularly for larger burns, involving >20% of total body surface area (TBSA) in adults or >10% TBSA in children or burns complicated by significant associated trauma, patients generally require intensive medical and supportive management, alongside specific care of the burn wound/s.[14,15] Characterisation of burn depth and estimation of TBSA involvement is of primary importance to treatment decision-making, both of which may be hampered by the subjective nature of clinical assessment and the dynamic nature of burn wounds in the acute phase.[16] Debridement of wound eschar and coverage of the burn wound, commonly with skin graft, are key objectives of early burn wound care, with longer term goals being preservation and restoration of anatomy, cosmetic appearance, and function.[17]

The rationale for removal of eschar from a burn wound includes providing an appropriate wound bed for subsequent definitive wound closure, prevention of infection, and to optimise supportive measures such as wound dressings.[18] Early removal of eschar, within 24 to 72 hours of the injury, is widely accepted as best practice and is associated with reduced mortality, though timing of eschar removal ultimately depends on multiple factors external to the wound itself, including overall condition of the patient, availability of expertise and resources.[19,20] Surgical excision is the most common method of eschar removal, with a number of different instruments and techniques available; tangential excision using a sharp, hand-held instrument is typical.[21] Hydrosurgery, using high-pressure water jets to debride necrotic tissue, may also be used depending on local expertise and practitioner preference. Options for non-surgical debridement include topical enzymatic debriding agents and proteolytics. Treatment decisions post eschar removal, including choice of wound closure and timing of wound closure, are individualised and depend on a range of variables.

The Australian Register of Therapeutic Goods (ARTG) does not currently include any products indicated for eschar removal from a burn wound, or debridement of DPT or FT burns.

[13] NSW Statewide Burn Injury Service. Clinical Guidelines: Burn Patient Management. 4th edition. Published 29 April 2019, amended February 2024. Available from: https://aci.health.nsw.gov.au/__data/assets/pdf_file/0009/250020/ACI-Burn-patient-management-guidelines.pdf

[14] Gauglitz GG, Williams FN, Jeschke MG, Collins KA. Overview of the management of the severely burned patient. UpToDate. Updated 15 November 2023. Available from https://www.uptodate.com/contents/overview-of-the-management-of-the-severely-burned-patient

[15] Royal Children's Hospital. Clinical Practice Guidelines: Burns- Acute management. Updated June 2020. Accessed 20 December 2024. Available from: https://www.rch.org.au/clinicalguide/guideline_index/burns/.

[16] Phelan HA, Bernal E, Jeschke MG, Collins KA. Treatment of deep burn injury. UpToDate. Updated 12 March 2024. Available from https://www.uptodate.com/contents/treatment-of-deep-burn-injury

[17] Phelan, 2023.

[18] Phelan, 2023.

[19] Phelan, 2023.

[20] De La Tejara G, Corona K, Efejuku T et al. Early wound excision within three days decreases risks of wound infection and death in burned patients. Burns. 2023;49(8):1816-1822.

[21] Leon-Villapalos J, Dziewulski P, Jeschke MG, Colwell AS, Collins KA. Overview of surgical procedures used in the management of burn injuries. UpToDate. Updated 29 March 2024.

Clinical rationale

The mechanism of action of Nexobrid is mediated by the proteolytic activity of its enzymes and is associated with selective debridement of eschar and denatured collagen while sparing healthy tissue.

The sponsor's stated rationale for product development is based on the need for timely debridement of eschar for burns patients to properly evaluate the burn, initiate wound healing and prevent complications; Nexobrid provides an option for non-surgical debridement, with utility in mass casualty events, where capacity for surgical debridement is limited, and facilitates rapid assessment of burn severity and planning for further intervention. In addition, regarding burns in paediatric patients, the sponsor notes clinical and physiological differences compared to adult patients, altered psychological response to burns, and greater technical difficulty of anaesthesia and burns surgery in paediatric patients, as rationale to support development of non-surgical options for burn debridement. Inherent in any method of wound debridement is the desire to remove dead eschar tissue whilst preserving non-injured tissue.

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes. Anacaulase-bcdb was designated an orphan drug by the TGA on 28 August 2023. On 5 February 2024 this designation was extended for 6 months, to 27 August 2024. The approved orphan indication was:

> *'for use as a temporary debriding agent for the removal of eschar in partial deep thickness dermal and full thickness burns in patients requiring hospitalization'*

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies.

Nexobrid was approved in the European Union via the centralized procedure by the European Medicines Agency on 18 December 2012, with the current approved indication

> *'Nexobrid is indicated in all age groups, for removal of eschar in patients with deep partial- and full-thickness thermal burns.'*

Nexobrid was first approved in the United States by the Food and Drug Administration for use in adults on 28 December 2022, with extension of indication to include paediatric patients approved on 15 August 2024, with the current approved indication

> *'Nexobrid is indicated for eschar removal in adults and pediatric patients with DPT and/or full thickness (FT) thermal burns.'*

Nexobrid was approved in Switzerland by SwissMedic on 25 April 2022, with an approved indication in adults only.

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 1: Timeline for Nexobrid, Submission PM-2024-02040-1-1

Description	Date
Designation (Orphan)	28 August 2023
Submission dossier accepted and first round evaluation commenced	5 July 2024
Evaluation completed	20 March 2025
Advisory committee meeting	8 August 2025
Registration decision (Outcome)	8 September 2025
Registration in the ARTG completed	15 September 2025
Number of working days from submission dossier acceptance to registration decision*	208

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

Quality evaluation summary

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the product information (PI), labels, consumer medicines information and the ARTG. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. From a quality perspective, compliance with Therapeutic Goods Legislation, regulations, and relevant Therapeutic Goods Orders as well as consistency with relevant guidelines and the Australian Regulatory Guidelines for Prescription Medicines has been demonstrated.

There are no objections to the approval of Nexobrid anacaulase-bcdb.

Nonclinical evaluation summary

The submitted nonclinical dossier was within the scope of the relevant ICH guideline for the nonclinical assessment of biological medicines (ICH S6[R1]).[22] The overall quality of the nonclinical dossier was adequate, with the pivotal safety-related studies conducted using the intravenous route (to monitor potential systemic toxicities) and in accordance with Good Laboratory Practice guidelines.

Anacaulase-bcdb (Nexobrid) is a purified extract from the stems of pineapples that contains mainly proteolytic enzymes enriched in bromelain. In vitro Nexobrid showed collagenase and gelatinase-type of protease activity against collagens and gelatin (denatured collagen)

[22] ICH S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals - Scientific guideline. Available at https://www.ema.europa.eu/en/ich-s6-r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals-scientific-guideline

substrates. The pig burn model was used in vivo to provide proof of mechanism evidence that Nexobrid can digest eschar tissue formed from thermal burns. In vivo studies with earlier generation of anacaulase drug product suggested possible attenuation of its eschar digesting properties by antibiotics silver sulfadizine and povidone-iodine.

Off-target effects of anacaulase/Nexobrid were not investigated in any stand-alone studies; however, published studies have reported on anti-inflammatory, anti-thrombotic and fibrinolytic effects of bromelain, which is a major constituent of anacaulase.

Specialised safety pharmacology studies were not conducted with Nexobrid, which is acceptable as it is intended for short-term, single occasion use for topical debridement of deep thermal burns. Sufficient history of clinical use from Europe (registered since 2012) also is available to support organ system safety.

There is evidence of systemic absorption of topically administered anacaulase-bcdb (Nexobrid) in patients. Nonclinical pharmacokinetic parameters were ascertained in toxicity studies in pigs, rats and rabbits that used intravenous dosing for the purposes of ascertaining relative exposures.

In vitro, anacaulase exhibited weak inhibitory activity against CYPs 2C8 and 2C19. Anacaulase-bcdb had a low order of acute dermal toxicity in pigs.

Repeat dose toxicity studies on anacaulase (Nexobrid) were conducted by the IV route in domestic pigs and minipigs (daily dosing up to 2 weeks). Duration of studies was appropriate for the intended end-use of Nexobrid, and study designs used were acceptable. The main treatment-related finding was generalised acute haemorrhage that was observed in various organs of both species and across all tested doses. As well, aberrant effects on coagulation parameters were also observed (prolongation of APTT and PT, lower levels of fibrinogen in juvenile pigs). These effects are likely pharmacologically mediated, due to the well-known anti- platelet and fibrinolytic effects of bromelain in Nexobrid and are clinically relevant.

Genotoxicity was evaluated in a standard battery of genotoxicity tests on clinical product Debrase/Nexobrid. Under the specified testing conditions, Debrase was not mutagenic or clastogenic in vitro or in vivo. Noting that the design of these studies was not suitable for a protein-containing drug product, it is not expected to be genotoxic. Carcinogenicity studies were not conducted or required, given the single occasion use of a protein-containing, enzymatic mixture, intended for burn wound debridement.

Embryofetal development studies were performed in rats and rabbits that received daily intravenous doses of Nexobrid during organogenesis. The test article proved to cause severe maternal toxicities in both species due to injection site reactions. However, no corresponding treatment related effects on litter parameters or embryofetal development were observed.

Because of the low maternal tolerability to Nexobrid, these studies have limited predictive value in identifying risks of use during pregnancy.

Topically applied Nexobrid, tested at strengths of up to 30% (cf. to 8.8% of clinical product formulation), was better tolerated by intact skin than skin that had abrasions, indicating risk of dermal irritation when applied to broken skin. Nexobrid was not found to cause skin sensitisation in a guinea pig maximisation test.

Overall, the nonclinical data set were adequate to support the use of Nexobrid for the proposed indication and there are no nonclinical objections to registration.

Clinical evaluation summary

Summary of clinical studies

The submitted clinical dossier was comprehensive, with clinical study reports (CSRs) for nine completed clinical studies including three pivotal phase 3 efficacy and safety studies, study MW2010-03-02 (DETECT) conducted in adult subjects >18 years old, study MW2004-11-02 conducted in adult and paediatric subjects ages 4-55 years, and study MW2012-01-01 (CIDS) conducted in paediatric subjects from 0 to 18 years. Each study includes statements in relation to principles of good clinical practice.

Pharmacology

Pharmacokinetics

Evaluable pharmacokinetic (PK) data was provided in phase 2 of the PK and safety study MW 2008-09-03, as well as the pivotal studies MW 2010-03-02 and MW 2012-01-01.

Study MW2008-09-03

This phase 2, open-label, single-arm, multicentre study to evaluate safety, efficacy and PK of Nexobrid enrolled 36 subjects, the majority (75%) male, with 44.4% classified as Caucasian, 30.6% Middle Eastern and 22.2% Asian, and mean age 32.0 years (range 9.0 – 60.9 years). In terms of burn wound characteristics, 91.8% of wounds had a partial thickness component, 18.6% a full thickness component, and 7.2% of wounds were classified as superficial. The mean treated wound (referred to as 'target wounds') %TBSA was 12.4% (range 2.0-34.0%). PK analysis sought to characterise transcutaneous absorption of Nexobrid, with PK endpoints exploratory in nature. Following wound cleansing, Nexobrid was applied to target wounds, with the wound then covered with occlusive dressing for 4 hours. In wounds with partial debridement after the first Nexobrid application an additional Nexobrid application per target wound was permitted according to the investigator's judgement.

Of the 36 subjects enrolled, 22 underwent a single application, and 14 subjects underwent double application of Nexobrid, with the interval between applications ranging from 4.5 to 26.3 hours. Study treatment with Nexobrid was in line with dosage sought in the application. If one application was planned (subjects with burns intended for Nexobrid treatment up to 15% TBSA), blood samples were collected at pre-application, and after Nexobrid application at the following time points: 2 hours ± 10 minutes, 4 hours ± 10 minutes, 12 hours ± 30 minutes, 24 hours ± 30 minutes and 48 hours ± 30 minutes. If two applications were planned (subjects with burns intended for Nexobrid treatment up to 30% TBSA), for the first application, samples were taken pre-treatment, and at 0.5 hours and 4 hours, whilst for the second application samples were taken at 0.5 hours, 4 hours, 24 hours, and 48 hours. PK parameters analysed were AUC_{0-4}, AUC_{last}, C_{max}, T_{max} and if possible, the elimination rate constant and elimination half-life. Dose normalised C_{max}, AUC_{0-4} and AUC_{last} were calculated. For subjects who received two applications the serum concentration versus time profile were treated as separate events for each application, and AUC calculations for the second application assumed a value of 0 at time 0.

In terms of PK results, all 36 subjects had quantifiable serum Nexobrid concentrations 48 hours post-application. Overall, median T_{max} was 2.0 to 4.0 hours depending on study site and application number, terminal half-life following a single application ranged 3.2 to 25 hours, with mean 12 hours, and following two applications ranged 9.0 to 15 hours, with mean of 12 hours. The clinical study report states that, given C_{max} and AUC_{0-4} and dose-normalised C_{max} and AUC_{0-4} after the first and second applications were comparable, with less than two-fold differences, that

accumulation following second application was not a major concern, however, the clinical evaluator noted that, given that AUC calculations following the second application were based on values of 0 at time 0, that assessment of accumulation was not possible.

The clinical evaluator also noted different exposure results between the two study sites used for PK analysis. Following first application of Nexobrid, at the first study site, median T_{max} (N=13) was 4.00 hours (range: 0.500 to 4.08 hours), median C_{max} (N=13) was 600 ng/mL (range: 222 to 2440 ng/mL), median AUC_{0-4} (N=8) was 2070 hr*ng/mL (range: 630 to 2830 hr*ng/mL) and median AUC_{last} (N=13) was 2090 hr*ng/mL (range: 455 to 10800 hr*ng/mL), compared to the second study site, with median T_{max} (N=22) was 2.00 hours (range:0.900 to 4.17 hours), median C_{max} (N=22) was 4690 ng/mL (range: 888 to 15700 ng/mL), median AUC_{0-4} (N=22) was 12200 hr*ng/mL (range: 2150 to 44100 hr*ng/mL) and median AUC_{last} (N=22) was 22800 hr*ng/mL (range: 4570 to 167000 hr*ng/mL). In response to a clinical question the sponsor commented further on this issue, primarily discussing bioanalytical methods used between the study sites; the clinical evaluator considered the issue not sufficiently resolved, commenting that clinical implications of the difference in PK results between study sites was unclear, whilst also noting that PK endpoints were exploratory in study MW 2008-09-03, and that these results should be interpreted in the context of the totality of evidence in the dossier.

Study MW2010-03-02 (DETECT)

PK aspects of this pivotal efficacy and safety study will be summarised here, with more detailed discussion of this study provided in relevant sections below. This phase 3, randomised, controlled, assessor blinded, multicentre study obtained blood samples from a subset of subjects randomised to the Nexobrid treatment arm for PK assessment. Blood samples for PK assessment were taken at times points up to 72 hours, with PK sampling undertaken for 36 subjects in total; of these subjects bioanalysis of PK samples was performed beyond stability limits for 15 subjects, with the main PK analysis therefore undertaken with data for 21 subjects. Only one subject received two applications of Nexobrid. Key PK parameters are summarised in Table 3.

Table 3. Summary of serum pharmacokinetic parameters following topical administration of Nexobrid, study MW2010-03-02 (DETECT)

Treatment	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)
1st	4.0 (0.50 - 12)	200 ± 184	16.4 ± 11.9	516 ± 546	39.8 ± 29.7	2030 ± 1790	178 ± 144	2500 ± 2330	215 ± 202
2nd	4.0	183	15.0	618	50.6	3020	248	6010	492

Values are reported as Mean ± SD, which the exception of Tmax, which is reported as Median (Min-Max).

For the 2nd treatment, there was only 1 subject.

For subjects with available results at 72 hours post application of Nexobrid (n=14), the majority had a serum concentration of 0.00 ng/mL. For subjects who received a single application of Nexobrid there was a positive correlation observed between C_{max} and both %TBSA (Pearson r =0.4810, p=0.0273), and dose (Pearson r =0.5820, p=0.0056), as well as between AUC_{0-4} and both %TBSA (Pearson r =0.5394, p=0.0116), and dose (Pearson r =0.6391, p=0.0018). Based on assessment of dose-normalised C_{max} and AUC_{0-4} systemic exposure was comparable between subjects with DPT wound depth for all wounds (n=8) and subjects with wounds of mixed wound depth (n=13).

Study MW2012-01-01 (CIDS)

PK aspects of this pivotal efficacy and safety study will be summarised here, with more detailed discussion of this study provided in relevant sections below. This was a phase 3, randomised, controlled, open-label, multicentre study conducted in children aged 0 to 18 years. For subjects

weighing over 7 kg and below 35 kg at screening, pharmacokinetic analysis was undertaken using a sparse sampling approach to create a composite profile. Subjects enrolled in the PK portion of the study were randomised in a 1:1 ratio to subgroup A, with blood samples taken at 2 hours and 12 hours post-treatment, or subgroup B, with samples taken at 4 and 24 hours post-treatment. For subjects with >15% TBSA planned to be treated with two applications of Nexobrid, blood samples were collected at 4 hours and 12 hours after the first application and at 4 hours and 24 hours after the second application. The resulting single composite profile for each of the younger age groups (0-2 years, 2-4 years, and 4-11 years) was used for PK parameter estimation, including T_{max}, C_{max}, C_{max}/dose, AUC, and AUC/dose. If data permitted, the half-life (t1/2) was also to be estimated.

For subjects weighing over 35 kg at screening, blood samples were collected before treatment with Nexobrid (time 0) and at 2, 4, 12, 24, 48 and 72 hours after the start of treatment. For subjects with >15% TBSA planned to be treated with two applications of Nexobrid, blood samples were collected prior to treatment (time 0), 2 hours and 4 hours after the first application, prior to the second application, and then at 2, 4, 12, 24, and 72 hours after the start of the second application.

Blood samples were collected from 19 subjects treated with Nexobrid in total, all of whom had received one application. Four subjects weighing over 7 kg and below 35 kg at screening and in the 4-11 years age group, had full PK sampling profiles; instead of a composite profile, the PK parameters were reported for each subject. For 2 subjects aged < 2 years for whom the sparse sampling approach was followed, their values were merged to create a composite profile. Two subjects, one in the 12-18 year age group and one in the 4-11 year age group, were removed from PK analysis due to insufficient data, whilst another subject in the 4-11 year age group was removed from descriptive statistics due to an inconsistent concentration time profile.

Ten subjects were included in the main PK analysis; 2 subjects in the <2 year age group (resulting in a single composite PK profile), 5 subjects in the 4-11 year age group, and 2 subjects in the 12-18 year age group. PK samples were analysed outside stability periods for 6 subjects, and were excluded from the main analysis, in addition to the three subjects excluded as noted above. PK parameters for each age group are summarised in Table 4, showing similar mean Cmax between age groups, shorter median T_{max} in the <2 years age group, and lower dose-adjusted AUC values in the 12-18 year age group, suggesting higher systemic Nexobrid exposure following topical administration in the younger age categories. However, low absolute numbers of subjects in each group warrant caution in interpretation. No subject had quantifiable serum Nexobrid concentration at 72 hours post application.

Table 4. Summary of serum pharmacokinetic parameters following topical administration of Nexobrid, study MW2012-01-01 (CIDS).

Age Group (years)	Dose (g)	TW area (cm^2)	% TBSA	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[a]	3.0	271	5.25	2.00	200	66.7	476	159	1020	340	876	292
4-11[b]	6.89±3.01	620±271	6.30±1.92	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[c]	12.2±12.6	1100±1140	6.67±3.79	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

AUC = area under the plasma concentration versus time curve, AUC_{0-4} = AUC from time = 0 to 4 hours post dose administration, AUC_{0-24} = AUC from time = 0 to 24 hours post dose administration, AUC_{last} = AUC from time 0 to the time of the last quantifiable concentration. C_{max} = maximum observed concentration occurring at T_{max}, Max = maximum value observed,

Min = minimum value observed, PK = pharmacokinetic, SD = standard deviation, TBSA = total body surface area, TW= target wound, Tmax = time at which Cmax occurred.

Values are reported as mean ± SD, with the exception of Tmax, which is reported as median (Min – Max).

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.

Efficacy

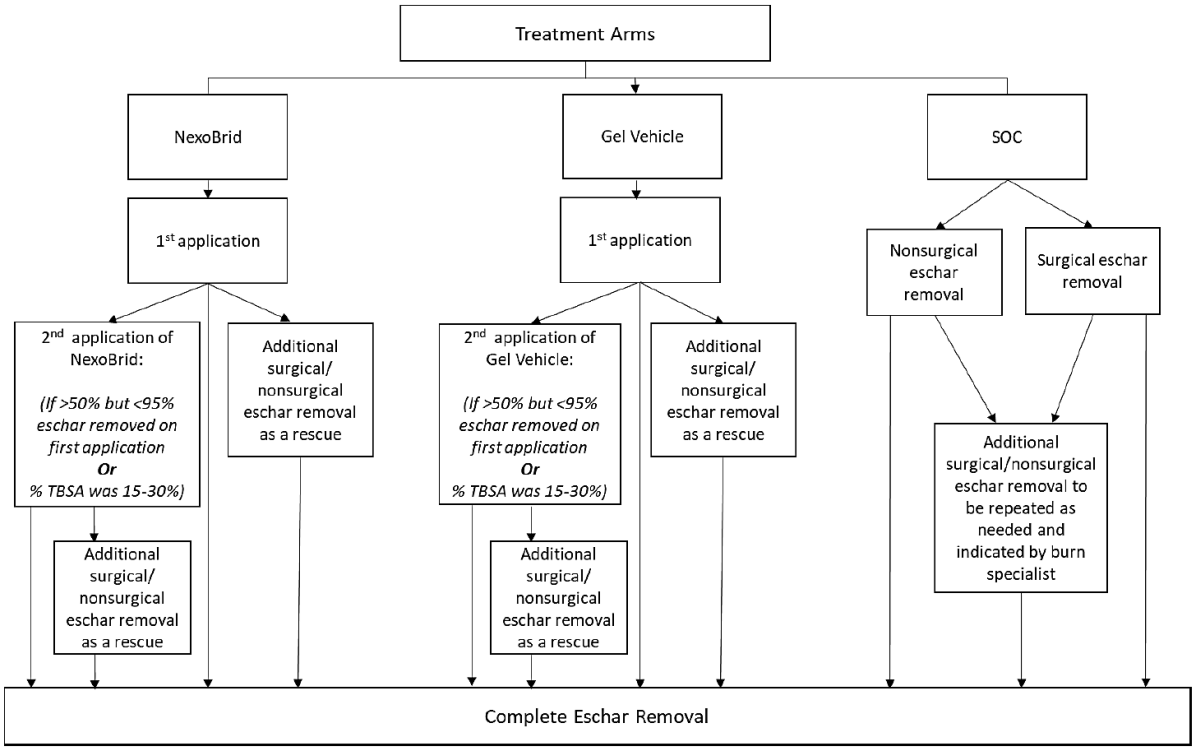
Evaluable efficacy data were provided in three pivotal phase 3 studies, study MW 2010-03-02 (DETECT) conducted in adults, study MW 2012-01-01 (CIDS) conducted in children aged 0-18 years, and study MW 2004-11-02 conducted in adults and children, with additional supportive efficacy data in four phase 2 studies, one phase 1/2 study, and a phase 3b study MW 2012-01-02, the long-term extension of pivotal study MW 2004-11-02.

Dose selection for the pivotal studies was based on the phase 2 dose ranging study MW 2001-10-03, a randomised, open-label, observer-blinded, multicentre study which compared 1 g, 2 g, and 4 g doses of Nexobrid (referred to as 'Debrase') in terms of debriding efficacy for DPT or FT burns. Median time to >95% epithelialization from last debridement was shortest in the 2 g treatment group, whilst rates of adverse events were similar across doses, with the majority being categorised as mild. The dose chosen for subsequent studies was 2 g Nexobrid powder mixed with 20 g gel vehicle (0.09 g Nexobrid/g gel vehicle) per 1% TBSA treated.

Study MW 2010-03-02 (DETECT), pivotal study

This was a phase 3, randomised, vehicle- and active-controlled, multicentre study which aimed to demonstrate superiority of Nexobrid over gel vehicle and standard-of-care (SOC) in adult patients with thermal burns, conducted between May 2015 and August 2020 across 32 sites in the USA, Europe and Israel. Efficacy objectives included comparison of complete eschar removal between Nexobrid and gel vehicle, and comparison of time to complete eschar removal, surgical burden, and blood loss between Nexobrid and SOC. The total study duration was 24 months following wound closure, comprising three distinct stages: stage 1 from baseline to 3 months post wound closure, stage 2 from 3 to 12 months post wound closure, and stage 3 from 12 to 24 months post wound closure. The study schematic is shown in Figure 1.

Figure 1. Study MW 2010-03-02 (DETECT) schematic.



The study included hospitalised burns patients with DPT and FT burns, with specific inclusion criteria pertaining to both the patient and wound; patients were male and female ≥18 years of age, with thermal burns caused by fire/flame, scalds, or contact, a total burn area ≥3% DPT and/or FT, total burn area ≤30% TBSA, informed consent within 84 hours of the burn injury, whilst criteria for wounds included at least 1 wound (a continuous burn area) which was ≥0.5% TBSA which did not include facial, perineal or genital wounds (all wounds meeting this criterion were denoted 'target wounds' and treated per randomisation). A target wound was further defined as a continuous burn area composed of DPT and/or FT depth that can be treated in 1 session, which may include superficial partial thickness areas only if they could not be separated from deeper areas and comprised <50% of the TBSA of the wound, with maximal burned area of a single target wound being ≤15% TBSA. A single patient could have more than one target wound. Key exclusion criteria included electrical or chemical burns, circumferential DPT/FT burns defined as >80% of limb circumference, and abraded wounds.

The Nexobrid study treatment was consistent with the product and proposed posology in this application, namely 2 g Nexobrid powder mixed with 20 g gel vehicle applied per 1% TBSA for 4 hours, or 5 g powder mixed with 50 g gel vehicle applied per 2.5% TBSA for 4 hours. The maximum TBSA to which Nexobrid was applied in a single session was 15%; for subjects with TBSA burns between 15% and 30% treatment was applied in two sessions, with the second application able to proceed anywhere from immediately after removal of the topical agent applied in the first application to 24 hours after start of the first application. Nexobrid could be applied to the same wound for a second time if removal of the eschar was incomplete after first application, but at least 50% of eschar was removed. Subjects with remaining eschar after Nexobrid treatment were treated with SOC, as shown in Figure 1. Gel vehicle treatment included 20 g gel per 1% TBSA for 4 hours, or 50 g gel per 2.5% TBSA for 4 hours, with a treatment protocol that mirrored that for the Nexobrid treatment arm. SOC comprised surgical and/or non-surgical procedures to remove eschar, with surgical methods including tangential, minor, avulsion, Versajet and dermabrasion excision, and non-surgical methods including collagenase ointment, antimicrobial solutions, and ointments/creams and/or silver dressings. Specific

treatment in the SOC arm was at the discretion of treating burn specialists. All subjects were followed up until complete wound closure was achieved.

Complete eschar removal was determined by a blinded assessor (although blinding was not possible for the SOC arm), with ≥95% removal of eschar considered complete, and this was denoted as the end of the eschar removal process, followed by initiation of specific treatment to close the viable debrided wound bed by skin grafting or epithelialization. A second assessor at each study site undertook weekly assessment of wound closure, long-term cosmesis and function. Confirmation of wound closure was undertaken by a blinded assessor. The primary efficacy endpoint was incidence of complete eschar removal, Nexobrid compared to gel vehicle. Secondary efficacy endpoints related to comparison of Nexobrid and SOC, and included incidence of surgical excision of eschar, time to complete eschar removal, and blood loss related to eschar removal.

Subjects were stratified according to %TBSA burns, ≤15% and >15%, and overall depth of target wounds, all FT, mixed FT and DPT, and all DPT, and study centre, with subjects within each stratification group randomised 3:3:1 to Nexobrid, SOC or gel vehicle. Four analysis populations were defined: the enrolled population included all subjects who passed screening, the full analysis set (FAS) all subjects randomised into the study, the per protocol set (PPS) all subjects who fulfilled inclusion/exclusion criteria without major protocol deviations, and safety analysis set (SAS) all subjects who received at least one treatment.

Sample size calculation in relation to the primary efficacy endpoint was based on the following assumptions, informed by results of the preceding phase 3 study MW 2004-11-02: estimated proportion of subjects achieving complete eschar removal in all target wounds was 0.595, standard error of 0.057, resulting in anticipated proportion of subjects achieving complete eschar removal with Nexobrid in this study of 0.5665, whilst estimated proportion in the gel vehicle arm achieving complete eschar removal was 0%, resulting in an anticipated proportion of 0.10 in the gel vehicle arm after accounting for 97.5% upper confidence limit on the 0.0 point estimate. A 2-sided significance level of 5% was specified; using Fishers exact test, for 90% overall power, calculated sample size was 65 subjects in the Nexobrid arm and 13 in the gel vehicle arm. Applying a similar approach calculated sample size for the secondary efficacy endpoints were 43 subjects in both the Nexobrid and SOC arms. Final sample size was increased to 175 subjects, 75 in the Nexobrid and SOC arms, and 25 in the gel vehicle arm, with the rationale of increased likelihood of meeting efficacy endpoints and greater safety data, which was considered reasonable by the clinical evaluator.

A hierarchical test procedure was implemented for primary and secondary efficacy endpoints. Statistical analysis was undertaken in 3 stages corresponding to the 3 stages of the study, with primary and secondary efficacy endpoints tested in stage 1, analysed using the FAS. For the primary efficacy endpoint logistic regression was used to compare the proportion of subjects in each arm who reached complete eschar removal at the end of the topical agent soaking period, with Fisher's exact test used for analysis. Odds ratio (OR), and its 95% confidence interval (CI), of achieving complete eschar removal was reported. Missing data was treated as not having achieved complete eschar removal. Planned sensitivity analyses included repeating analysis using the PPS, a positive analysis and complete case analysis. Planned supportive analyses, if feasible, included comparison adjusted for wound depth, and inclusion of total %TBSA and treatment centre strata in the logistic regression model. Primary efficacy analysis was to be repeated at the level of the wound as an additional analysis, using a mixed logistic regression model.

With respect to the secondary efficacy endpoint incidence of surgical removal of eschar, a binary yes/no variable was used, with comparison between treatment Nexobrid and SOC arms undertaken using logistic regression, with explanatory variables treatment, target wound strata,

total %TBSA per patient, and number of target wounds. The OR of requiring surgery, and 95% CI, was estimated. The secondary endpoint time to complete eschar removal was defined as number of days from randomisation to complete eschar removal at a subject level (all target wounds of an individual subject). Kaplan-Meier curves were used to demonstrate the comparison between Nexobrid and SOC arms, whilst a Cox regression model using similar explanatory variables as for the first secondary efficacy endpoint was used for the comparison.

The endpoint blood loss related to eschar removal was assessed at the subject-level, with a supportive analysis at the procedure-level. Distribution of acute blood loss was compared between Nexobrid and SOC arms, with normality of data was tested using a Shapiro-Wilk test. If the normal distribution hypothesis was not rejected at the 0.5% significance level in either arm, then differences between arms were analysed using a t-test, whereas if the normal distribution hypothesis was rejected in either arm, analysis was with a Mann-Whitney test. Subgroup analyses were undertaken for primary and secondary efficacy endpoints including early (within 7 days) and late (after 7 days) autografted wounds, target wounds on the hand, subjects with percentage of area of all target wounds with superficial partial thickness burn <25% and ≥25%, subjects with total TBSA ≤15% and >15%, and wound depth strata.

Overall, 175 subjects were enrolled and randomised, 75 in both the Nexobrid and SOC arms and 25 in the gel vehicle arm, comprising the FAS. The SAS comprised 77 in the Nexobrid group, 68 in the SOC group, and 24 in the gel vehicle group after accounting for loss to follow up and other protocol deviations. The proportion completing the acute phase (stage 1) of the study were 89.33%, 84.00% and 92.00% respectively. The proportion of subjects completing the 12 month and 24 month follow up periods were similar between treatment groups; 74.67% and 57.33% respectively in the Nexobrid group, 77.33% and 48.00% in the SOC group, and 80.00% and 40.00% respectively in the gel vehicle group. There were 12 major protocol deviations recorded in 12 subjects, 8 in the SOC group, including 2 incorrectly treated with Nexobrid, 5 subjects not treated and 1 subject who did not have eschar removal assessment, 3 in the gel vehicle group and 1 in the Nexobrid group, who was enrolled with <3%TBSA of DPT/FT burns.

Baseline demographics and clinical parameters were generally similar between treatment groups. Mean ages were 41.28 years in the Nexobrid group, range 18 to 75 years, in the SOC group mean was 40.91 years, range 18 to 72 years, and in the gel vehicle group mean was 40.68 years, range 18 to 70 years. The majority of subjects across groups were of White background and male, however, the SOC group had a higher proportion of male subjects (78.67%) compared to Nexobrid (65.33%) and gel vehicle (60.00%) groups. The majority of burns in all groups were of flame/fire aetiology, with lesser proportions of other thermal burn aetiologies. There were no significant differences in terms of anatomical distribution of burns. Burn characteristics when considered at both the target wound level and patient level were comparable between groups. Table 5 summarises data relating to %TBSA for target wounds at the patient level, showing similar mean %TBSA of target wounds between groups, and similar distribution of DPT and FT thickness burns between groups, though showing differences in range of %TBSA within groups and burn depth.

Table 5. Target wound description at baseline, patient level, FAS population, study MW 2010-03-02.

		Treatment		
Variable		**NexoBrid (N=75)**	**SOC (N=75)**	**Gel Vehicle (N=25)**
Percent TBSA SPT (TWs only)	n	75	75	25
	Mean	0.83	0.90	1.53
	SD	1.26	1.40	2.17
	Min	0.00	0.00	0.00
	Median	0.00	0.00	0.20
	Max	6.00	6.00	7.00
Percent TBSA DPT (TWs only)	n	75	75	25
	Mean	3.83	3.79	3.56
	SD	2.73	2.52	1.95
	Min	0.00	0.00	0.00
	Median	3.00	3.00	4.00
	Max	13.60	14.50	7.00
Percent TBSA FT (TWs only)	n	75	75	25
	Mean	1.62	1.23	1.44
	SD	2.58	1.70	2.04
	Min	0.00	0.00	0.00
	Median	1.00	0.50	0.50
	Max	13.50	6.00	8.00
Percent TBSA (TWs only)	n	75	75	25
	Mean	6.28	5.91	6.53
	SD	3.68	3.06	3.60
	Min	1.00	2.00	1.50
	Median	5.00	5.00	6.50
	Max	21.10	14.50	18.00

DPT = deep partial thickness; FAS = full analysis set; FT = full thickness; N = number of target wounds in the Full Analysis Set; Max = maximum; Min = minimum. n = number of target wounds with observed variable; NMiss = number of missing values; SPT = Superficial Partial Thickness; SD = standard deviation; TBSA = Total body surface area; TW = target wound.

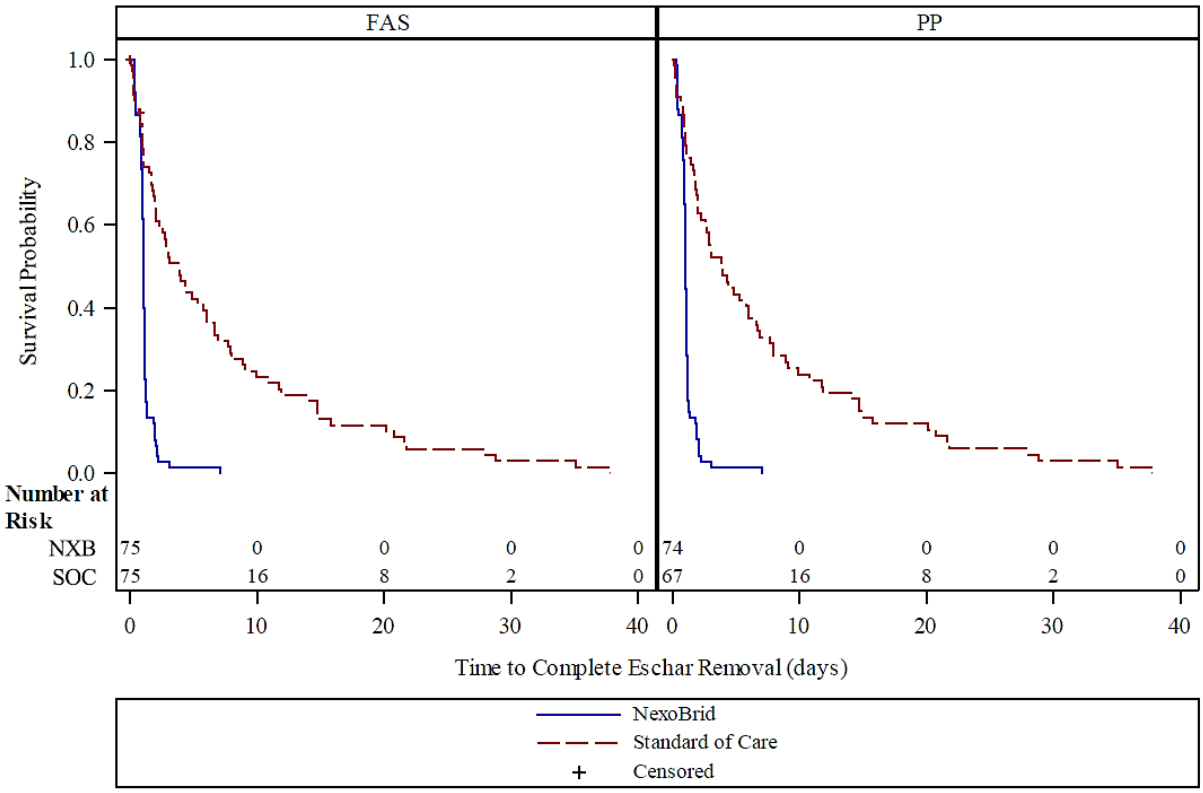
For this analysis. treatment arm indicates assignment based on randomisation.

For the primary efficacy endpoint, incidence of complete eschar removal in Nexobrid versus gel vehicle groups, at the end of the topical soaking period of the first, or if required second, treatment session, 70/75 (93.33%) had complete removal in the Nexobrid group compared to 1/25 (4.00%) in the gel vehicle group, with 5 subjects in the Nexobrid group receiving two applications. For subjects who achieved complete eschar removal, the odds of exposure to Nexobrid was estimated to be 288.281 (95% CI [35.549, 13984.356], p<0.0001) times the odds of exposure to the gel vehicle. Results were similar when considered at the wound level, whilst analyses adjusting for %TBSA, study site, and sex were supportive of the primary analysis. These results were considered by the clinical evaluator as both statistically significant and clinically meaningful. Of note, only 5 subjects received two applications of Nexobrid.

The first key secondary efficacy endpoint in the statistical hierarchy was incidence of surgical excision in Nexobrid versus SOC groups. Results showed statistically significant less incidence of

surgical excision in the Nexobrid group, 3/75 subjects (4.00%), compared to the SOC group, 54/75 (72.00%), for an OR of 0.011 (95% CI [0.03, 0.044], p= 0.011). The secondary efficacy endpoint time to complete eschar removal, Nexobrid versus SOC, defined as time in days from randomisation to complete eschar removal, median time to removal was 1.0232 days in the Nexobrid group compared to 3.8279 days in the SOC group. Results for this endpoint are presented in the Kaplan-Meier curve in Figure 2 for both the FAS and PPS populations.

Figure 2. Kaplan-Meier estimates for time to complete eschar removal for Nexobrid versus standard-of-care, FAS and PPS, study MW 2010-03-02.



For results of the secondary efficacy endpoint blood loss related to eschar removal results for the Nexobrid group were median blood loss of -79.36 mL (range -956.76 to 1425.29 mL), and median loss of 577.00 mL in the SOC group (range -452.03 to 1065.74 mL). The negative median value for the Nexobrid group reflects 'blood gain', with the investigator speculated could result from haemodynamic changes during eschar removal, or variations in laboratory measured haemoglobin. Using Wilcoxon test, with missing values imputed using multiple imputation, this comparison was statistically significant, p<0.0001.

Study MW 2012-01-01 (CIDS), pivotal study

This was a phase 3, randomised, active-controlled, open-label, multicentre study conducted across 36 centres in the USA, UK, Europe and India between May 2015 and May 2022, assessing efficacy and safety of Nexobrid compared to SOC in children aged 0-18 years. The study was conducted in 3 stages based on age; stage 1 was to have at least 24 children aged 4-18 years hospitalised in burns units, stage 2 at least an additional 26 children aged 1-18 years, and stage 3 was to have up to 160 children aged 0-18 years. Progression through the study stages was based on review of safety results by a Data Safety Monitoring Board. For analysis of safety data 4 periods were defined, baseline to 12 weeks after wound closure, 3 to 12 months after wound closure, 12 to 24 months after wound closure, and ≥30 months after wound closure; at the time of dossier submission the 30-month period was ongoing.

As for study MW 2010-03-02, second Nexobrid application could be used in the event of target wound >15% TBSA or incomplete eschar removal on first application. The definition of target wound in the study protocol was similar to that for study MW 2010-03-02. In addition to age criteria for each study stage outlined above, other patient-level inclusion criteria included thermal burns caused by fire/flame, scalds, or contact, patient total burns area ≥1% DPT and/or FT, total burns area ≤30% TBSA, and wound-level criteria included wound that was ≥1% TBSA DPT and/or FT, not including the face, perineal or genital areas. Key exclusion criteria included weight <3 kg, continuous burn area >15% TBSA, and other factors related to pre-enrolment burn treatment and medical comorbidities. The Nexobrid group received 2 g Nexobrid powder mixed with 20 g gel vehicle per 180 cm2 for 4 hours, applied to a maximum 15% TBSA in one session. This dosing was approximately equivalent to the 2 g per 1% TBSA dose applied to adult subjects in study MW 2010-03-02. The SOC group received surgical and/or non-surgical eschar removal determined by the treating burns specialist. Study treatment must have been received within 84 hours of the burn injury.

The primary efficacy endpoint was comparison of Nexobrid to SOC in terms of time to complete eschar removal at the subject-level, whilst key secondary efficacy endpoints were incidence of surgical excision for eschar removal, blood loss related to eschar removal, percent area of wound autografted for DPT wounds, and incidence of autograft in DPT wounds. Subjects were stratified by age group, total burns area by %TBSA, and study site. Eschar removal and wound closure assessments in this study were not blinded. Four analysis populations were defined: the enrolled population comprised all subjects who passed screening and for whom there was signed informed consent, the FAS comprised all subjects randomised into the study, the PPS comprised all subjects who met inclusion/exclusion criteria and did not have any major protocol deviations, and the SAS comprising all subjects who received at least one treatment.

A sample size of 160 was originally planned, however, due to the COVID-19 pandemic the sample size was re-calculated based on assumptions informed by data from preceding studies MW 2004-11-02 and 12-month data from study MW 2010-03-02, with power calculations based on a sample size of 145 subsequently accepted by paediatric committees of the EMA and FDA, divided between age groups. This sample size was insufficient to provide 90% power for the secondary efficacy endpoints incidence of autografts in DPT wounds and area of autograft in DPT wounds. A hierarchical testing approach was utilised, with each efficacy outcome in the procedure to be interpreted inferentially only if a statistically significant treatment effect at a significance level of 5% was demonstrated for the preceding outcome. Analyses were performed at the conclusion of each stage of the three stages of the study with stage 3 analysis pending at the time of submission. The p-values reported for efficacy outcomes were performed on the FAS based on the re-randomisation test, which was described in the statistical analysis plan. Kaplan-Meier curves were to be constructed for the primary efficacy endpoint, and treatment arms were compared using a Cox regression model, adjusted for study site, age,

%TBSA, proportion of FT for a subject, and number of target wounds, whilst the treatment variable was Nexobrid or SOC. The secondary endpoint relating to surgical excision was tested using logistic regression. The secondary endpoint relating to blood loss was tested using two methods, one using the entire eschar removal process as a continuous procedure, and the other summing blood loss from each eschar removal procedure.

In total 153 patients were screened, with 145 subjects randomised, 72 to Nexobrid and 73 to SOC. Over 90% of subjects in both groups completed to 12-week follow-up, a slightly higher proportion completed to 12-month follow-up in the Nexobrid group (88.9%) compared to SOC (83.6%), similarly to 24-month follow-up, 77.8% for the Nexobrid group and 72.6% for the SOC group. There were 17 major protocol deviations in 15 subjects, comparable in terms of number and type between treatment groups. There were no major differences between groups in terms

of baseline demographics, mean age was 5.77 years (median 3.54 years), with an age range of 0.6 to 18.6 years, the majority (62.1%) were male, and White ethnicity, and median weight was 15.00 kg with a large range, 7 to 102 kg. There was a longer median time from injury to randomisation in the Nexobrid group, 42.5 hours compared to 32.5 hours for SOC.

The majority of burns in both groups were scald burns (68.1% Nexobrid, 65.8% SOC), and there were no major differences between groups in terms of anatomical location of burns, with the most common location being anterior trunk. In terms of baseline target wound characteristics there were some differences between groups. A higher majority of target wounds in the Nexobrid group were classified as all DPT (80.6%, compared to 71.2% in SOC) and a slightly higher proportion in the SOC group were mixed DPT/FT depth (21.9%, compared to 13.9% in Nexobrid), with a small number of burns in both groups all FT (5.6% Nexobrid, 6.8% SOC). At the subject-level, median overall target wound %TBSA was 4.00% in both groups, with comparable %TBSA of DPT and FT burns between groups. A small number in both groups had an overall total area of burns >15% to ≤30% (4 subjects [5.6%] Nexobrid group, 3 subjects [4.1%] SOC group). There was only 1 subject in the Nexobrid group who received two applications of study treatment, on the basis of both incomplete eschar removal and target wound area >15% TBSA; the clinical evaluator subsequently highlighted the limited supporting evidence for two applications of Nexobrid in this clinical study.

For the primary efficacy endpoint, estimated median time to complete eschar removal was 0.99 days (95% CI [0.88, 1.04]) in the Nexobrid group compared to 5.99 days (95% CI [2.71, 9.84]) in the SOC group. Using a Wilcoxon-Gehan test adjusted for study site, %TBSA, proportion of FT area and number of target wounds, the resulting positive test statistic supported shorter time to complete eschar removal in the Nexobrid group, which was statistically significant. Sensitivity analyses and subgroup analyses by age were supportive of the main analysis.

In terms of the key secondary efficacy endpoints, incidence of surgical excision of eschar was lower in the Nexobrid group (6/72 subjects [8.33%]) compared to SOC (47/73 subjects [64.38%]), resulting in an odds of exposure to Nexobrid for those undergoing surgical excision of 0.025 (95% CI [0.007, 0.090] p<0.0001). For the endpoint blood loss related to eschar removal, mean blood loss using the subject-oriented methodology was lower in the Nexobrid group (32.26 mL versus 202.55 mL in SOC), however, the comparison was not statistically significant, resulting in stopping of the hierarchical testing procedure. For the subsequent secondary efficacy endpoints, descriptive statistics showed similar mean percent area of wound autografted for DPT wounds between treatment groups, and the proportion of DPT target wounds for which autografting was performed was lower in the Nexobrid group.

Study MW 2004-11-02, pivotal study

This was a phase 3, randomised, open-label, two-arm multicentre study conducted between February 2006 and January 2010 across study sites in Israel, Australia, Brazil, India, UK and other EU countries. Overall objectives were to evaluate and compare efficacy and safety of Nexobrid (referred to as Debrase Gel Dressing in the CSR, but Nexobrid throughout this summary) and SOC among hospitalised child and adult patients with DPT and/or FT burns. The first subject at each site was assigned to Nexobrid as training for investigators, with subsequent subjects stratified into two subgroups based on %TBSA of burn wounds, subgroup A ≥ 5% to ≤15% and Subgroup B >15% to ≤30%. Wound closure, defined as % epithelialisation and/or graft coverage, was assessed weekly following debridement. Subjects were followed-up for 3 months post-wound closure to assess the maintenance of wound closure and function and cosmesis.

Key inclusion criteria were patients aged 4 to 55 years with DPT and/or FT thermal burns that were ≥ 5% to ≤ 30% TBSA and were hospitalised within 24 hours of the burn injury, with at

least one wound of ≥2% TBSA DPT and/or FT burn, and at least 50% of the DPT and/or FT burn wound area intended for surgical debridement. Key exclusion criteria were severe cutaneous trauma at the same sites as the burns, facial burn wounds >0.5% TBSA, and perineal and/or genital burns.

The dose of Nexobrid used was 2 g per 100 cm^2 of skin, corresponding to approximately 1% TBSA for an average adult, applied for 4 hours, applied at a thickness of 1.5 to 3 mm. Two treatment sessions could be used in the event of incomplete eschar removal, and if wound area to be treated was >15 % TBSA, with second treatment to be no later than 48 hours after the start of first debridement. SOC included surgical and/or non-surgical procedures at the discretion of the treating specialist. Following wound debridement routine care usually included autografting of FT burns and treatment of mixed dermal burns with protective biological covers, skin substitutes or topical medications, and may have varied between wounds and between subjects. Co-primary efficacy endpoints included percent treated wound excised or dermabraded in first surgery, with complete or mixed FT wounds excluded from this analysis; surgical excision/dermabrasion in first surgery was defined as tangential/minor/Versajet excision or dermabrasion performed as the initial eschar removal procedure in the surgical SOC group, or as the first surgical debridement performed after initial eschar removal in the Nexobrid or non-surgical debridement SOC groups. The other co-primary endpoint was percent treated wound autografted, which pertained to autografting of DPT wounds where the potential tissue-sparing effect of Nexobrid may be seen, with FT wounds excluded from the analysis. Four secondary efficacy outcomes included the percent treated wound excised or dermabraded in first surgery for all wounds, time to complete wound closure, timely eschar removal (defined as ≥90% of eschar removed), and blood loss, measured as change in haemoglobin and haematocrit from pre- to post-treatment.

Efficacy endpoints were evaluated in the modified intention to treat population (mITT), comprising all randomised subjects with at least one wound that was entirely DPT as evaluated in the pre-debridement phase, and subset B of the evaluable population, which comprised mITT subjects who fulfilled all inclusion/exclusion criteria and were not excluded due to major protocol deviations. Sample size calculation for the co-primary endpoints was based on alpha 0.05, for percent treated wound excised a sample of 68 in each arm would have at least 80% power to detect treatment difference of 22% with an assumed pooled SD of 45%, whilst for percent treated wound autografted, assuming a treatment difference of 11% and pooled SD of 40%, 210 wounds per treatment group would be required for 80% power to detect the treatment difference at 0.05 alpha. Assuming two wounds per subject 105 per group would be required, increased to 120 per group to account for dropouts.

Statistical tests were conducted against a two-sided alternative hypothesis and using a significance level of 0.05, unless otherwise specified. A sequential testing procedure was used to control for type 1 error from multiple comparisons. Both primary efficacy endpoints were tested at a significance level of 0.05. The secondary efficacy endpoint percent treated wound excised was tested after the co-primary endpoints, with the other secondary efficacy endpoints not included in the hierarchical testing procedure. The analysis of treatment main effect of continuous variables, except for time to event, was undertaken using a two-way analysis of variance (ANOVA), with treatment, centre and baseline stratification level as terms. A repeated measurement ANOVA model with treatment and baseline stratified %TBSA level as terms, and subject as the random effect, was used for the wound-based efficacy outcomes. Time to event efficacy outcomes were analysed using the log-rank test. The Kaplan-Meier method was used to estimate the median time to event and distribution and a Cox regression model was used to estimate the hazard ratio. For categorical efficacy outcomes, Chi-squared test or Fisher's exact test were used to compare the treatments.

A pre-planned interim analysis was to be undertaken when 152 randomised subjects had completed the study. Stopping rules for efficacy and futility were specified. If the two-sided p-value was <0.02 for % wound excised, % wound autograft was tested. If the two-sided p-value for each of the co-primary outcomes was <0.02, accrual was to be stopped and the study was considered to have met its objectives. The study was stopped for futility if the two-sided p-value for each of the co-primary outcomes was >0.5.

In total 182 subjects were randomised, 26 as site training, 75 to Nexobrid and 81 to SOC, with 85.3% in the Nexobrid group completing the study compared to 77.8% in the SOC group. Out of total study enrolment there were 34 paediatric subjects. The mITT population, on which analysis of co-primary efficacy endpoints was based, included 49 (65.3%) subjects in the Nexobrid group and 48 (59.3%) subjects in the SOC group. In total 39 major protocol deviations were reported among 32 subjects. Baseline demographics and burn characteristics were generally similar between groups. Most subjects were male (72.0% Nexobrid, 75.3% SOC) and of Caucasian ethnicity, median age in the Nexobrid group was 32.6 years (range 4.4 to 55.7 years) and 26.6 years (range 5.1 to 55.7 years) in the SOC group. In each of the analysis populations, the proportion of subjects by each age group stratum (≤18 years, > 18 years) was generally similar in each treatment group. The most common aetiology of burn was fire/flame. The proportion of wounds in the Nexobrid group that were DPT depth (65.0%) was slightly higher than in the SOC group (51.8%), corresponding with a slightly lower proportion of burns with any FT component in the Nexobrid group (33.7%, compared to 45.9% in SOC). The median treated TW % TBSA was 5.0% in each treatment arm.

Based on the interim analysis, the two-sided p-value for each of the co-primary outcomes was <0.02, accrual was stopped and the study was considered to have met its objectives. The proportion of wounds for which excision or dermabrasion was performed was lower in the Nexobrid group compared to SOC group; 16/106 (15.1%) and 55/88 (62.5%) respectively, p<0.0001. For the co-primary endpoint percent wound area excised/dermabraded in first surgery, mean (SD) in the Nexobrid group was 5.5% (14.6) and 52.0% (44.5) in the SOC group, with p-value using parameter square root for the treatment comparison <0.0001. There was no difference in subgroup analysis by age, ≤ 18 years, > 18 years. The proportion of DPT wounds autografted was lower in the Nexobrid group (16/106, 17.9%) compared to the SOC group (55/88, 34.1%). For the co-primary endpoint percent wound area autografted, mean (SD) in the Nexobrid group was 8.4% (21.3), and in the SOC group 21.5% (34.8), with p-value <0.0054.

Results for the secondary efficacy endpoint percent treated wound excised or dermabraded in first surgery for all wounds reflected results for the co-primary endpoint, which concerned DPT wounds only. Whilst hierarchical testing had stopped for the remaining secondary efficacy endpoints, of note, time to complete wound closure from date of informed consent was longer in the Nexobrid group, mean (SD) 36.2 (18.5) days compared to 28.8 (15.6) days for the SOC group, with no major differences noted by age group. Descriptive statistics for the endpoint of timely eschar removal showed shorter median time in the Nexobrid group (2.0 days, range 1.0 to 8.0) compared to 8.5 days (range 0.0 to 23.0 days) for SOC. For the blood loss endpoint, mean change in haemoglobin from screening to 2 hours post-treatment was smaller in the Nexobrid group compared to SOC.

Other efficacy studies

As noted above the dose-ranging study MW 2001-10-03 provided evidence to support Nexobrid dosing based on efficacy endpoints including achievement of wound closure and time to wound closure, however, the study was small (20 subjects randomised) with very high rates of early withdrawal across all treatment groups.

Study MW 2002-04-01 was a phase 2, randomised, observer-blind, three-arm multicentre study comparing efficacy and safety between Nexobrid (referred to as Debrase Gel), gel vehicle and SOC, which randomised 148 adult subjects aged 18-69 with DPT and/or FT burns ranging 2-15% TBSA. Nexobrid dosing reflected that in the subsequent pivotal studies. The primary efficacy endpoint, time to complete wound closure from the time of injury, was similar across the three treatment groups; mean (SD) 34.7 (17.8) days in the Nexobrid group, 37.0 (22.6) days in the gel vehicle group, and 32.4 (21.4) days in the SOC group.

Study MW 2005-10-05 was a phase 2, randomised, open-label three-arm safety study with exploratory efficacy endpoints. In total 31 adult subjects were randomised 1:1:1 Nexobrid (referred to as Debrase Gel), gel vehicle or SOC. Descriptive statistics showed complete wound debridement achieved for 8/10 subjects in the Nexobrid group, 0/9 subjects in the gel vehicle group, and 11/11 subjects in the SOC group, with similar time to debridement between Nexobrid and SOC.

Study MW 2008-09-03 was a phase 2, non-randomised, open-label study, with exploratory efficacy endpoints, enrolling patients aged 4 and over. All treated subjects received Nexobrid dosed in line with that for subsequent pivotal studies. In total 36 subjects were enrolled, the youngest 9 years. Descriptive statistics based on the ITT population showed successful eschar removal in 31/35 (88.6%) subjects, and surgical excision as required for 31/97 (32.0%) of wounds treated.

Study MW 2012-01-02 was a phase 3b, non-interventional, assessor-blinded multicentre study to evaluate long-term scar formation and quality of life for adult and child subjects who had participated in the pivotal study MW 2004-11-02. The Modified Vancouver Scar Scale (MVSS) was used, assessing pigmentation, pliability, height, vascularity, pain and pruritus, with a total score calculated based on the sum of scores for each of these characteristics. Validated self-administered (SF-36) or parent-administered (BOQ) questionnaires were used for quality if life assessment. The study involved a single assessment visit during which scar and quality of life assessments were undertaken. In total 89 subjects with documented wound closure in study MW 2004-11-02 were enrolled, comprising 17 paediatric subjects. Of the 89 subjects, 54 (60.7%) received Nexobrid in the preceding study, and 35 (39.3%) received SOC. Results of scar assessment using MVSS were similar between groups, with a median score of 3.0 in both. Results of quality of life assessment showed no major differences between study groups.

Safety

Evaluable safety data submitted in the dossier included data related to wound closure, cosmesis and function, long-term function, and quality of life, in addition to data relating to adverse events, vital signs, pain assessment and blood transfusions, among other outcomes. This section will proceed by summarising patient exposure to Nexobrid, before summarising evaluable safety data in subsections according to specific study or pooled analysis. Safety data is available for each pivotal study and select supportive studies, and pooled data comprising safety data from the pivotal study MW 2004-11-02, the phase 2 study 2002-04-01, the phase 2 study MW 2005-10-05, the phase 2 dose-ranging study MW 2001-10-03, the phase 2 study MW 2008-09- 03, and pivotal study MW 2010-03-02. Two cohorts were defined for the integrated analyses on pooled data; Cohort 1 comprising all six of the listed studies, and Cohort 2 comprising only the phase 3 pivotal studies MW 2010-03-02 and MW 2004-11-02. The Acute Phase was defined as up to 3 months after complete wound closure of all treated wounds.

Integrated safety analyses were also undertaken on pooled safety data in paediatric subjects from studies MW 2004-11-02, MW 2008-09-03 and MW 2012-01-01. The safety analysis population for pooled paediatric data was called the Pooled Paediatric Cohort, including acute

phase data up to 3 months post wound closure. The paediatric age categories included the protocol-specified age groups for Study MW 2012-01-01 (0 to 23 months; 24 months to 3 years; 4 to 11 years; 12 to 18 years) and FDA-requested age groups (0 to < 1 year; 1 to < 6 years; 6 to < 12 years; 12 to 18 years).

Patient exposure

Pivotal studies

In study MW 2010-03-02, in the Nexobrid treatment group 72/77 subjects received one application with median amount of Nexobrid 10.0 grams, with 5 subjects receiving two applications with median amount 25.0 grams. In the paediatric pivotal study MW 2012-01-01 only one subject received two applications, whilst exposure data was available for 65 subjects receiving a single application, with median amount applied 2.889 grams. The highest number of subjects treated with Nexobrid was in the 1 to <6 years age group (37 subjects). In study MW 2004-11-02 based on 96 subjects for which data was available, the highest proportion received 10 g Nexobrid plus 100 grams of gel vehicle, with 5 subjects receiving quantities higher than 40 g Nexobrid.

Supportive studies

In study MW 2001-10-03 there were 16 subjects with available data, with the largest dose of Nexobrid received being 40 g in 200 grams of hydrating gel, a concentration of 0.17 g/g. In study 2002-04-01 ten subjects received two applications of Nexobrid, with the largest dose applied 30 g Nexobrid in 300 grams of hydrating gel. Study MW 2008-09-03 had range of Nexobrid doses applied 5 g to 60 g, equating to 2.5% to 30% TBSA.

Pooled studies

In Cohort 1 total patient (person)-years (PY) in the study was 81.62 PY in the Nexobrid treatment arm, 57.16 PY in the SOC treatment arm and 20.11 PY in the Gel Vehicle treatment arm. Based on Cohort 2, total PY in the study for subjects in the Nexobrid treatment arm was 61.89 PY, 54.03 PY following one application of Nexobrid (N=159) and 7.86 PY following two applications of Nexobrid (N=18). Based on the Pooled Paediatric Cohort, which was comprised of 89 subjects treated with Nexobrid and 86 subjects treated with SOC, the majority of subjects (96.6% (86/89)) received one application of Nexobrid. Three paediatric subjects received two applications of Nexobrid. Based on 70 subjects, the median %TBSA treated with Nexobrid was 3.40 % (range: 0.6 to 26.8%). The mean %TBSA treated with Nexobrid was similar (mean (SD): 5.39 (5.824)%). Median person-years of follow-up was the same in each treatment arm (Nexobrid: 0.35 person-years (range: 0.1 to 0.6 person-years); SOC: 0.35 person-years (range: 0.1 to 0.5 person-years). Mean and median person-years of follow-up were the same.

Treatment-emergent adverse events

Integrated analyses on pooled data

Analyses undertaken on pooled safety data within Cohort 1 found comparable rates of treatment-emergent adverse events (TEAEs) among age subgroups, though noting small numbers of paediatric subjects in this cohort (N=36), by gender subgroup, or by race subgroup. Of the 300 subjects in Cohort 1, 40 received two applications of Nexobrid, with a higher rate of TEAEs among this subgroup.

Based on pooled phase 3 data in Cohort 2, there were similar rates of TEAEs reported between groups; 62.7% Nexobrid, 55.7% SOC and 62.5% gel vehicle. The TEAE tachycardia was reported in 5 subjects receiving Nexobrid and no subjects receiving other treatments, whilst the TEAE

rash was reported in 6 subjects receiving Nexobrid and no others. The exposure- adjusted incidence rates for pruritus, pyrexia and anaemia were notably higher in the Nexobrid treatment group compared with the other two treatment arms. Subjects in the Nexobrid and SOC groups with TBSA of TWs >15% had higher rates of serious TEAEs, though numbers of subjects in these subgroups were small; 5/19 (26.3%) in the Nexobrid group, and 2/13 (15.4%) in SOC.

The Pooled Paediatric Cohort showed similar proportions of TEAEs between Nexobrid, 49.4%, and SOC, 45.3%. The TEAEs reported in the highest proportion of subjects in the Nexobrid treatment group were pruritus (Nexobrid: 16.9% (15/89); SOC: 9.3% (8/86)) and pyrexia (Nexobrid: 12.4% (11/89); SOC: 8.1% (7/86)).

Study MW 2010-03-02, pivotal study

In the acute phase of the study up to the 3-month follow-up visit the proportion of subjects experiencing at least one TEAE was similar between groups: 61.0% Nexobrid, 57.4% SOC, 62.5% gel vehicle. The rate of severe TEAEs was highest for gel vehicle, 12.5%, compared to 5.2% in the Nexobrid group and 4.4% for SOC. The following TEAEs were reported in the Nexobrid group only: leukocytosis (3.9% subjects in the Nexobrid group), tachycardia (6.49%), vomiting (6.49%), and rash (5.19%).

In stage 2 of the study covering 3-month to 12-month follow-up rates of subjects with at least one TEAE were similar between groups with the highest rate for gel vehicle: 24.7% Nexobrid, 26.5% SOC, 29.2% gel vehicle. In stage 2 the most commonly reported TEAE across all groups was joint range of motion decreased.

Over the cumulative study period 0 to 24 month follow-up the proportion of subjects with at least one TEAE was similar across treatment groups. In addition to the TEAEs listed above as occurring only in the Nexobrid group during the acute phase, urinary tract infection was recorded in this cumulative period in 4 subjects (5.19%) in the Nexobrid group and no subjects in either of the other treatment groups.

Study MW 2012-01-01 (CIDS), pivotal paediatric study

For the acute phase up to 12-week follow-up the proportion of subjects with at least one TEAE was similar between groups, and lower than seen in study MW 2010-03-02: 44.9% Nexobrid, 42.9% SOC. There were 4 subjects in the Nexobrid group with at least 1 severe TEAE compared to 1 subject in the SOC group. By preferred term (PT), the following TEAEs were reported in >3 subjects in the Nexobrid group and at a higher rate compared to SOC: vomiting (5/69 subjects, 7.2%), constipation (3/69, 4.3%), nausea (3/69, 4.3%), pyrexia (7/69, 10.1%), nasopharyngitis (3/69, 4.3%), wound complication (5/69, 7.2%), and pruritus (9/69, 13.0%).

The proportion of subjects in each treatment group reported with at least one TEAE during the period between the 12-week follow-up and 12 months post-wound closure was similar (Nexobrid: 10.1% (7/69); SOC: 12.9% (9/70)).

Over the cumulative study period 0 to 24 month follow-up the proportion of subjects in each group with at least one TEAE was similar, 46.4% in the Nexobrid group and 44.3% in the SOC group, with a slightly higher number of subjects with severe TEAEs recorded for Nexobrid, 5/69 (7.2%) compared to 1/70 (1.4%).

Study MW 2004-11-02, pivotal study

The proportion of subjects with both any TEAE and severe TEAE was slightly higher in the Nexobrid group, 68.0% and 12.0% respectively, compared to SOC, 59.3% and 8.6% respectively. Pruritus was reported in 23/100 (23.0%) in the Nexobrid group and 15/81 (18.5%) in the SOC group. Local AEs were reported in 42.0% (42/100) of subjects in the Nexobrid treatment group

compared with 33.3% (27/81) of subjects in the SOC group. The proportion of subjects reported with wound infection, wound decomposition and pruritus, respectively, were generally similar in each treatment group. Skin graft failure was reported for 4 subjects (4.0%) in the Nexobrid group compared with a single subject in the SOC group.

Other studies

Safety data from the supportive phase 2 studies was generally reflective of the pivotal studies, with the majority of recorded TEAEs mild in severity. Of note, in the phase 2 study MW 2002-04-01 pain was reported as a TEAE in 19/70 (27.1%) subjects in the Nexobrid group compared to 5/35 (14.3%) in the gel vehicle group and 3/35 (8.6%) in the SOC group.

Deaths and other serious adverse events

Integrated analyses on pooled data

In Cohort 1 TEAEs leading to death were reported in 6 subjects (2.0%) in the Nexobrid group and 1 subject (0.5%) in the SOC group with no deaths in the gel vehicle group. None of the deaths were considered related to study treatment by investigators. In terms of serious AEs (SAEs) the exposure-adjusted incidence rate of sepsis was 2.64 events per person-year (PY) after 1 application and 21.83 events per PY after 2 applications of Nexobrid.

In Cohort 2 TEAEs leading to death were recorded for 2 subjects (1.1%) in the Nexobrid group and 1 subject (0.7%) in the SOC group with none in the gel vehicle group. Again, none were considered related to study treatment. There were no deaths reported in the pooled paediatric cohort.

Study MW 2010-03-02, pivotal study

In terms of deaths, in the acute phase of the study one subject who received Nexobrid treatment died from acute respiratory failure. In the 12-month follow-up period one subject died from an unknown cause, with the case narrative detailing SAEs of thermal burn, urosepsis, osteomyelitis and sepsis. There were no further deaths at 24-month follow-up. The two deaths were determined by the investigator, data safety monitoring board and sponsor as not related to study treatment.

In the acute phase treatment-emergent SAEs were reported for 6 subjects (7.8%) in the Nexobrid group, 4 subjects (5.9%) in the SOC group and 3 subjects (12.5%) in the gel vehicle group, which in the Nexobrid group included 2 cases of bacterial wound infection, osteomyelitis, sepsis, urosepsis and acute respiratory failure. Overall, for the cumulative period 0 to 24-months follow-up rates of treatment-emergent SAEs were similar between groups, 9/77 (11.7%) for Nexobrid, 9/68 (13.2%) for SOC, and 3/24 (12.5%) for gel vehicle. Two subjects in the Nexobrid group had an SAE of sepsis classified as severe.

Study MW 2012-01-01 (CIDS), pivotal paediatric study

There were no TEAEs leading to death recorded. In the acute phase 2 subjects (2.9%) in the Nexobrid group and 5 subjects (7.1%) in the SOC group had SAEs; one in the Nexobrid group with tachycardia, pyrexia and systemic inflammatory response, determined possibly or remotely related to Nexobrid. For the cumulative period 0 to 24-months, 2/69 (2.9%) in the Nexobrid group and 6/70 (8.6%) in the SOC group had SAEs reported.

Study MW 2004-11-02, pivotal study

One subject in each treatment group had an AE with an outcome of death, including cardiac arrest and homicide, not considered related to study treatment. SAEs were reported in 12/100

(12.0%) in the Nexobrid group, including sepsis in 2 subjects, and single events including disseminated intravascular coagulation, cardiac arrest, anaphylactic shock, and deep vein thrombosis, and in 6/81 (7.4%) in the SOC group.

Other studies

In study MW-2002-04-01 there were four deaths in the Nexobrid group, from multi-organ failure, respiratory failure, vomiting and aspiration, assessed as not related to the study treatment. There was also a higher rate of SAEs recorded in the Nexobrid group (8/70, 11.4%) than the SOC group (2/35, 5.7%) or gel vehicle group (3/35, 8.6%). Reported SAEs in Nexobrid treated subjects included skin graft failure, pain in extremity, oedema peripheral, dyspnoea, deep vein thrombosis and epileptic seizure.

Discontinuations due to adverse events

In the pooled safety data 1 subject who received Nexobrid in Cohort 1 discontinued due to a TEAE of pain, classified as severe. There were no TEAEs leading to discontinuation in Cohort 2 or the pooled paediatric cohort.

Issues with possible regulatory impact

Evaluation of liver function and renal function results identified no notable trends or safety signals. In the pivotal study MW 2010-03-02 shifts in liver function tests from normal values to high values during the study were more commonly reported in SOC and gel vehicle treated subjects. In terms of clinical chemistry parameters there were similar trends evident across treatment groups, not necessarily more common in one treatment group, including shifts in calcium from normal to low, in glucose from normal to high, and in albumin from normal to low.

In terms of haematological parameters, in the pivotal study MW 2010-03-02 the proportion of subjects treated with Nexobrid with a shift in neutrophil value from normal to high (21/77, 27.3%) was higher than for SOC-treated subjects (10/68, 14.7%) and gel vehicle-treated subjects (3/24, 12.5%), however, in the pivotal paediatric study MW 2012-01-01 the proportion was higher in the SOC group (9/40, 22.5%) compared to Nexobrid (5/45, 11.0%).

In terms of effect on coagulation parameters, changes from normal parameters at baseline to abnormal post-baseline were generally comparable between treatment groups. In the pivotal study MW 2010-03-02 8/77 subjects (10.4%) in the Nexobrid group and 6/68 (8.8%) in the SOC group had shifts in prothrombin international normalised ratio (INR) from normal to high during the acute phase of the study. The same shift in INR was reported for 3 subjects (5.9%) treated with Nexobrid in the pivotal paediatric study MW 2012-01-01, and for no subjects in the SOC group, though shifts observed were not considered clinically significant.

Electrocardiograph findings and cardiovascular safety

In pivotal study MW 2010-03-02 twelve-lead electrocardiograms (ECGs) were performed before eschar removal was commenced, specifically at baseline 60±5 min, 40±5 min and 20±5 minutes prior to start of the eschar removal process. ECGs were also collected after the start of eschar removal, specifically at 30±15 min, 120±15 min, 4±0.5 hour, 12±0.5 hour, 24±1 hour, 48±2 hour, and 1 week after eschar removal was commenced. These ECGs, which were performed, where feasible, in triplicate, formed part of the evaluation of QT prolongation.

Pharmacokinetic-Pharmacodynamic (PK-PD) analysis was performed on all subjects in the ECG Analysis Population who had at least one time-matched pair of serum concentration and ECG measurements obtained at the same nominal time point. This was the defined PK-PD Analysis Population. As ECGs were collected in triplicate and the collection of blood for pharmacokinetic

analysis was taken after completion of the ECGs, the ECG and collection of the blood sample for pharmacokinetic analysis may not have been at exactly the same time. The ECG parameters assessed were heart rate, PR interval, QRS interval, QT interval, QTcF interval and QTcB interval. The QTcF interval was used for the primary endpoint. The primary endpoint was the change from baseline in QTc intervals measured using the Fridericia (QTcF) correction method.

A negative study (i.e. no evidence of a QTc prolongation) based on the study results was defined as a model based (model-predicted) upper bound of the two-sided 90% CI of the predicted mean placebo-adjusted change from baseline that was less than 10 msec at the observed mean Cmax for the therapeutic dose of Nexobrid. The ECG population was comprised of 128 subjects. The PK-PD population was comprised of 97 subjects.

The time-averaged mean change from baseline in heart rate, in beats per minute (bpm), was generally comparable in each treatment group (Nexobrid: 4.0, SOC: 3.7, Gel Vehicle: 6.1). The time-averaged mean change from baseline in QTcF interval was -1.7 ms in the Nexobrid group,

1.4 ms in the SOC group and -4.6 ms in the gel vehicle group. In each treatment group, no subject had QTcF values > 500 ms after the start of treatment and no subject had increases in QTcF interval values > 60 ms. The proportion of subjects with increases in QTcF>30-60 ms from baseline was highest in the SOC group. The predicted placebo-adjusted change from baseline in QTcF interval at predicted mean Cmax for serum Nexobrid was 4.962 ms (90% CI [-0.485 ms, 9.925 ms]). The clinical evaluator concluded that this sub-study showed no evidence of cardiac safety signal.

Vital signs and clinical examination findings

In the pivotal study MW 2010-03-02 of 18 subjects overall with potentially clinically significant shifts in temperature, which were predominantly from normal to a low value, the Nexobrid group had the lowest proportion. Overall, there were no identifiable trends or signals in terms of vital signs or clinical examination findings.

Immunogenicity

In the pivotal study MW 2010-03-02 the anti-drug antibody (ADA) evaluable population was defined as subjects who had at least one ADA test result prior to and after Nexobrid treatment and included 62 subjects. Of these, 25/62 (40.3%) had a positive ADA result in the pre-treatment sample, and 58/62 (93.5%) had treatment-induced or treatment boosted ADA. There were 36 subjects ADA negative at baseline and ADA positive post-treatment. Based on subjects with a result at each assessment time point the median ADA titre was highest 4 weeks post-treatment. It appeared that there was no relationship between baseline ADA titre and maximum post-dose ADA titre, maximum post-treatment ADA titre and size of the burn wound treated as a %TBSA, maximum post-treatment ADA titre and the dose of Nexobrid applied, baseline ADA titre and dose adjusted Cmax and AUC_{0-4}. There also appeared to be no notable relationship between baseline ADA status (negative/positive) and median dose adjusted C_{max} and AUC_{0-4}.ADA titre at baseline did not appear to be related to achievement of complete eschar removal. Hypersensitivity reactions did not appear to be related to the presence of ADA at baseline.

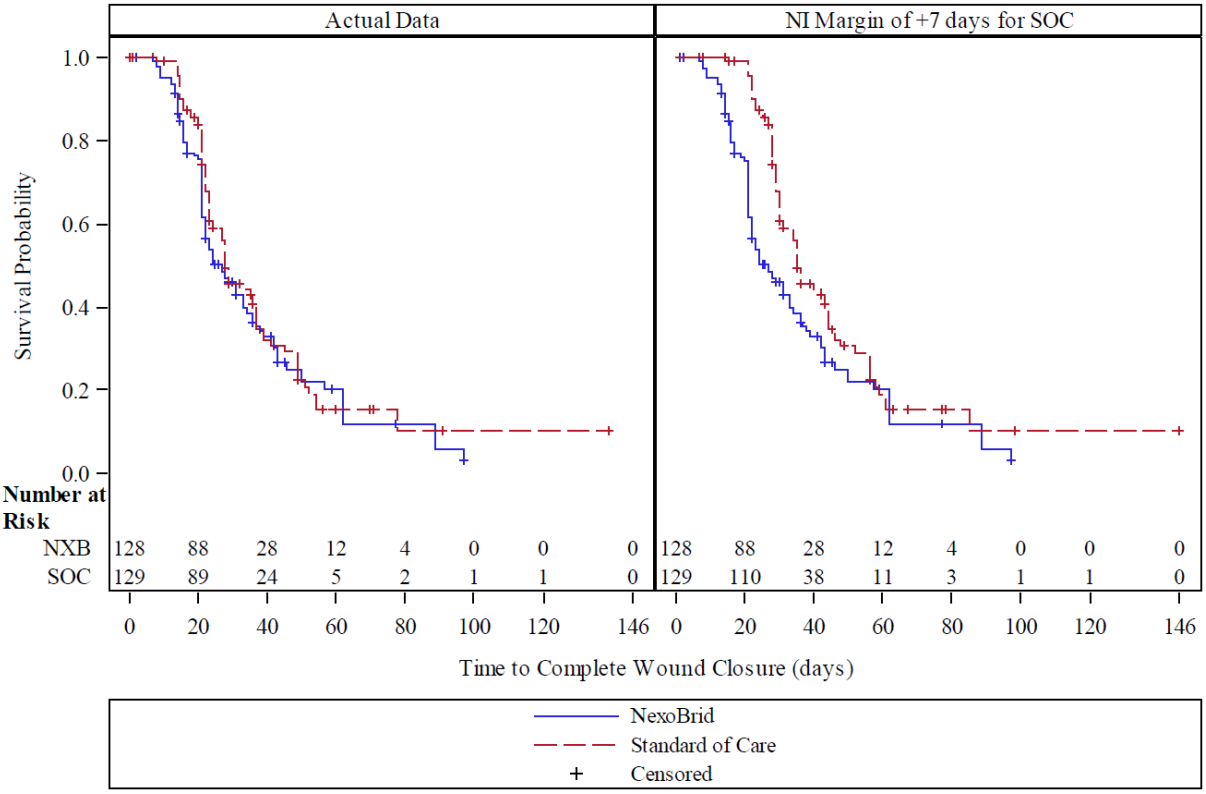
In the pivotal paediatric study MW 2012-01-01 the ADA evaluable population comprised 17 subjects, of which 5 subjects (29.4%) had positive ADA pre-treatment. Most subjects (14/17, 82.4%) had either treatment-induced ADA or treatment-boosted ADA.

Time to wound closure

Based on integrated analysis of pooled data in Cohort 1, for treated target wounds, the median time to 100% wound closure, estimated using the Kaplan-Meier method, was comparable for Nexobrid (37.0 days) and SOC (36.0 days) groups. Results for Cohort 2 were similar; 36.0 days for Nexobrid and 37.0 days for SOC. In the pooled paediatric cohort, for treated target wounds, the median time to complete wound closure, estimated using the Kaplan-Meier method, was the same between treatment groups at 31.0 days.

In the pivotal study MW-2010-03-02 time to wound closure considered at the target wound level, opposed to the subject-level, showed median time 27.00 days for Nexobrid and 28.00 days for SOC, with Kaplan-Meier curves for time to complete wound closure overlapping for the Nexobrid and SOC groups, as shown in Figure 3.

Figure 3. Kaplan-Meier estimates for time to complete wound closure, Nexobrid versus standard-of-care, at the target wound level, study MW 2010-03-02 (FAS).



In the pivotal paediatric study MW 2012-01-01 at the target wound level median time to complete wound closure estimated using the Kaplan-Meier method was 32.00 days in the Nexobrid group and 41.00 days in the SOC group, though descriptive statistics showed similar mean and median days to complete closure in both groups.

Adverse events of special interest

Pain

The pivotal studies included proactive preventative actions for pain. In the pooled phase 2 and 3 data in Cohort 1 TEAE classified as severe was reported in 3.7% of subjects in the Nexobrid group, and 1.5% of subjects in the SOC group. There were no major differences between groups in the pooled paediatric cohort.

Pyrexia

In pooled phase 2 and 3 data in Cohort 1 the TEAE fever was reported at a similar rate for Nexobrid and gel vehicle, and at a lower rate for SOC. This was reflected in the pooled paediatric cohort, in which 15/89 (16.9%) subjects in the Nexobrid group had fever recorded, compared to 8/86 (9.3%) for SOC.

Wound infection

Notable trends included 3 subjects in pooled phase 3 data in Cohort 2 with wound fungal infections, compared with no subjects in the other treatment groups. In the pooled paediatric cohort rates of wound infection were higher in the SOC group (7/86 subjects, 8.1%) compared to Nexobrid (1/89 subjects, 1.1%).

Sepsis

Whilst overall rates of sepsis were low in pooled data there was a slightly higher proportion recorded for subjects treated with Nexobrid. In Cohort 1 sepsis was reported in 8/300 (2.7%) in the Nexobrid group, 1/195 (0.5%) in the SOC group, and 1/68 (1.5%) in the gel vehicle group, a trend reflected in the pooled paediatric cohort.

Cosmesis, function and quality of life

Study MW 2010-03-02, pivotal study in adults

Relevant endpoints in this study included the MVSS, Lower Extremity Functional Scale (LEFS), Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaires, and range of motion (ROM) measurements. Long-term quality of life was assessed using the EQ-5D and Burn Specific Health Scale-Brief (BSHS-B). Median MVSS score at 24 months from wound closure were generally similar between treatment groups, whilst median MVSS was lower in the Nexobrid group at 12 months from wound closure (4.00) compared to SOC and gel vehicle, 5.17 and 5.88 respectively. Assessment of long-term functionality using LEFS and QuickDASH were hampered by missing data, however, there were no major differences noted between treatment groups.

Results for quality-of-life assessments at 12 and 24 months post wound closure were also generally similar across the treatment groups.

Study MW 2012-01-01, pivotal paediatric study

MVSS scores at both 12 and 24 months post wound closure were lower in the Nexobrid group compared to SOC; at 12 months median MVSS was 3.00 for Nexobrid compared to 4.00 for SOC, and at 24 months median MVSS was 2.13 and 3.00 respectively. Functionality assessments were hampered by low numbers of subjects completing assessment measures.

Post-marketing experience

Periodic Safety Update Reports were provided covering the period December 2014 to December 2022, with an estimated 10,205 patients exposed to Nexobrid worldwide in the post-market setting, with no new safety signals identified for Nexobrid in the post-market setting. Off-label use of Nexobrid has been reported, including in lower limb chronic ulcer.

Targeted review by the sponsor of post-market safety data outside of the USA identified 5 cases that described events related to possible allergic or hypersensitivity reactions.

Late-breaking information

In submission sequence 004 the sponsor's cover letter included the statement 'the applicant also takes this opportunity to withdraw the 2 g presentation'. The Round 2 Clinical Evaluation Report (CER) had been drafted by the clinical evaluator prior to submission of this information by the sponsor, subsequently dealt with by inclusion of Section 16.1 'Late-breaking information' in the Round 2 CER, with additional questions to the sponsor seeking justification of the validity of the efficacy and safety data in the dossier considering the pivotal studies used both the 5 g and 2 g presentations of Nexobrid, and justification relating to dosing in paediatric patients given the withdrawal of the smaller volume presentation, again noting that both presentations were utilised in the pivotal paediatric study. Importantly, despite initially recommending approval of the product, given this late-breaking information, the clinical evaluator stated that they were now unable to provide a recommendation to the Delegate regarding approval of the product.

The sponsor's response stated that clinical data pertaining to efficacy and safety are influenced by the concentration of the active pharmaceutical ingredient in the drug product, which is the same (8.8% w/w) for both presentations, and that choice of presentation used in the clinical studies was based on availability or random choice, without any clinical considerations. The sponsor contended that the use of one presentation over the study should not have influenced efficacy or safety data. They stated that the parent company has decided to discontinue the 2g presentation of Nexobrid as it was commercially unviable, providing additional information relating to cost structure, clinical and economic considerations underlying this decision. They confirmed that the 2 g presentation is no longer marketed in any jurisdiction, with the exception of some European countries. There is no change to proposed paediatric dosing or administration instructions.

Risk management plan

Nexo Pharmaceuticals Pty Ltd has submitted EU-RMP version 9.4 (dated 10 November 2023; DLP 17 December 2021) and ASA version 1.0 (dated 30 April 2024) in support of this application. The sponsor has submitted an updated version of the ASA version 1.0 (dated 30 April 2024), however, the version number and the date were not updated. The sponsor submitted an updated ASA version 3.0 (dated 20 April 2025).

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below. The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases.

Table 6. Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Pain	✓*	–	✓	✓†‡
	Pyrexia/hyperthermia	✓*	–	✓	✓†‡
	Wound complications (including wound infections)	✓*	–	✓	✓†‡

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
	Allergic reactions (including anaphylactic reaction)	✓*	–	✓	✓†‡
Important potential risks	Severe irritation	✓*	–	✓	✓†‡
	Increased tendency to bleeding	✓*	–	✓	✓†‡
Missing information	Use in pregnancy and breastfeeding§	✓*	–	✓	–
	The efficacy and safety of two applications of Nexobrid§	✓*	–	✓	✓†‡

§ Australia-specific safety concerns

*Follow-up questionnaire

†Healthcare Professional Information Pack

‡Training for Healthcare Professionals

The summary of safety concerns has been approved by the EMA. At Round 3, the sponsor has added 'breastfeeding' to 'use in pregnancy' and 'the efficacy and safety of two applications of Nexobrid' as Australia-specific missing information in the updated ASA. The summary of safety concerns is acceptable from an RMP perspective.

The sponsor has proposed routine pharmacovigilance activities, which include a follow- up questionnaire for all safety concerns. No additional pharmacovigilance activities have been proposed. The sponsor confirmed that no additional pharmacovigilance activities have been or anticipated to be carried out for the missing information 'use in pregnancy and breastfeeding', noting that no safety findings have been identified. The pharmacovigilance plan is acceptable from an RMP perspective.

Routine risk minimisation measures have been proposed for all safety concerns. Additional risk minimisation measures in the form of educational materials (Healthcare Professional Information Pack and Training) have been proposed for all safety concerns except the missing information 'use in pregnancy and breastfeeding'. Examples of Healthcare Professional Information Packs from other approved countries have been provided, along with details on the implementation of additional risk minimisation activities in Australia. The sponsor confirmed that the information pack and training materials will be updated in accordance with Australian approved details. Drafts of the finalised materials will be submitted for review and acceptance prior to product launch.

The risk minimisation plan is acceptable from an RMP perspective.

Risk-benefit analysis

This application seeks to register the new chemical entity anacaulase-bcdb (Nexobrid) 8.8% gel in a 5 g lyophilised powder and 50 g gel presentation, for eschar removal in both adult and paediatric patients with DPT and/or FT thermal burns. The original application also included a 2

g lyophilised powder and 20 g gel presentation; this was subsequently withdrawn by the sponsor during the evaluation phase, citing a commercial decision by the parent company to discontinue the smaller presentation.

Nexobrid is a concentrate of proteolytic enzymes enriched in Bromelain extracted from the stem of the pineapple Ananas comosus. Mixing of the Nexobrid powder and gel vehicle prior to application results in the final product with concentration of 0.09 g/g of proteolytic enzymes enriched in Bromelain.

Burns represent a significant public health challenge both globally and within Australia, with published evidence indicating a disproportionate burden among Aboriginal and Torres Strait Islander peoples. Australian hospitalisation data show the highest incidence of burns in children aged five years and younger, underscoring the importance of including paediatric populations in clinical development for products intended for burn treatment.

The current standard of care for DPT and FT burns involves multidisciplinary management within specialised burns units, with early eschar removal—whether surgical or non-surgical—considered critical to enabling definitive wound care and promoting optimal healing outcomes. Nexobrid presents a non-surgical option for debridement of eschar from DPT and FT burn wounds.

The application is primarily supported by three pivotal phase 3 efficacy and safety studies covering different age groups and with different primary efficacy endpoints comparing Nexobrid to both gel vehicle and SOC as determined by the treating burns specialist.

Study MW 2010-03-02 enrolled hospitalised adults with DPT and/or FT thermal burns with the primary efficacy endpoint incidence of complete eschar removal comparing Nexobrid and gel vehicle, and secondary efficacy endpoints comparing Nexobrid with SOC in terms of incidence of surgical eschar removal, time to complete eschar removal and blood loss.

Study MW 2012-01-01, the pivotal paediatric study, enrolled children aged 0-18 years with thermal DPT and/or FT burns and compared Nexobrid to SOC only, the primary efficacy endpoint being time to complete eschar removal, and secondary endpoints also including comparison of incidence of surgical excision of eschar and blood loss, as well as endpoints relating to autografting of wounds.

Study MW 2004-11-02 enrolled hospitalised adults and children aged 4-55 years with DPT and/or FT burns ≥ 5% to ≤ 30% TBSA, comparing Nexobrid and SOC in terms of co-primary efficacy endpoints percent of treated wound excised or dermabraded in the first surgery, and percent of treated wound autografted, with secondary endpoints assessing time to eschar removal and wound closure, and blood loss. Safety data from the clinical development program was supplemented by post-market safety data, whilst PK data was adequately described primarily via the pivotal studies, and the phase 2 study MW 2008-09-03.

While the clinical evaluator was unable to make a final recommendation to the Delegate due to late-breaking information regarding the sponsor's withdrawal of the 2 g presentation, the overall benefit-risk profile of Nexobrid appears favourable based on the submitted evidence. However, outstanding uncertainties remain regarding the efficacy and safety of second applications of Nexobrid, particularly in patients with burns >15% TBSA or where eschar removal is incomplete after the first application

Proposed indication

The proposed indication in Australia is:

Nexobrid is indicated for eschar removal in adults and paediatric patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.

Of note, no age group or age cutoff is specified for paediatric patients. Overall, the proposed indication is adequately supported by evidence from the pivotal studies. Whilst broad in scope, the proposed wording 'in adults and paediatric patients' reflects pivotal study populations and is appropriate considering the epidemiology of burns in Australia.

The pivotal studies demonstrated the effectiveness of Nexobrid specifically in DPT and FT burns, and the proposed indication is consistent with approved indications in comparable international jurisdictions. Based on the totality of evidence, the Delegate considers the proposed indication to be acceptable.

Efficacy

Study MW2010-03-02 enrolled 175 adult subjects with thermal burns: 75 in each of the Nexobrid and SOC treatment groups, and 25 in the gel vehicle group. The study met all primary and key secondary efficacy endpoints. Target wounds ranged from ≥0.5% to ≤15% TBSA and were predominantly DPT and/or FT in depth. Individual subjects could have more than one target wound.

Nexobrid treatment in the study reflected dosing and administration instructions proposed in this application, namely 2 g Nexobrid powder mixed with 20 g gel vehicle applied per 1% TBSA for 4 hours, or 5 g powder mixed with 50 g gel vehicle applied per 2.5% TBSA for 4 hours. The maximum allowable TBSA to which Nexobrid was applied in a single session was 15%. A second application was permitted in two scenarios; subjects with target wounds covering 15- 30% TBSA, and subjects for whom eschar removal was incomplete but greater than 50% following the first application.

Complete eschar removal was defined as ≥95% removal, assessed by a blinded evaluator for the Nexobrid group. Blinding was not possible for the SOC group. A second assessor at each site conducted weekly assessment of wound closure, cosmesis and function. Subjects were stratified by %TBSA, target wound depth, and study centre, the latter strata considered important to account for potential differences in SOC for burns between centres.

There was a high rate of completion of the acute phase (baseline to 3 months post-wound closure) across all treatment groups, with lower but comparable completion rates at 12- and 24-month follow-up.

Baseline demographic and burn characteristics were generally similar between treatment groups. Most subjects were male and of white ethnicity. Mean target wound %TBSA was 6.26% in the Nexobrid group, 5.91% in the SOC group, and 6.53% in the gel vehicle group, with the predominant wound depth being DPT among all target wounds.

The primary efficacy endpoint compared Nexobrid to gel vehicle in terms of complete eschar removal, with results clearly favouring Nexobrid; 70/75 (93.33%) subjects in the Nexobrid group compared to 1/25 (4.00%) in the gel vehicle group achieved complete removal, with an OR of 288.281 (95% CI [35.549, 13984.356], p<0.0001). The key secondary efficacy endpoints compared Nexobrid to SOC, showing markedly less incidence of surgical excision in those treated with Nexobrid (OR 0.011, 95% CI [0.03, 0.044], p= 0.011), shorter time to complete eschar removal and reduced blood loss for the Nexobrid group. These results demonstrate the debriding effect of Nexobrid against inactive comparator, and lower surgical burden compared to those receiving SOC. No major differences were observed across stratified groups.

It is notable that only 5 subjects received two applications of Nexobrid in this study, mandating careful consideration of the sponsor's proposed dosing and administration instructions which permit a second application. Further advice on this point will be sought from the ACM.

As detailed in the FDA Center for Drug Evaluation and Research multi-discipline review report,[23] issues were identified during clinical inspections of trial sites, including unblinding in the assessment of eschar removal and wound closure, and reliance on photographic assessments contrary to protocol requirements for clinical evaluation. However, the FDA concluded that the efficacy results were convincingly statistically significant, that systematic bias was unlikely, and that re-analysis of source data confirmed the primary endpoint would still have been met even if assessments affected by unblinding or photographic review were treated as non-responders. The Delegate is satisfied that, despite these concerns, the efficacy data are both statistically and clinically meaningful.

Study MW2012-01-01 (CIDS) provides pivotal evidence for the use of Nexobrid in paediatric patients, enrolling 145 subjects (72 Nexobrid, 73 SOC) with a mean age of 5.77 years (range: 0.6 to 18.6 years). Burn characteristics were similar between groups at the subject level, with median %TBSA of 4.00% and comparable proportions of DPT and FT burns. Differences in burn composition at the target wound level were not considered to detract from efficacy outcomes. Patients weighing <3 kg were excluded.

Nexobrid dosing was 2 g powder mixed with 20 g gel vehicle per 180 cm^2 for 4 hours, applied to a maximum of 15% TBSA. The primary efficacy endpoint was time to complete eschar removal, with median time of 0.99 days (95% CI [0.88, 1.04]) in the Nexobrid group versus 5.99 days (95% CI [2.71, 9.84]) in the SOC group. Results were consistent across age groups, burn size, and study sites.

For key secondary endpoints, the odds of undergoing surgical excision were significantly lower in the Nexobrid group (OR 0.025; 95% CI [0.007, 0.90]; p<0.0001), supporting findings from the adult study. Mean blood loss was lower in the Nexobrid group, though the difference did not reach statistical significance. Descriptive statistics showed similar percent area of autografted DPT wounds between groups, with a lower incidence of autografting in the Nexobrid group (25.93% vs. 37.68%).

Importantly, evidence supporting a second application of Nexobrid in paediatric patients is very limited. Only two subjects in the Nexobrid group and one in the SOC group had target wound areas >15% TBSA, with only one paediatric subject receiving a second application. In the absence of supportive data, the benefit–risk balance for second application in paediatric patients must be carefully considered. Further advice will be sought from the ACM. It remains uncertain whether efficacy data from second applications in adults or initial applications in paediatric patients can be extrapolated to support second application use in paediatric populations.

Study MW2004-11-02 met both of its co-primary efficacy endpoints, demonstrating a lower percentage of wound excised during first surgery and a reduced need for autografting of DPT wounds in subjects treated with Nexobrid. A total of 182 subjects were randomised—75 to Nexobrid and 81 to SOC—including 34 paediatric subjects. The median age in the Nexobrid group was 32.6 years (range: 4.4 to 55.7 years), with most subjects being male and of Caucasian ethnicity.

In the Nexobrid group, the mean (SD) percentage of DPT wound area excised or dermabraded in the first surgery was 5.5% (14.6), compared to 52.0% (44.5) in the SOC group (p<0.0001).

[23] Food and Drug Administration, Center for Drug Evaluation and Research, Application number 761192Orig1s000 Multi-Discipline Review, available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/761192Orig1s000MultidisciplineR.pdf.

Subgroup analysis by age showed no significant differences. Additionally, 16/106 (17.9%) DPT wounds in the Nexobrid group underwent autografting, compared to 55/88 (34.1%) in the SOC group, reflecting a lower overall percentage of wound area autografted in the Nexobrid group (8.4%) versus 21.5% in the SOC group. This reduction in autografting can be interpreted as a decreased surgical burden and reduced need for harvesting healthy tissue.

Although not included in hierarchical testing, secondary endpoints showed a slightly longer time to complete wound closure in the Nexobrid group (mean 36.2 days, SD 18.5) compared to SOC (mean 28.8 days, SD 15.6). This is relevant given that complete wound closure is a key clinical objective in burn treatment. However, this difference may be partially attributable to the higher rate of autografting in the SOC group, which typically results in faster wound closure. Therefore, this data should be weighed against the reduced surgical burden observed in the Nexobrid group.

Additional efficacy data from three Phase 2 studies and a non-interventional Phase 3b study were supportive of the findings from the pivotal trials. While there is no TGA-adopted regulatory guidance specific to products intended for burn treatment, the FDA's guidance document, "Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment," is instructive. Key elements of study design outlined in this guidance were incorporated into Nexobrid's clinical development program, including comparisons against gel vehicle and SOC, stratification by burn depth and study site, and selection of efficacy outcomes relevant to wound healing and wound care.

Regarding the FDA's concerns about photographic wound assessments in Study MW2010-03-02, the guidance recommends standardisation of lighting, distance, exposure, and camera type when photographs are used. These measures were not confirmed for the study in question.

Overall, the efficacy of Nexobrid has been demonstrated through three well-designed, adequately powered clinical studies covering both adult and paediatric populations. These studies employed a range of clinically relevant endpoints aligned with international guidance. Outstanding uncertainties remain, particularly regarding the use of a second application of Nexobrid and its application to burns covering >15% TBSA. Across the clinical development program, 41 subjects received two applications of Nexobrid, and 30 subjects were treated for burns involving >15% TBSA.

Concerns identified with the conduct of Study MW2010-03-02 are not considered by the Delegate to materially impact the overall assessment of efficacy.

The Delegate shares the clinical evaluator's concern regarding interpretation of efficacy data, given that both the 5 g and 2 g presentations of Nexobrid were used in pivotal studies, and the 2 g presentation was withdrawn during the evaluation phase. However, the Delegate accepts that the clinical data reflect use of a single concentration of the active ingredient (8.8% w/w), and that the availability of only the 5 g presentation is unlikely to have significant clinical implications for adult patients. Nonetheless, further input from the ACM is sought regarding whether the withdrawal of the 2 g presentation may impact paediatric patients.

Safety

Comprehensive safety data were provided from the clinical development program, supplemented by multiple post-market Periodic Safety Update Reports. These included data on long-term cosmesis, functional outcomes, and quality of life. The safety profile of Nexobrid appears consistent between adult and paediatric populations. Rates of TEAEs were generally similar across treatment groups in the pivotal studies, with most events classified as mild or moderate in severity.

Across the three pivotal studies, specific TEAEs reported more frequently in subjects treated with Nexobrid included leukocytosis, tachycardia, vomiting, constipation, nausea, pyrexia, nasopharyngitis, and pruritus. The latter four were specifically recorded in paediatric subjects in Study MW2012-01-01, though in low absolute numbers.

Pooled safety data from Phase 2 and Phase 3 studies included TEAEs leading to death in six subjects treated with Nexobrid and one subject treated with SOC. No deaths occurred in paediatric subjects, and none of the deaths were attributed to study treatment by investigators, the data safety monitoring board, or the sponsor. Case narratives were included in the dossier. The Delegate is satisfied that the deaths recorded during clinical development were unlikely to be related to study treatment and acknowledges the inherent morbidity and mortality risks associated with burn injuries.

The overall rate of SAEs was low, with no identifiable trends among Nexobrid-treated subjects. In the pivotal studies, infectious SAEs reported in Nexobrid-treated subjects included bacterial wound infection, osteomyelitis, sepsis, and urosepsis, though none occurred in more than two subjects.

No safety signals were identified in clinical chemistry or haematological parameters. Observed changes were consistent across treatment groups and likely attributable to the burn injury itself or general supportive care. Importantly, no signal for deranged coagulation parameters was observed with Nexobrid use, which is reassuring given the demonstrated systemic absorption in pharmacokinetic data. A sub-study within MW2010-03-02 investigating the effect of Nexobrid on QT interval did not identify any clinically significant QT prolongation or other cardiac safety concerns.

Data from the pivotal studies suggest similar time to wound closure between Nexobrid-treated subjects and those receiving SOC, with wound closure being a clinically meaningful endpoint in burn management. Although analysis of cosmesis and function at 12- and 24-month time points was conducted outside the statistical hierarchy, descriptive data suggest similar or superior outcomes for Nexobrid compared to SOC.

As noted in the efficacy section, the Delegate shares the clinical evaluator's concern that the withdrawal of the 2 g presentation of Nexobrid during the evaluation phase may raise questions regarding interpretation of clinical data from pivotal studies, in which both the 5 g and 2 g presentations were used. However, on balance, the Delegate accepts that all studies used the same concentration of active ingredient (8.8% w/w), and that the choice of presentation was not based on clinical considerations.

The Delegate considers it unlikely that the absence of the 2 g presentation will have a clinically meaningful impact on safety or efficacy in the adult population. However, the Delegate seeks the ACM Committee's perspective on whether the withdrawal of the smaller-volume presentation may have implications for dosing accuracy, administration feasibility, or safety in paediatric patients—particularly those with small TBSA burns.

Conclusions

The clinical development program for Nexobrid, supported by three pivotal Phase 3 studies and additional Phase 2 and post-marketing data, demonstrates a favourable benefit–risk profile for the proposed indication:

> *Eschar removal in adults and paediatric patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.*

Efficacy has been consistently demonstrated across adult and paediatric populations, with statistically and clinically significant outcomes in terms of eschar removal, reduced need for

surgical excision, and lower autografting rates. These findings reflect meaningful reductions in surgical burden and associated morbidity. While time to wound closure was slightly longer in some analyses but unlikely to impact the conclusions on the overall clinical benefit.

The safety profile of Nexobrid is acceptable and comparable between adults and children. Most adverse events were mild to moderate, and serious adverse events were infrequent and not attributed to the study drug. No safety signals were identified in laboratory parameters, coagulation profiles, or cardiac assessments, and long-term outcomes in cosmesis and function were favourable.

Outstanding uncertainties remain regarding the safety and efficacy of second applications of Nexobrid, particularly in patients with burns >15% TBSA and in paediatric patients, where supporting data are limited. Additionally, the withdrawal of the 2 g presentation during evaluation raises questions about dosing flexibility, especially in small children. However, the consistent concentration of active ingredient (8.8% w/w) across presentations and the sponsor's justification mitigate concerns for adult use.

On balance, the Delegate considers the benefit–risk profile of Nexobrid to be favourable for its proposed indication, while seeking further advice from the ACM Committee on the implications of second application use and the withdrawal of the 2 g presentation in paediatric patients.

Advisory committee considerations

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

1. ***Is the proposed dosing regimen (up to 15% TBSA per application, with a maximum of 30% TBSA across two sessions) adequately supported by the existing pharmacokinetic and safety data?***

The ACM were supportive of a maximum coverage of 15% TBSA per application of Nexobrid, with a maximum coverage of 10% TBSA for patients under the age of six years based on the available pharmacokinetic and safety data from the MW2008-09-03 study, the DETECT study, and the CIDS study.

2. ***Given the limited number of subjects who received a second application of Nexobrid, does the Committee consider the current data adequate to support this dosing option?***

    a. **Should the second application be permitted in clinical practice, or should it be restricted pending further safety and pharmacokinetic data?**

    The ACM held the opinion that the data supporting a second application in the paediatric population was limited but were satisfied with the applicability of the acceptable adult data to this population, as the dosing is based on TBSA, limiting the risk of toxicity. The ACM noted that there was some evidence of higher systemic exposure in younger patients. The ACM, however, was reassured by guidance in the product information limiting the total TBSA application to 10% for patients under the age of six.

    b. **What minimum interval between applications would be considered safe, given the estimated systemic half-life of ~12 hours?**

    The ACM considered the PK data provided, as well as the data from the clinical trials that demonstrated complete clearance by 72 hours. They advised that an interval of 24 hours between applications of Nexobrid would be reasonable to ensure safety.

3. ***Does the Committee consider the paediatric data from the CIDS study sufficient to support its approval?***

The CIDS study is a multicentre phase 3, randomised, controlled, open label trial that examined the efficacy of Nexobrid against standard of care mechanical debridement. It had 145 participants randomised into two arms at a 1:1 ratio. The results supported efficacy of Nexobrid with limited adverse outcomes. The ACM considered this data to be useful in determining the approvability of Nexobrid.

4. ***Does the Committee consider the withdrawal of the 2 g presentation to impact the interpretability or applicability of the clinical data used to support efficacy and safety, especially in paediatric patients?***

The ACM held the view that as Nexobrid is applied uniformly over a percentage of TBSA, the 2g presentation is prepared at the same concentration as the 5g presentation, and therefore no difference in efficacy or safety would be expected. The ACM considered the interpretability and applicability of the clinical data to be unchanged.

   a. **Should the Committee recommend any changes to the proposed paediatric dosing guidance or administration instructions in light of the absence of the smaller volume presentation?**

      Some study protocols utilised a method of application over body surface area measured in cm^2. Proposed guidance instead refers to percentage of TBSA, with application of a consistent thickness. Due to this change, the ACM advised that paediatric dosing guidance would be identical with the 2g and 5g presentation of Nexobrid.

   b. **Is the continued use of only the 5 g presentation appropriate for all patient populations, including small children, from a dosing accuracy and safety perspective?**

      The ACM advised that they expected no difference in safety or efficacy in any patient population, including small children. This is due to the consistent application over a defined area relative to the size of the patient.

5. ***Does the Committee consider the modest delay in wound closure observed in pooled data and Study 2004 to be clinically relevant?***

The ACM held the view that the delay in wound closure was not clinically relevant as final wound closure is not related to the method of debridement used.

   a. **Is further clarification or labelling guidance warranted to help clinicians interpret wound closure expectations when using Nexobrid?**

      The ACM advised that wound closure expectations would be determined by a clinician's serial assessment of the wound bed and would not be improved with changes to the labelling guidance.

Advisory committee conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *"Nexobrid is indicated for eschar removal in adults and paediatric patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns."*

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Nexobrid (anacaulase-bcdb) for the following indication:

> *Nexobrid is indicated for eschar removal in adults and paediatric patients with deep partial thickness (DPT) and/or full thickness (FT) thermal burns.*

Specific conditions of registration

- Nexobrid (anacaulase-bcdb) is to be included in the Black Triangle Scheme. The PI and CMI for Nexobrid must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Nexobrid EU-Risk Management Plan (RMP) (version 9.4, dated 10 November 2023, data lock point 17 December 2021), with Australia-Specific Annex (version 3.0, dated 20 April 2025), included with submission PM-2024-02040-1-1, to be revised to the satisfaction of the TGA, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).
- Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- **Laboratory testing & compliance with Certified Product Details (CPD)**

  All batches of < Nexobrid anacaulase-bcdb 4.85 g powder vial with diluent gel bottle composite pack> supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

  When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.
- **Certified Product Details**

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website:

[for the form] https://www.tga.gov.au/resources/resources/forms/certified-product-details-cpd-biological-prescription-medicines

[for the CPD guidance] https://www.tga.gov.au/resources/guidance/submitting-certified-product-details-cpd-biological-prescription-medicines

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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