Clinical trial results:
A multicenter, multinational, randomized, controlled, open label study, performed in children with thermal burns, to evaluate the efficacy and safety of NexoBrid as compared to standard of care (SOC) treatment

Summary

EudraCT number	2014-003066-24
Trial protocol	CZ ES SK DE BE AT BG NL FR SE GB HU PL IT
Global end of trial date	19 December 2022

Results information

Result version number	v1 (current)
This version publication date	25 September 2024
First version publication date	25 September 2024

Trial information

Trial identification

Sponsor protocol code	MW2012-01-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02278718
WHO universal trial number (UTN)	-
Other trial identifiers	US (FDA): IND065448

Notes:

Sponsors

Sponsor organisation name	MediWound, Ltd.
Sponsor organisation address	42 Hayarkon Street, North Industrial Area, Yavne, Israel, 8122745
Public contact	Asi Haviv, DMD, Medical Director, MediWound, Ltd., 972 7797141000,
Scientific contact	Asi Haviv, DMD, Medical Director, MediWound, Ltd., 972 7797141000,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000142-PIP02-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2022
Global end of trial reached?	Yes
Global end of trial date	19 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is:
-To demonstrate enzymatic eschar removal efficacy of NexoBrid by providing earlier, complete eschar removal.
-To demonstrate enzymatic eschar removal efficacy of NexoBrid by reducing patients' surgical burden and resulting in non inferior final outcomes of cosmesis and function as compared to SOC.
-To assess the safety of NexoBrid compared to SOC.

Protection of trial subjects:

The study will be carried out in accordance with accepted international standards, which meet regulations relating to Good Clinical Practice (GCP). These standards are drawn from the following guidelines: ICH Guideline for Good Clinical Practice 1.5.96, amended September 1997 (Post step errata July 2002) and Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), concerning medical research in humans. In the Netherlands, the NVK (The Netherlands Association for Paediatric Medicine) code of conduct for dealing with subjects' expressions of objection in the course of the research will be adhered to as well. The investigator(s) will ensure that this study is conducted in full conformity with the principles of the "Declaration of Helsinki" and with the laws and regulations of the participating countries, whichever affords the greater protection to the individual. It is the responsibility of the investigator to obtain informed consent in written form (according to local legal requirements) from each subject participating in this study. All patients will be informed of the aims, methods, anticipated benefits, potential hazards and confidentiality of data. Candidates will also be told that they are free to refuse participation at any time.

Background therapy:

Patients will be treated in the same way in all study arms (NexoBrid or SOC) except for the Eschar Removal stage which will be performed as per the randomization study arm. Subsequent to complete eschar removal, all wounds will be assessed and treated in the same manner, in accordance with post-eschar removal wound care strategy. Post eschar removal, subjects will undergo Vital Signs and pain assessments, daily, until HD (Hospital Discharge) and weekly assessments of wound progress thereafter, until wound closure. Following wound closure confirmation, subjects will be followed up for 3 months (at week 6 and 12) and after that at 6, 12, 18 and 24 months post wound closure for long term outcomes evaluation. In addition, all subjects will be invited to one additional extended follow up visit that will occur at least 30 months after wound closure confirmation for a blinded assessment of cosmesis, function and QoL evaluation.

Evidence for comparator:

Comparators: Standard of Card (SOC) Conservative, non-surgical treatment by the antimicrobial SSD (Silver Sulphadiazine) dressing followed by daily dressing change and bathing is designed basically to slowly slough and debride the eschar-covered- wound by autolysis without excessive infection. SSD should not be used on a clean bed as it decreases epithelialization.

Actual start date of recruitment	01 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 28
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Georgia: 4
Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Bulgaria: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	145
EEA total number of subjects	59

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	45
Children (2-11 years)	80
Adolescents (12-17 years)	20
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients included in this study were hospitalized burn victims with DPT (deep partial thickness) and FT (full thickness) thermal burns

Pre-assignment

Screening details:

Signing of Informed Consent, demographics, medical history, concomitant medication, physical examination, vital signs, pain assessment, burn etiology, clinical assessment of the burn, randomization

Period 1

Period 1 title	12-Week Follow-up
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Assessor was blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NexoBrid

Arm description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Arm type	Experimental
Investigational medicinal product name	NexoBrid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and gel for gel
Routes of administration	Cutaneous use

Dosage and administration details:

Two grams or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle to obtain NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2g NexoBrid/20g Gel per 180cm² for four hours. In most cases, NexoBrid is effective after a single application; however it may be applied for a second time to the same burn area based on the investigator's judgment of debridement efficacy.
NexoBrid should not be applied more than twice to the same burn wound area.
NexoBrid should not be applied to more than 15% TBSA in one session.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Arm title	SOC (Standard of Care)

Arm description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Arm type	Standard of care
Investigational medicinal product name	Standard of care procedures
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream, Cutaneous solution, Ointment
Routes of administration	Conjunctival use , Topical use

Dosage and administration details:

Surgical procedures intended for eschar removal are pre-specified in the protocol for standardization and will include tangential/ minor/ avulsion/ Versajet/ dermabrasion excision.

Non-surgical procedures intended for eschar removal are pre-specified below for standardization and will include the application of antimicrobial solutions (e.g. Dakin's Solution, Sulfa-Nystatin Solution), ointments/creams (e.g. Bacitracin, Polysporin, Silvadene) and/or Silver dressings (e.g. Mepilex Ag, Aquacel Ag, Acticoat). Non-Surgical procedure is considered as one procedure for the whole period of any continuous dressing changes of more than 24h until either complete eschar removal is achieved or until surgical eschar removal is conducted. The need of either non-surgical or surgical procedures will be determined by the burn specialists and can be repeated as needed until complete debridement. Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Number of subjects in period 1	NexoBrid	SOC (Standard of Care)
Started	72	73
Completed	66	66
Not completed	6	7
Consent withdrawn by subject	1	3
Adverse event, non-fatal	1	-
Randomized Patient but did not receive Study IMP	-	1
Lost to follow-up	2	3
The Patient was randomized but did not receive Stu	2	-

Period 2

Period 2 title	12-Month Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Assessor was blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NexoBrid

Arm description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Arm type	Experimental
Investigational medicinal product name	NexoBrid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and gel for gel
Routes of administration	Cutaneous use

Dosage and administration details:

Two grams or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle to obtain NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2g NexoBrid/20g

Gel per 180cm² for four hours. In most cases, NexoBrid is effective after a single application; however it may be applied for a second time to the same burn area based on the investigator's judgment of debridement efficacy.
NexoBrid should not be applied more than twice to the same burn wound area.
NexoBrid should not be applied to more than 15% TBSA in one session.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Arm title	SOC (Standard of Care)

Arm description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Arm type	Standard of care
Investigational medicinal product name	Standard of care procedures
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream, Cutaneous solution, Ointment
Routes of administration	Conjunctival use , Topical use

Dosage and administration details:

Surgical procedures intended for eschar removal are pre-specified in the protocol for standardization and will include tangential/ minor/ avulsion/ Versajet/ dermabrasion excision.
Non-surgical procedures intended for eschar removal are pre-specified below for standardization and will include the application of antimicrobial solutions (e.g. Dakin’s Solution, Sulfa-Nystatin Solution), ointments/creams (e.g. Bacitracin, Polysporin, Silvadene) and/or Silver dressings (e.g. Mepilex Ag, Aquacel Ag, Acticoat). Non-Surgical procedure is considered as one procedure for the whole period of any continuous dressing changes of more than 24h until either complete eschar removal is achieved or until surgical eschar removal is conducted. The need of either non-surgical or surgical procedures will be determined by the burn specialists and can be repeated as needed until complete debridement.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Number of subjects in period 2	NexoBrid	SOC (Standard of Care)
Started	66	66
Completed	64	61
Not completed	2	5
Consent withdrawn by subject	2	1
Lost to follow-up	-	4

Period 3

Period 3 title	24-Month Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Assessor was blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	NexoBrid

Arm description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Arm type	Experimental
Investigational medicinal product name	NexoBrid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and gel for gel
Routes of administration	Cutaneous use

Dosage and administration details:

Two grams or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle to obtain NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2g NexoBrid/20g Gel per 180cm² for four hours. In most cases, NexoBrid is effective after a single application; however it may be applied for a second time to the same burn area based on the investigator's judgment of debridement efficacy.
NexoBrid should not be applied more than twice to the same burn wound area.
NexoBrid should not be applied to more than 15% TBSA in one session.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Arm title	SOC (Standard of Care)

Arm description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Arm type	Standard of care
Investigational medicinal product name	Standard of care procedures
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream, Cutaneous solution, Ointment
Routes of administration	Conjunctival use , Topical use

Dosage and administration details:

Surgical procedures intended for eschar removal are pre-specified in the protocol for standardization and will include tangential/ minor/ avulsion/ Versajet/ dermabrasion excision.
Non-surgical procedures intended for eschar removal are pre-specified below for standardization and will include the application of antimicrobial solutions (e.g. Dakin’s Solution, Sulfa-Nystatin Solution), ointments/creams (e.g. Bacitracin, Polysporin, Silvadene) and/or Silver dressings (e.g. Mepilex Ag, Aquacel Ag, Acticoat). Non-Surgical procedure is considered as one procedure for the whole period of any continuous dressing changes of more than 24h until either complete eschar removal is achieved or until surgical eschar removal is conducted. The need of either non-surgical or surgical procedures will be determined by the burn specialists and can be repeated as needed until complete debridement.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Number of subjects in period 3	NexoBrid	SOC (Standard of Care)
Started	64	61
Completed	58	53
Not completed	6	8
Consent withdrawn by subject	1	2
Not arrived to the final visit	1	-
Lost to follow-up	4	6

Period 4

Period 4 title	30-Month Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Assessor was blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NexoBrid

Arm description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Arm type	Experimental
Investigational medicinal product name	NexoBrid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and gel for gel
Routes of administration	Cutaneous use

Dosage and administration details:

Two grams or 5 grams of NexoBrid sterile powder are mixed in 20 grams or 50 grams of sterile Gel Vehicle to obtain NexoBrid Gel. NexoBrid Gel is applied to the burn wound at a dose of 2g NexoBrid/20g Gel per 180cm² for four hours. In most cases, NexoBrid is effective after a single application; however it may be applied for a second time to the same burn area based on the investigator's judgment of debridement efficacy.
NexoBrid should not be applied more than twice to the same burn wound area.
NexoBrid should not be applied to more than 15% TBSA in one session.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Arm title	SOC (Standard of Care)

Arm description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Arm type	Standard of care
Investigational medicinal product name	Standard of care procedures
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream, Cutaneous solution, Ointment
Routes of administration	Conjunctival use , Topical use

Dosage and administration details:

Surgical procedures intended for eschar removal are pre-specified in the protocol for standardization and will include tangential/ minor/ avulsion/ Versajet/ dermabrasion excision.
Non-surgical procedures intended for eschar removal are pre-specified below for standardization and will include the application of antimicrobial solutions (e.g. Dakin’s Solution, Sulfa-Nystatin Solution), ointments/creams (e.g. Bacitracin, Polysporin, Silvadene) and/or Silver dressings (e.g. Mepilex Ag, Aquacel Ag, Acticoat). Non-Surgical procedure is considered as one procedure for the whole period of any continuous dressing changes of more than 24h until either complete eschar removal is achieved or until surgical eschar removal is conducted. The need of either non-surgical or surgical procedures will be determined by the burn specialists and can be repeated as needed until complete debridement.
Treatment was only applied at the beginning of the Study, no application at the Follow-Up Visits.

Number of subjects in period 4	NexoBrid	SOC (Standard of Care)
Started	58	53
Completed	45	36
Not completed	13	17
Consent withdrawn by subject	4	4
N/A	2	-
The patient did not arrive to the final visit	1	-
Lost to follow-up	6	13

Baseline characteristics

Reporting groups	
Reporting group title	12-Week Follow-up

Reporting group description: -

Reporting group values	12-Week Follow-up	Total	
Number of subjects	145	145	
Age categorical			
0 Months - 18 Years			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	45	45	
Children (2-11 years)	80	80	
Adolescents (12-17 years)	20	20	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	55	55	
Male	90	90	

End points

End points reporting groups

Reporting group title	NexoBrid

Reporting group description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Reporting group title	SOC (Standard of Care)

Reporting group description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Reporting group title	NexoBrid

Reporting group description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Reporting group title	SOC (Standard of Care)

Reporting group description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Reporting group title	NexoBrid

Reporting group description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Reporting group title	SOC (Standard of Care)

Reporting group description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Reporting group title	NexoBrid

Reporting group description:

NexoBrid is presented as partially purified Bromelain powder and gel vehicle for preparation of a gel for cutaneous use. Following mixing of the powder with the gel vehicle, each gram of the prepared product contains 0.09 g partially purified Bromelain. Partially purified Bromelain is a mixture of enzymes extracted from the stem of Ananas comosus (pineapple plant).

Reporting group title	SOC (Standard of Care)

Reporting group description:

Standard of care. Includes surgical and/or non surgical eschar removal procedures.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Includes all patients who were randomized into the trial.

Primary: Time to complete eschar removal

End point title	Time to complete eschar removal

End point description:

Eschar removal was measured at the end of debridement starting from randomisation date. Eschar removal (days) can demonstrate superiority of NexoBrid over SoC as measured by a survival analysis of incidence of complete eschar removal when complete eschar removal was achieved for each patient, from the time of randomization.

End point type	Primary

End point timeframe:

From the time of randomization - baseline until 12-Month Follow-Up.

End point values	NexoBrid	SOC (Standard of Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: Days	1	6		

Statistical analyses

Statistical analysis title	Efficacy

Statistical analysis description:

Time until complete eschar removal was defined as the time until complete echar removal has been achieved.

Comparison groups	NexoBrid v SOC (Standard of Care)
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Wilcoxon-Gehan

Primary: Percent Wound Area Surgically Excised for Eschar Removal

End point title	Percent Wound Area Surgically Excised for Eschar Removal

End point description:

Demonstrate superiority over SOC in reduction in surgical need for excisional eschar removal as measured by an analysis of percent wound area surgically excised for eschar removal (tangential/ minor/ avulsion/ Versajet and/or dermabrasion excision).

End point type	Primary

End point timeframe:

From the time of randomization - baseline until 12-Month Follow-up.

End point values	NexoBrid	SOC (Standard of Care)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: percent wound area	2	48		

Statistical analyses

Statistical analysis title	% wound area surgically excised for eschar removal
Comparison groups	NexoBrid v SOC (Standard of Care)
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	45.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.6
upper limit	58.9
Variability estimate	Standard error of the mean
Dispersion value	6.83

Primary: Cosmesis and Function	
End point title	Cosmesis and Function
End point description:	
To demonstrate non-inferiority to SoC in quality of scars of burns (using MVSS) treated with NexoBrid, measured at 12 and 24 month from wound closure	
End point type	Primary
End point timeframe:	
Cosmesis assessment at 12-Month and 24-Month Follow-Up.	

End point values	NexoBrid	SOC (Standard of Care)	NexoBrid	SOC (Standard of Care)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	72	73	66	66
Units: MVSS score	4	5	3	4

Statistical analyses

Statistical analysis title	MVSS Regression Results 12-Month Follow-Up
Comparison groups	NexoBrid v SOC (Standard of Care)
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	2.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.85
upper limit	3.67
Variability estimate	Standard deviation
Dispersion value	0.91

Statistical analysis title	MVSS Regression Results 24- Month Follow-Up
Comparison groups	NexoBrid v SOC (Standard of Care)
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Linear
Parameter estimate	Mean difference (net)
Point estimate	2.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	3.25
Variability estimate	Standard deviation
Dispersion value	0.86

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Per protocol amendment, the extended long-term FU visit at ≥ 30M did not include documentation of AEs and SAEs that occurred after the 24M FU visit.

Adverse event reporting additional description:

For 24M FU Period, TEAEs (Treatment-Emergent Adverse Events) were analysed separately for 2 different periods:
1. Between the 12 months FU and the 24 months FU (12M-24M FU Period)
2. In the cumulative period (0-24M FU Period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	NexoBrid AE

Reporting group description:

Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Intensity – 12M-24M FU Period (SAS)

Reporting group title	SOC AE

Reporting group description: -

Serious adverse events	NexoBrid AE	SOC AE	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 69 (7.25%)	1 / 70 (1.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Withdrawal syndrome			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			

subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngospasm			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Joint contracture			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	NexoBrid AE	SOC AE	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 69 (39.13%)	30 / 70 (42.86%)	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	4 / 69 (5.80%)	6 / 70 (8.57%)	
occurrences (all)	4	6	
Pyrexia			
subjects affected / exposed	7 / 69 (10.14%)	4 / 70 (5.71%)	
occurrences (all)	7	4	
Chills			
subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	
Immune system disorders			

Seasonal allergy			
subjects affected / exposed	1 / 69 (1.45%)	1 / 70 (1.43%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Asthma			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 69 (1.45%)	2 / 70 (2.86%)	
occurrences (all)	1	2	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	2 / 69 (2.90%)	0 / 70 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 69 (2.90%)	0 / 70 (0.00%)	
occurrences (all)	2	0	
Accidental overdose			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	1 / 69 (1.45%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Wound complication			
subjects affected / exposed	6 / 69 (8.70%)	5 / 70 (7.14%)	
occurrences (all)	6	5	
Injury			

subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 69 (1.45%)	3 / 70 (4.29%)	
occurrences (all)	1	3	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 69 (1.45%)	2 / 70 (2.86%)	
occurrences (all)	1	2	
Neuralgia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 69 (0.00%)	3 / 70 (4.29%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 69 (4.35%)	1 / 70 (1.43%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	3 / 69 (4.35%)	3 / 70 (4.29%)	
occurrences (all)	3	3	
Vomiting			
subjects affected / exposed	5 / 69 (7.25%)	4 / 70 (5.71%)	
occurrences (all)	5	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 69 (5.80%)	0 / 70 (0.00%)	
occurrences (all)	4	0	
Pruritus			
subjects affected / exposed	9 / 69 (13.04%)	7 / 70 (10.00%)	
occurrences (all)	9	7	
Blister			
subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	

Bromhidrosis			
subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Joint contracture			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 69 (5.80%)	3 / 70 (4.29%)	
occurrences (all)	4	3	
Folliculitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	
Rhinovirus infection			
subjects affected / exposed	2 / 69 (2.90%)	0 / 70 (0.00%)	
occurrences (all)	2	0	
Ear infection			
subjects affected / exposed	2 / 69 (2.90%)	0 / 70 (0.00%)	
occurrences (all)	2	0	
Wound infection			
subjects affected / exposed	0 / 69 (0.00%)	2 / 70 (2.86%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2014	Protocol Version 4
08 September 2014	Protocol Version 5
02 December 2014	Protocol Version 6
28 December 2014	Protocol Version 6.01
31 December 2014	Protocol Version 6.02
02 January 2017	Protocol Version 7
28 March 2017	Protocol Version 7.01
01 June 2017	Protocol Version 7.02
26 December 2017	Protocol Version 8
29 July 2019	Protocol Version 9.01
26 August 2019	Protocol Version 9
16 November 2020	Protocol Version 10
16 November 2020	Protocol Version 10.01
16 June 2021	Protocol Version 11
16 June 2021	Protocol Version 11.01

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

17 September 2020	Study was re-submitted in Belguim due to already closed Study. A new Eudra-CT.-No needed to be used: 2022-001909-53 The site was closed on 17-Sep-2020 when all patients completed the study at site (however, in other countries the study was ongoing). Because also the authorities were informed about the site/study closure in Belgium (only 1 site participated) a new trial must be submitted and this was done on 29-Jun-2022. Site was re-initiated again on 09-Nov-2022.	09 November 2022

Notes:

Limitations and caveats

None reported