Clinical trial results:
A multicenter, multinational, randomized, controlled, assessor blinded study, performed in subjects with thermal burns, to evaluate the efficacy and safety of NexoBrid compared to Gel Vehicle and compared to Standard of Care

Summary

EudraCT number	2014-001672-55
Trial protocol	DE CZ RO LV IT
Global end of trial date	20 August 2020

Results information

Result version number	v1 (current)
This version publication date	13 November 2021
First version publication date	13 November 2021
Summary attachment (see zip file)	CSR 12 month (MW2010-03-02_CSR_20200524.pdf) CSR 24 month (NexoBrid_24M CSR_Addendum.pdf)

Trial information

Trial identification

Sponsor protocol code	MW2010-03-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02148705
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MediWound Ltd
Sponsor organisation address	42 Hayarkon Street, Yavne, Israel, 8122745
Public contact	Lior Rosenberg, MediWound Ltd, 972 779714100, liorr@mediwound.com
Scientific contact	Lior Rosenberg, MediWound Ltd, 972 779714100, liorr@mediwound.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	23 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 August 2020
Global end of trial reached?	Yes
Global end of trial date	20 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstration of safety and efficacy of NexoBrid® in removing burn eschar in hospitalized patients with deep partial thickness and full thickness thermal burn wounds.

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 May 1996 amended September 1997 and Declaration of Helsinki (as amended in Seoul, October 2008), concerning medical research in humans. 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, SOC or Gel vehicle) except for the eschar removal stage which will be performed as per the randomization study arm.
Prior to initiation of eschar removal treatment subjects will be medicated with appropriate analgesia and undergo wound cleansing and dressing of all wounds with antibacterial solutions. Following wound cleansing and antibacterial treatments, subjects will undergo the eschar removal process as per treatment assignment (NexoBrid, SOC or Gel Vehicle, following randomization).
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 daily vital signs and pain assessments, until hospital discharge (HD) and weekly assessments of wound progress, until wound closure.

Evidence for comparator:

Comparators: Standard of Card (SOC) and Gel Vehicle (Collagenase Santyl®):

Eschar removal is considered a critical initial stage of the comprehensive wound care process. Early (ie, within 1 to 2 days/before the onset of inflammation) and rapid debridement of eschar is essential to initiate body’s own wound healing process, to allow clinical visual evaluation of burn severity and depth, preserve viable tissue, and prevent further complications.

The SOC for burn eschar removal relies primarily on surgical tangential excision to mechanically remove the eschar. According to 1 estimate, these nonselective methods are estimated to excise tissue that consists of 30% to 50% viable dermal tissue, thereby increasing the surface area needed for autografting along with increased risk of scar formation and functional compromise.

Alternatively, physicians can use a nonsurgical debridement, which includes collagenase ointment (Collagenase Santyl®), antimicrobial agents such as silver sulfadiazine (SSD), or various hydrogels which result in a lengthy sloughing period. Collagenase Santyl ointment is a licensed, nonsurgical debridement product that currently exists on the US market.

Actual start date of recruitment	01 January 2015
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: 98
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Georgia: 11
Worldwide total number of subjects	175
EEA total number of subjects	64

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	159
From 65 to 84 years	16
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	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

For patients who were randomized to one of the topical treatment arms, NexoBrid or Gel Vehicle, eschar removal assessment was performed by an assessor blinded to the treatment arm. The eschar removal assessment was performed by an individual who was not involved in the treatment of the patient or wound, as the treating physician could distinguish between treatments administered to each patient. For the purpose of standardization, if feasible, the same blinded assessor was assigned at each center

Arms

Are arms mutually exclusive?	Yes
Arm title	NexoBrid

Arm description:

NexoBrid is presented as lyophilised Bromelain powder and gel vehicle for preparation of a gel for cutaneous use, including concentrate of proteolytic enzymes enriched in Bromelain as the active component. 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:

2 or 5 g of NexoBrid sterile powder was mixed in 20 or 50 g of sterile Gel Vehicle (ratio of 1:10), NexoBrid was applied to the burn wound at a dose of 2 g NexoBrid sterile powder mixed with 20 g sterile Gel Vehicle per 1% of TBSA (~ surface of an adult palm) for 4 hours (or 5 g NexoBrid sterile powder mixed with 50 g sterile Gel Vehicle per 2.5% of TBSA). The NexoBrid powder and the Gel Vehicle were mixed at the patient's bedside ≤15 minutes prior to use.

Arm title	SOC (Standard of Care)

Arm description:

Standard of care. Includes surgical and/or non surgical eschar remomal 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	Cutaneous use, Topical use

Dosage and administration details:

SOC arm will include surgical and/or non-surgical eschar removal procedures.
Surgical procedures will include tangential/ minor/ avulsion/ Versajet/ dermabrasion excisions. Non-surgical procedures will include the application of (collagenase ointment (e.g. Santyl), 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).
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.

Arm title	Gel Vehicle

Arm description:

Gel Vehicle will be applied on the burn skin.

Arm type	Placebo
Investigational medicinal product name	Gel Vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Cutaneous use

Dosage and administration details:

Twenty (20) grams or 50 grams of sterile Gel Vehicle will be applied on the burn skin. Gel Vehicle is applied to the burn wound at a dose of 20 grams sterile Gel per 1% of TBSA (~ surface of an adult palm) or 50 grams per 2.5% TBSA for four hours.
Gel Vehicle may be applied for a second time to the same burn area, if eschar removal from the target wound after the first application is not complete but at least 50% of the eschar was removed during the first application. The Gel Vehicle may only be applied twice to the same burn wound area.
Gel Vehicle should not be applied to more than 15% TBSA (±3% TBSA) in one session.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: For patients who were randomized to 1 of the topical treatment arms, NexoBrid or Gel Vehicle, escharremoval assessment was performed by an assessor blinded to the treatment arm. The eschar removal assessment was performed by an individual who was not involved in the treatment of the patient orwound, as the treating physician could distinguish between treatments administered to each patient.

Number of subjects in period 1	NexoBrid	SOC (Standard of Care)	Gel Vehicle
Started	75	75	25
First stage	67	63	23
Second stage	56	58	20
Third stage	43	36	10
Completed	43	36	10
Not completed	32	39	15
Adverse event, serious fatal	2	-	-
Consent withdrawn by subject	4	8	-
Subject received no study drug treatment	-	1	-
Patient withdrew due to relocation	-	1	-
Pregnancy	-	1	-
Lost to follow-up	24	27	13
Patient in incarcerated	-	1	-
Jail	1	-	-
Left country	1	-	-
Site closure	-	-	1

Not treated	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	NexoBrid
Reporting group description:	
NexoBrid is presented as lyophilised Bromelain powder and gel vehicle for preparation of a gel for cutaneous use, including concentrate of proteolytic enzymes enriched in Bromelain as the active component. 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 remomal procedures.	
Reporting group title	Gel Vehicle
Reporting group description:	
Gel Vehicle will be applied on the burn skin.	

Reporting group values	NexoBrid	SOC (Standard of Care)	Gel Vehicle
Number of subjects	75	75	25
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	69	69	21
From 65-84 years	6	6	4
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	26	16	10
Male	49	59	15

Reporting group values	Total		
Number of subjects	175		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	159		
From 65-84 years	16		

85 years and over	0		

Gender categorical Units: Subjects			
Female	52		
Male	123		

End points

End points reporting groups

Reporting group title	NexoBrid

Reporting group description:

NexoBrid is presented as lyophilised Bromelain powder and gel vehicle for preparation of a gel for cutaneous use, including concentrate of proteolytic enzymes enriched in Bromelain as the active component. 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 remomal procedures.

Reporting group title	Gel Vehicle

Reporting group description:

Gel Vehicle will be applied on the burn skin.

Subject analysis set title	Full analysis set including only NexoBrid and Gel Vehicle trea
Subject analysis set type	Full analysis

Subject analysis set description:

Subset of the FAS including only NexoBrid and Gel Vehicle treatment arms

Primary: Incidence of Complete Eschar Removal

End point title	Incidence of Complete Eschar Removal[1]

End point description:

The primary efficacy endpoint was analyzed using a subset of the FAS including only NexoBrid and Gel Vehicle treatment arms. The main analysis was based on the binary variable (yes/no): "has complete eschar removal been achieved in all TWs" and compared NexoBrid with the Gel Vehicle.

End point type	Primary

End point timeframe:

Stage 1: Acute Phase – baseline to 3 months after wound closure

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Following the goal to seek an indication for NexoBrid that focuses on non surgical eschar removal, this primary endpoint will assess whether non-surgical eschar removal by NexoBrid allows effective removal of the offending eschar compared with its comparator.

End point values	NexoBrid	Gel Vehicle	Full analysis set including only NexoBrid and Gel Vehicle trea	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	75	25	100	
Units: Patients	75	25	100	

Statistical analyses

Statistical analysis title	Primary Endpoint

Statistical analysis description:

The primary efficacy endpoint was analyzed using a subset of the FAS including only NexoBrid and Gel Vehicle treatment arms. The main analysis was based on the binary variable (yes/no): "has complete

eschar removal been achieved in all TWs” and compared NexoBrid with the Gel Vehicle.

Comparison groups	NexoBrid v Gel Vehicle
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	288.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	35.549
upper limit	13984.356

Notes:

[2] - Demonstrate the superiority of NexoBrid treatment over Gel Vehicle

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All stages: from study start to study termination	
Adverse event reporting additional description:	
Adverse event data is based on CRF data entry	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	SOC AE
Reporting group description:	
The analysis of AEs was based on the Safety Analysis Set consisting of 68 patients treated with SOC	
Reporting group title	Gel Vehicle AE
Reporting group description:	
The analysis of AEs was based on the Safety Analysis Set consisting of 24 patients treated with Gel Vehicle	
Reporting group title	NexoBrid AE
Reporting group description:	
The analysis of AEs was based on the Safety Analysis Set consisting of 77 patients treated with NexoBrid.	

Serious adverse events	SOC AE	Gel Vehicle AE	NexoBrid AE
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 68 (13.24%)	3 / 24 (12.50%)	10 / 77 (12.99%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity	Additional description: Preferred Term		

subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Phlebitis superficial	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholecystectomy	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eventration repair	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal fixation of fracture	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Therapeutic procedure	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Failure to thrive	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Death	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chest pain	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion site thrombosis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neonatal respiratory failure	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient tachypnoea of the newborn	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Graft loss	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital tricuspid valve incompetence	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngomalacia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patent ductus arteriosus	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persistent foetal circulation	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular septal defect	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trisomy 21	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome	Additional description: Prefererred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bifascicular block	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Cerebral ventricle dilatation	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Appendicitis noninfective	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection bacterial	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	3 / 77 (3.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic metabolic decompensation	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	SOC AE	Gel Vehicle AE	NexoBrid AE
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 68 (60.29%)	15 / 24 (62.50%)	49 / 77 (63.64%)
Vascular disorders			
Arterial thrombosis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Extremity necrosis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Haemorrhage	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Hypertension	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
Hypotension	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Phlebitis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Phlebitis superficial	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Varicose vein	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Colon operation	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Wound drainage	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			

Asthenia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Cyst	Additional description: Prferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Hyperthermia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Pain	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	0 / 24 (0.00%)	6 / 77 (7.79%)
occurrences (all)	2	0	11
Hypothermia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Pyrexia	Additional description: Preferred Term		
subjects affected / exposed	6 / 68 (8.82%)	2 / 24 (8.33%)	6 / 77 (7.79%)
occurrences (all)	8	3	7
Peripheral swelling	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to arthropod sting	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Drug hypersensitivity	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Dyspnoea	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Increased viscosity of bronchial secretion	Additional description: Preferred Term		

subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Laryngospasm	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Pulmonary oedema	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Adjustment disorder	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Agitation	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Alcoholism	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Drug dependence	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Anxiety	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Depression	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Insomnia	Additional description: Preferred Term		
subjects affected / exposed	4 / 68 (5.88%)	1 / 24 (4.17%)	4 / 77 (5.19%)
occurrences (all)	4	1	4
Emotional distress	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1

Major depression	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Panic disorder	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Mental status changes	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Substance use disorder	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Post-traumatic stress disorder	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Sleep disorder	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Suicide attempt	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Investigations			
Bacterial test	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Bacterial test positive	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Body temperature increased	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
C-reactive protein increased	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Haemoglobin decreased	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased	Additional description: Prferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Lymphocyte count decreased	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	2 / 24 (8.33%)	1 / 77 (1.30%)
occurrences (all)	0	2	1
Inflammatory marker increased	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
White blood cell count increased	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accidental overdose	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Contusion	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Craniocerebral injury	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Graft loss	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	1 / 24 (4.17%)	3 / 77 (3.90%)
occurrences (all)	2	1	4
Hand fracture	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Incisional hernia	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Intentional overdose	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Limb injury	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Muscle strain	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Paravenous drug administration	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Post procedural haemorrhage	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Post-traumatic pain	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Skin abrasion	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Skin graft failure	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Skin laceration	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Subcutaneous haematoma	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Sunburn	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Wound complication	Additional description: Preferred Term		

subjects affected / exposed	2 / 68 (2.94%)	0 / 24 (0.00%)	3 / 77 (3.90%)
occurrences (all)	3	0	3
Thermal burn	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Cardiac disorders			
Sinus tachycardia	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Tachycardia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	5 / 77 (6.49%)
occurrences (all)	0	0	5
Nervous system disorders			
Dizziness	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Cervical radiculopathy	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Headache	Additional description: Preferred Term		
subjects affected / exposed	3 / 68 (4.41%)	3 / 24 (12.50%)	3 / 77 (3.90%)
occurrences (all)	3	3	7
Seizure	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Leukocytosis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	4
Thrombocytosis	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1
Haemorrhagic anaemia	Additional description: Preferred Term		

subjects affected / exposed	2 / 68 (2.94%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Ear and labyrinth disorders			
Tinnitus	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Ascites	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Constipation	Additional description: Preferred Term		
subjects affected / exposed	7 / 68 (10.29%)	2 / 24 (8.33%)	4 / 77 (5.19%)
occurrences (all)	7	2	4
Diarrhoea	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Dyspepsia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Gastritis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Melaena	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Nausea	Additional description: Preferred Term		
subjects affected / exposed	6 / 68 (8.82%)	4 / 24 (16.67%)	5 / 77 (6.49%)
occurrences (all)	6	4	5
Tooth loss	Additional description: Preferred Term		

subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Vomiting	Additional description: Preferred Term		
subjects affected / exposed	3 / 68 (4.41%)	1 / 24 (4.17%)	5 / 77 (6.49%)
occurrences (all)	4	1	5
Skin and subcutaneous tissue disorders			
Dermatitis contact	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Erythema	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Hypertrophic scar	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Milia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Rash	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	4
Skin lesion	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Skin warm	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Acute kidney injury	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Urinary retention	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Renal failure	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Preferred Term		
subjects affected / exposed	2 / 68 (2.94%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	4	0	2
Arthritis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Arthralgia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Extremity contracture	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Joint contracture	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Costochondritis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Muscle spasms	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Joint range of motion decreased	Additional description: Preferred Term		
subjects affected / exposed	5 / 68 (7.35%)	4 / 24 (16.67%)	3 / 77 (3.90%)
occurrences (all)	30	21	8
Neck pain	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Myalgia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Pain in extremity	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	3 / 77 (3.90%)
occurrences (all)	0	1	3
Osteoarthritis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
Spinal pain	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Temporomandibular joint syndrome	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Periarthritis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Infections and infestations			
Bacterial infection	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Abscess jaw	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Bronchitis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Candida infection	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Cellulitis	Additional description: Preferred Term		
subjects affected / exposed	4 / 68 (5.88%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	4	0	1
Ear infection	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Folliculitis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	1 / 24 (4.17%)	2 / 77 (2.60%)
occurrences (all)	1	1	4

Fungal skin infection	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Gastrointestinal viral infection	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Herpes zoster	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Hordeolum	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Influenza	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	1 / 24 (4.17%)	2 / 77 (2.60%)
occurrences (all)	4	1	2
Otitis media	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Pneumonia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Rhinitis	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	1 / 24 (4.17%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Sepsis	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Septic arthritis staphylococcal	Additional description: Prferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Sinusitis	Additional description: Preferred Term		
subjects affected / exposed	3 / 68 (4.41%)	1 / 24 (4.17%)	1 / 77 (1.30%)
occurrences (all)	4	1	1

Subcutaneous abscess	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Staphylococcal skin infection	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Tooth abscess	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Wound infection	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	3 / 77 (3.90%)
occurrences (all)	1	0	3
Urinary tract infection	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	4 / 77 (5.19%)
occurrences (all)	1	0	5
Wound infection bacterial	Additional description: Preferred Term		
subjects affected / exposed	4 / 68 (5.88%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	4	0	3
Wound infection staphylococcal	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Wound infection fungal	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Bacterial disease carrier	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Diabetes mellitus	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Dehydration	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Hyperkalaemia	Additional description: Preferred Term		

subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Hypoalbuminaemia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia	Additional description: Preferred Term		
subjects affected / exposed	1 / 68 (1.47%)	0 / 24 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	1 / 24 (4.17%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Malnutrition	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Vitamin D deficiency	Additional description: Preferred Term		
subjects affected / exposed	0 / 68 (0.00%)	0 / 24 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	Protocol Version 7
22 February 2015	Protocol Version 8
12 August 2015	Protocol Version 9
23 June 2016	Protocol Version 11

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported