Clinical trial results:
A Phase 3, Multi-centre, Randomised, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa

Summary

EudraCT number	2014-002288-14
Trial protocol	AT NL GB IT DE PL ES LT BE
Global end of trial date	05 July 2017

Results information

Result version number	v1 (current)
This version publication date	12 July 2018
First version publication date	12 July 2018

Trial information

Trial identification

Sponsor protocol code	SD-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02384460
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Scioderm, Inc., An Amicus Therapeutics Company
Sponsor organisation address	1 Cedar Brook Drive, Cranbury, United States, NJ 08512
Public contact	Patient Advocacy, Amicus Therapeutics, Inc, clinicaltrials@amicusrx.com
Scientific contact	Patient Advocacy, Amicus Therapeutics, Inc, clinicaltrials@amicusrx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001590-PIP01-13
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	05 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 July 2017
Global end of trial reached?	Yes
Global end of trial date	05 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the efficacy and safety of SD-101-6.0 versus SD-101-0.0 (placebo) in subjects with simplex, recessive dystrophic, or junctional non-Herlitz epidermolysis bullosa (EB).

Protection of trial subjects:

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice, as required by the major regulatory authorities and in accordance with the Declaration of Helsinki and its updates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Lithuania: 4
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	United States: 60
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Israel: 6
Worldwide total number of subjects	169
EEA total number of subjects	76

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)	11
Children (2-11 years)	84
Adolescents (12-17 years)	31
Adults (18-64 years)	42
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 210 subjects screened for this study, 169 subjects were randomly assigned, on a 1:1 basis, to treatment with SD-101-6.0 or placebo at 31 study centres in 13 countries. The first subject was enrolled on 11 March 2015 and the last subject completed the study on 05 July 2017.

Pre-assignment

Screening details:

Subjects had to be 1 month of age or older with a diagnosis of simplex, recessive dystrophic, or junctional non-Herlitz EB and a target wound with a surface area of 10 to 50 cm^2 in size and at least 21 days old to be considered for participation in the study. Subjects who did not meet all inclusion/exclusion criteria were eligible for rescreening.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All study centre personnel, subjects, and the sponsor were blinded to study drug assignment. Tubes of study drug were identical and SD-101-6.0 and SD-101-0.0 (placebo) were indistinguishable with regard to appearance, smell, and sensation.

Arms

Are arms mutually exclusive?	Yes
Arm title	SD-101-6.0

Arm description:

Subjects applied SD-101-6.0 cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.

Arm type	Experimental
Investigational medicinal product name	SD-101-6.0
Investigational medicinal product code	
Other name	Allantoin 6% concentration, Zorblisa
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

SD-101 is a white, crystalline powder that is formulated within an odourless, soft, white cream base. SD-101-6.0 cream contains allantoin, a diureide glyoxlylic acid, at a concentration of 6% and other excipients. Subjects applied the cream topically, once a day to the entire body.

Arm title	Placebo

Arm description:

Subjects applied SD-101-0.0 (placebo) cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.

Arm type	Placebo
Investigational medicinal product name	SD-101-0.0
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

SD-101 is a white, crystalline powder that is formulated within an odourless, soft, white cream base. SD-101-0.0 (placebo) cream contains no allantoin, but otherwise contains the same excipients as SD-101-6.0. Subjects applied the cream topically, once a day to the entire body.

Number of subjects in period 1	SD-101-6.0	Placebo
Started	82	87
Completed	75	80
Not completed	7	7
Other: elective medical treatment	1	-
Consent withdrawn by subject	-	3
Adverse event, non-fatal	5	2
Other: non compliance	1	-
Other: returned to previous therapeutic regimen	-	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	SD-101-6.0
Reporting group description:	
Subjects applied SD-101-6.0 cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.	
Reporting group title	Placebo
Reporting group description:	
Subjects applied SD-101-0.0 (placebo) cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.	

Reporting group values	SD-101-6.0	Placebo	Total
Number of subjects	82	87	169
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)	5	6	11
Children (2-11 years)	37	47	84
Adolescents (12-17 years)	19	12	31
Adults (18-64 years)	21	21	42
From 65-84 years	0	1	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	13.8	13.9	
standard deviation	± 13.15	± 13.12	-
Gender categorical Units: Subjects			
Female	33	48	81
Male	49	39	88
Race Units: Subjects			
White/Caucasian	69	72	141
Black/African American	5	3	8
Asian	4	8	12
Other	1	1	2
Not Reported	3	3	6
EB type Units: Subjects			
Simplex	10	8	18
Recessive dystrophic	57	62	119
Junctional non-Herlitz	15	17	32

End points

End points reporting groups

Reporting group title	SD-101-6.0

Reporting group description:

Subjects applied SD-101-6.0 cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.

Reporting group title	Placebo

Reporting group description:

Subjects applied SD-101-0.0 (placebo) cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.

Primary: Time to Complete Target Wound Closure Within 3 Months.

End point title	Time to Complete Target Wound Closure Within 3 Months.

End point description:

Target wounds were monitored at each study visit for complete closure, defined as skin re-epithelialisation without drainage. Time to target wound closure was measured from the date of the first administration of the study drug to the date of target wound closure. Subjects were censored if they did not have a response within 3 months, or withdrew earlier before the confirmation of their target wound closing.

This primary end point displays the mean time to complete target wound closure, analysed using a Kaplan-Meier approach. Analysis was performed on subjects from the intent-to-treat (ITT) population with post-baseline wound closure data and whose target wound had closed within 3 months.

End point type	Primary

End point timeframe:

From baseline to Month 3 visit

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39[1]	45[2]		
Units: Days				
arithmetic mean (standard deviation)	41.6 (± 25.50)	53.6 (± 28.59)		

Notes:

[1] - Number of subjects analysed were those whose target wound had closed within 3 months.

[2] - Number of subjects analysed were those whose target wound had closed within 3 months.

Statistical analyses

Statistical analysis title	Cox Model Analysis

Statistical analysis description:

Cox proportional hazards model compares treatment groups with baseline target wound size, target wound age and EB type as covariates.

Comparison groups	SD-101-6.0 v Placebo

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.985 [3]
Method	Cox Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.651
upper limit	1.549

Notes:

[3] - p-value is from Type 3 tests to present as overall p-value for each term in the model.

Primary: Percentage of Subjects Experiencing Complete Closure of The Target Wound Within 3 Months

End point title	Percentage of Subjects Experiencing Complete Closure of The Target Wound Within 3 Months

End point description:

Target wounds were monitored at each study visit for complete closure, defined as skin re-epithelialisation without drainage. Subjects were considered responders if they experienced complete wound closure at the Week 2 or Months 1, 2, or 3 visits. If a target wound was documented to have closed at a given visit, it was considered closed at all subsequent visits.

This primary end point displays the percentage of subjects from the ITT population who had complete target wound closure by the end of the study period (i.e. 3 months). Analysis was performed on subjects with post-baseline wound closure data.

End point type	Primary

End point timeframe:

From baseline to Month 3 visit

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	84		
Units: Percentage of Subjects				
number (not applicable)	49.4	53.6		

Statistical analyses

Statistical analysis title	Logistic Regression Analysis

Statistical analysis description:

Comparison between treatment groups of complete closure of target wound within 3 months was performed using logisitic regression modelling with multiple imputation.

Comparison groups	SD-101-6.0 v Placebo

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.39 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.733
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.365
upper limit	1.474

Notes:

[4] - Multiple imputation is implemented by two steps. First step using Markov Chain Monte Carlo (MCMC) to get monotonic missing data pattern. In second step, a logistic regression model is used, with the following covariates included in the imputation model: treatment, EB type, baseline target wound size, target wound age, and non-missing data from earlier time points. The seed number is 010005 and the number of imputations is 5.
[5] - p-value is from Type 3 tests to present as overall p-value for each term in the model

Secondary: Percentage of Subjects Experiencing Complete Closure of The Target Wound at Month 1 and Month 2 Visits

End point title	Percentage of Subjects Experiencing Complete Closure of The Target Wound at Month 1 and Month 2 Visits

End point description:

Target wounds were monitored at each study visit for complete closure, defined as skin re-epithelialisation without drainage. The percentage of subjects who completed target wound closure at the Month 1 and Month 2 study visits is displayed. If a target wound was documented to have closed at a given visit, it was considered closed at all subsequent visits. Analysis was performed on subjects from the ITT population with post-baseline wound closure data.

End point type	Secondary

End point timeframe:

From baseline to Month 1 and Month 2 visits

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	84		
Units: Percentage of Subjects				
number (not applicable)				
Month 1	31.6	22.6		
Month 2	43.0	42.9		

Statistical analyses

Statistical analysis title	Logistic Regression Analysis at Month 1

Statistical analysis description:

Comparison between treatment groups of complete closure of target wound within 1 month was performed using logisitic regression modelling with multiple imputation.

Comparison groups	SD-101-6.0 v Placebo

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.212 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.633
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.758
upper limit	3.517

Notes:

[6] - Multiple imputation is implemented by two steps. First step using MCMC to get monotonic missing data pattern. In second step, a logistic regression model is used, with the following covariates included in the imputation model: treatment, EB type, baseline target wound size, target wound age, and non-missing data from earlier time points. The seed number is 010005 and the number of imputations is 5.

[7] - p-value is from Type 3 tests to present as overall p-value for each term in the model

Statistical analysis title	Logistic Regression Analysis at Month 2

Statistical analysis description:

Comparison between treatment groups of complete closure of target wound within 2 months was performed using logisitic regression modelling with multiple imputation.

Comparison groups	SD-101-6.0 v Placebo
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.802 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.891
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.436
upper limit	1.821

Notes:

[8] - Multiple imputation is implemented by two steps. First step using MCMC to get monotonic missing data pattern. In second step, a logistic regression model is used, with the following covariates included in the imputation model: treatment, EB type, baseline target wound size, target wound age, and non-missing data from earlier time points. The seed number is 010005 and the number of imputations is 5.

[9] - p-value is from Type 3 tests to present as overall p-value for each term in the model

Secondary: Change from Baseline in Body Surface Area Index (BSAI) of Lesional Skin at Month 3 Visit

End point title	Change from Baseline in Body Surface Area Index (BSAI) of Lesional Skin at Month 3 Visit

End point description:

Lesional skin was defined as areas that contained any of the following: blisters, erosions, ulcerations, scabbing, bullae, or eschars, as well as areas that were weeping, sloughing, oozing, crusted, or denuded. BSAI was calculated as a percentage, ranging from 0% to 100%, of affected body surface area, recorded for each defined body region (ie, head/neck, upper limbs, trunk [includes groin], and lower limbs), multiplied by the weighting factor, then summed for all body regions. Analysis was performed on the ITT population.

End point type	Secondary

End point timeframe:
From baseline to Month 3 visit

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	78		
Units: Percentage of BSAI				
least squares mean (standard error)	-4.637 (± 1.404)	-5.319 (± 1.354)		

Statistical analyses

Statistical analysis title	Mixed Model Repeated Measures (MMRM) Analysis

Statistical analysis description:

The MMRM approach (using restricted maximum likelihood [REML] estimation) is used on each multiply-imputed data set. The model includes treatment, baseline BSAI of lesional skin, EB type, visit, and visit-treatment interaction as the fixed effects.

Comparison groups	SD-101-6.0 v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.706 [11]
Method	Mixed models analysis
Parameter estimate	Least squares (LS) mean difference
Point estimate	0.682
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.873
upper limit	4.238

Notes:

[10] - Multiple imputation is used by two steps. First step using MCMC to get monotonic missing data pattern. In second step, a linear regression model is used, with the following covariates included in the imputation model: treatment, EB type, baseline BSAI of lesional skin, and non-missing data from earlier time points. The seed number is 010005 and the number of imputations is 5.

[11] - The p-value is calculated based on the hypothesis testing for the difference of LS-means between treatment and placebo.

Secondary: Change from Baseline in BSAI of Total Body Wound Burden at Month 3 Visit

End point title	Change from Baseline in BSAI of Total Body Wound Burden at Month 3 Visit

End point description:

Total body wound burden was calculated using BSAI. A wound was defined as an open area on the skin (ie, epidermal covering disrupted). BSAI was calculated as a percentage, ranging from 0% to 100%, of affected body surface area, recorded for each defined body region (ie, head/neck, upper limbs, lower limbs,trunk [includes groin], and multiplied by the weighting factor, then summed for all body regions. Analysis was performed on the ITT population.

End point type	Secondary

End point timeframe:
From baseline to Month 3 visit

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	79		
Units: Percentage of BSAI				
least squares mean (standard error)	-3.050 (± 0.816)	-2.922 (± 0.813)		

Statistical analyses

Statistical analysis title	MMRM Analysis

Statistical analysis description:

The MMRM approach (using REML estimation) is used on each multiply-imputed data set. The model includes treatment, baseline BSAI of lesional skin, EB type, visit, and visit-treatment interaction as the fixed effects.

Comparison groups	SD-101-6.0 v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.9 [13]
Method	Mixed models analysis
Parameter estimate	LS mean difference
Point estimate	-0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.116
upper limit	1.861

Notes:

[12] - Multiple imputation is used by two steps. First step using MCMC to get monotonic missing data pattern. In second step, a linear regression model is used, with the following covariates included in the imputation model: treatment, EB type, baseline BSAI of lesional skin, and non-missing data from earlier time points. The seed number is 010005 and the number of imputations is 5.

[13] - The p-value is calculated based on the hypothesis testing for the difference of LS-means between treatment and placebo.

Secondary: Change from Baseline in Itching Score at Day 7

End point title	Change from Baseline in Itching Score at Day 7

End point description:

Itching was assessed using the 5 point Itch Man Pruritus Assessment Tool. For subjects up to 5 years of age itching was assessed using caretaker's response and subjects 6 years of age and older self-reported their itching assessments based on the following scores: 0=Comfortable, no itch, 1=itches a little, does not interfere with activity, 2=itches more, sometimes interferes with activity, 3=itches a lot, difficult to be still, concentrate, 4=itches most terribly, impossible to sit still or concentrate. Itching scores were categorised into three groups based on improvement: Improved or No Itching, Not Improved, and Missing. An itching score reduction from baseline greater than or equal to 1 point on the scale was classed as improved. Analysis was performed on the ITT population.

End point type	Secondary

End point timeframe:
From baseline to Day 7

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	79		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.5 (± 1.31)	-0.3 (± 1.24)		

Statistical analyses

Statistical analysis title	Logistic Regression Analysis

Statistical analysis description:

The proportion of subjects experiencing improvement in itching versus non-improvement (including missing) was compared between the two treatment groups for Day 7 using the logistic regression model with baseline itching score, and EB type as covariates.

Comparison groups	SD-101-6.0 v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.262 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.445
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.759
upper limit	2.752

Notes:

[14] - p-value is from Type 3 Tests to present as overall p-value for each term in the model.

Secondary: Change from Baseline in Pain Score at Day 7

End point title	Change from Baseline in Pain Score at Day 7

End point description:

Change in pain assessed at Day 7, compared to baseline was measured using the Face, Legs, Activity, Cry, Consolability (FLACC) Behavioural Scale for subjects 1 month to 3 years of age. Each of the five FLACC categories is scored from 0-2, which results in a total score between 0 and 10 with 0=Relaxed and comfortable, 1-3=Mild discomfort, 4-6=Moderate pain and 7-10=Severe discomfort/pain. For Subjects 4 years of age and older the “Wong Faces Pain Scale” was used. This scale shows a series of faces ranging from a happy face at 0 which represents "no hurt" to a crying face at 10 which represents "hurts worst".
Pain scores were categorised into three groups based on improvement: Improved or No Pain, Not Improved, and Missing. A pain score reduction from baseline greater than or equal to 2 points on the scale was classed as improved. Analysis was performed on the ITT population.

End point type	Secondary

End point timeframe:

From baseline to Day 7

End point values	SD-101-6.0	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	80		
Units: Units on a scale				
arithmetic mean (standard deviation)	-0.3 (± 2.57)	-0.6 (± 3.07)		

Statistical analyses

Statistical analysis title	Logistic Regression Analysis

Statistical analysis description:

The proportion of subjects experiencing improvement in pain versus non-improvement (including missing) was compared between the two treatment groups for Day 7 using the logistic regression model with baseline pain score, and EB type as covariates.

Comparison groups	SD-101-6.0 v Placebo
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.098 [15]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.596
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.323
upper limit	1.1

Notes:

[15] - p-value is from Type 3 Tests to present as overall p-value for each term in the model.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 3 months.

Adverse event reporting additional description:

Adverse events (AE) were defined as treatment emergent (TEAEs) if the AE occurred on or after the first date of application of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SD-101-6.0

Reporting group description:

Subjects applied SD-101-6.0 cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.

Reporting group title	Placebo

Reporting group description:

Subjects applied SD-101-0.0 (placebo) cream once a day for a period of 90 days. The first study drug treatment was applied at the study centre after randomisation and completion of baseline assessments. Efficacy measurements and safety assessments were carried out at study visits at Week 2 and Months 1, 2 and 3.

Serious adverse events	SD-101-6.0	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 82 (4.88%)	8 / 87 (9.20%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	1 / 82 (1.22%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Cardiopulmonary failure			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 82 (2.44%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
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			
Acute respiratory failure			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Aggression			

subjects affected / exposed	1 / 82 (1.22%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 82 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 82 (0.00%)	1 / 87 (1.15%)	
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: 2 %

Non-serious adverse events	SD-101-6.0	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 82 (59.76%)	46 / 87 (52.87%)	
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	2 / 82 (2.44%)	3 / 87 (3.45%)	
occurrences (all)	2	3	
Fall			
subjects affected / exposed	3 / 82 (3.66%)	1 / 87 (1.15%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 82 (3.66%)	2 / 87 (2.30%)	
occurrences (all)	3	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 82 (6.10%)	9 / 87 (10.34%)	
occurrences (all)	6	12	
Pain			
subjects affected / exposed	1 / 82 (1.22%)	4 / 87 (4.60%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 82 (2.44%)	2 / 87 (2.30%)	
occurrences (all)	3	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 82 (4.88%)	4 / 87 (4.60%)	
occurrences (all)	4	6	
Rhinorrhoea			
subjects affected / exposed	2 / 82 (2.44%)	4 / 87 (4.60%)	
occurrences (all)	2	5	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 82 (10.98%)	8 / 87 (9.20%)	
occurrences (all)	11	8	
Blister			

subjects affected / exposed	3 / 82 (3.66%)	2 / 87 (2.30%)	
occurrences (all)	3	3	
Rash			
subjects affected / exposed	2 / 82 (2.44%)	3 / 87 (3.45%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	2 / 82 (2.44%)	2 / 87 (2.30%)	
occurrences (all)	2	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 82 (13.41%)	3 / 87 (3.45%)	
occurrences (all)	12	3	
Upper respiratory tract infection			
subjects affected / exposed	4 / 82 (4.88%)	9 / 87 (10.34%)	
occurrences (all)	5	11	
Skin infection			
subjects affected / exposed	3 / 82 (3.66%)	9 / 87 (10.34%)	
occurrences (all)	5	11	
Wound infection			
subjects affected / exposed	6 / 82 (7.32%)	5 / 87 (5.75%)	
occurrences (all)	8	5	
Staphylococcal skin infection			
subjects affected / exposed	1 / 82 (1.22%)	6 / 87 (6.90%)	
occurrences (all)	1	7	
Ear infection			
subjects affected / exposed	1 / 82 (1.22%)	4 / 87 (4.60%)	
occurrences (all)	1	4	
Pharyngitis			
subjects affected / exposed	1 / 82 (1.22%)	4 / 87 (4.60%)	
occurrences (all)	1	4	
Skin bacterial infection			
subjects affected / exposed	1 / 82 (1.22%)	4 / 87 (4.60%)	
occurrences (all)	1	5	
Wound infection staphylococcal			

subjects affected / exposed occurrences (all)	1 / 82 (1.22%) 1	4 / 87 (4.60%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2014	• The primary efficacy endpoint was clarified to be complete closure of the target wound within 2 months. • Median time to complete target wound closure was added as a secondary efficacy endpoint. • Some secondary efficacy endpoints were re-categorised. • Sample size was increased from 90 subjects to 130 subjects and the number of study centres was increased from 10 to 15. • The option to enter Study SD-006, extension study, was added. • The minimum target lesion size specified was increased from 5 cm^2 to 10 cm^2 based on results from Study SD-003. • Investigator responsibilities for reporting Serious AEs was added at the request of a European regulatory agency. •A statement indicating that a draft statistical analysis plan (SAP) would be completed before randomisation of the first subject was added, as requested by Food and Drugs Administration (FDA). • Regulatory requirements were broadened to include those that are applicable outside the United States, at the request of European regulatory agencies.
19 September 2016	• The single primary endpoint (i.e, complete target wound closure within 2 months) was revised to be 2 co-primary efficacy endpoints: the time to complete target wound closure within 3 months and the proportion of subjects experiencing complete target wound closure within 3 months. • Estimation of total body wound burden was re-categorised from an exploratory efficacy endpoint to be a secondary efficacy endpoint. • Secondary efficacy endpoints were added to capture the proportion of subjects experiencing complete target wound closure within 2 months and 1 month. • Exploratory efficacy endpoints were added to capture percentage change from baseline in total body wound burden and lesional skin based on BSAI at additional time points. • Enrollment was changed from approximately 130 subjects to up to 150 subjects to allow for 2 potential interim analyses after ~90 and ~125 subjects were enrolled. • Statistical methods were modified to support the evaluation of co-primary and secondary endpoints in a step-down procedure while controlling the type I error rate and addressing multiplicity.
10 March 2017	• Co-primary efficacy endpoints were renamed as 2 primary efficacy endpoints for consistency with the SAP in response to comments from FDA. Secondary efficacy endpoints were renamed as key secondary efficacy endpoints, and exploratory endpoints were renamed as other secondary efficacy endpoints. • Other secondary efficacy endpoints were re-ordered to reflect the SAP and change in target wound characteristics was added as another secondary efficacy endpoint. • The interim analyses were omitted because enrollment increased and it was no longer considered necessary.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported