Clinical trial results:
A Study in Patients with Hard-to-Heal Venous Leg Ulcers to Measure Efficacy and Safety of Locally Administered LL-37; A Phase IIb, Double-blind, Randomised, Placebo-controlled, Multi-centre Trial

Summary

EudraCT number	2018-000536-10
Trial protocol	PL
Global end of trial date	13 July 2020

Results information

Result version number	v1 (current)
This version publication date	26 July 2021
First version publication date	26 July 2021

Trial information

Trial identification

Sponsor protocol code	LL-37002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Promore Pharma AB
Sponsor organisation address	Karolinska Institutet Science Park Fogdevreten 2 , Stockholm, Sweden, SE-171 65
Public contact	Margit Mahlapuu Chief Scientific Officer, Promore Pharma AB, +46 706310109, margit.mahlapuu@promorepharma.com
Scientific contact	Margit Mahlapuu Chief Scientific Officer, Promore Pharma AB, +46 706310109, margit.mahlapuu@promorepharma.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	30 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 July 2020
Global end of trial reached?	Yes
Global end of trial date	13 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the efficacy of LL-37, at concentrations of 0.5 and 1.6 mg/mL, in increasing the incidence of complete wound closure compared with placebo in the treatment of hard-to-heal (HTH) venous leg ulcers (VLUs).

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki that are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements. Informed consent was obtained from all patients prior to initiation of the study.

Pain was part of efficacy assessment and was monitored throughout the study using a graded visual analogue scale (VAS) score (0-10).

Safety was monitored at all visits based on adverse events (AEs) and local tolerability assessments. The investigator and/or delegated study nurse carefully monitored the treated ulcers with regard to ulcer characteristics at each dressing change, 2 times per week. In order to detect drug-related reactions, patients reported any AEs occuring between dressing changes.

Cream containing lidocaine or prilocaine could be used for pain relief before cleansing and dressing both on the wound itself and in surrounding tissues.

Background therapy:

No background therapy was used in the study.

Evidence for comparator:

No comparator was used in the study. The test product was compared to a placebo.

Actual start date of recruitment	26 August 2018
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	Poland: 146
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	149
EEA total number of subjects	149

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)	58
From 65 to 84 years	82
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The first patient was screened and treated in the run-in period on 2018-09-26. The first patient was randomised and treated (during the treatment period) on 2018-10-15. The last patient's last visit (treatment period) was on 2020 03-20 and the last patient's last folow-up visit was on 2020-07-13.

Pre-assignment

Screening details:

Screening was performed in 190 patients. Of those, 149 were randomised. The main reason for screening failure was unfulfilment of inclusion/exclusion criteria. One randomised patient withdrew consent and the remaining 148 paitents entered and completed the run-in period, during which they were treated with placebo and received standart ulcer care.

Pre-assignment period milestones

Number of subjects started	149
Number of subjects completed	149

Period 1

Period 1 title	Randomisation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The blinding was broken for analysis of data when all patients completed the treatment period and the post-wound closure visits. To reduce the risk of bias, the blinding was maintained during the follow-up period among patients, site staff and other people not involved in the statistical analysis or writing of the clinical study report.

Arms

Are arms mutually exclusive?	Yes
Arm title	LL37 0.5 mg/mL group

Arm description:

Patients were allocated to receive 0.5 mg/mL of LL-37
During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 0.5 mg/mL of LL-37 and active doses of 12.5 µg/cm2.

Arm type	Experimental
Investigational medicinal product name	LL-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The IMP was provided in glass syringes, which contained 0.4 mL solution. The diluent (13.1% polyvinyl alcohol [PVA]) was provided in a sealed glass vial, containing 5.0 mL solution. The IMP and diluent were shipped and stored temperature-controlled at +2 to +8°C. The syringes and vials provided were intended for single use.
The IMP was prepared by mixing 0.4 mL of the test product or placebo with 1.6 mL of diluent immediately before use. The ready-to-use product had to be used within 3 hours after preparation. The doses were selected based on the results of the phase I/II study LL-37001B, which demonstrated the most pronounced effect on early wound healing response for the doses of 0.5 and 1.6 mg/mL.
All patients, regardless of treatment group, also received standard ulcer care including appropriate dressing and compression bandaging.

Arm title	LL37 1.6 mg/mL group

Arm description:

Patients were allocated to receive 1.6 mg/mL of LL-37 During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 1.6 mg/mL of LL-37 and active doses of 40 µg/cm2.

Arm type	Experimental
Investigational medicinal product name	LL-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The IMP was provided in glass syringes, which contained 0.4 mL solution. The diluent (13.1% polyvinyl alcohol [PVA]) was provided in a sealed glass vial, containing 5.0 mL solution. The IMP and diluent were shipped and stored temperature-controlled at +2 to +8°C. The syringes and vials provided were intended for single use.
The IMP was prepared by mixing 0.4 mL of the test product or placebo with 1.6 mL of diluent immediately before use. The ready-to-use product had to be used within 3 hours after preparation. The doses were selected based on the results of the phase I/II study LL-37001B, which demonstrated the most pronounced effect on early wound healing response for the doses of 0.5 and 1.6 mg/mL.
All patients, regardless of treatment group, also received standard ulcer care including appropriate dressing and compression bandaging.

Arm title	Placebo

Arm description:

Patients were allocated to receive placebo (reference product) every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

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

Dosage and administration details:

The reference product, placebo, was identical to the composition of the test product with the exception that it contained no LL-37. The ready-to-use reference product was prepared by mixing the reference product with the diluent provided (13.1% PVA).
During the run-in period and the treatment period, the ready-to-use reference product was applied every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

Number of subjects in period 1	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo
Started	48	49	52
Completed	48	49	51
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The blinding was broken for analysis of data when all patients completed the treatment period and the post-wound closure visits. To reduce the risk of bias, the blinding was maintained during the follow-up period among patients, site staff and other people not involved in the statistical analysis or writing of the clinical study report.

Arms

Are arms mutually exclusive?	Yes
Arm title	LL37 0.5 mg/mL group

Arm description:

Patients were allocated to receive 0.5 mg/mL of LL-37. During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 0.5 mg/mL of LL-37 and active doses of 12.5 µg/cm2.

Arm type	Experimental
Investigational medicinal product name	LL-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The IMP was provided in glass syringes, which contained 0.4 mL solution. The diluent (13.1% polyvinyl alcohol [PVA]) was provided in a sealed glass vial, containing 5.0 mL solution. The IMP and diluent were shipped and stored temperature-controlled at +2 to +8°C. The syringes and vials provided were intended for single use.
The IMP was prepared by mixing 0.4 mL of the test product or placebo with 1.6 mL of diluent immediately before use. The ready-to-use product had to be used within 3 hours after preparation. The doses were selected based on the results of the phase I/II study LL-37001B, which demonstrated the most pronounced effect on early wound healing response for the doses of 0.5 and 1.6 mg/mL.
All patients, regardless of treatment group, also received standard ulcer care including appropriate dressing and compression bandaging.

Arm title	LL37 1.6 mg/mL group

Arm description:

Patients were allocated to receive 1.6 mg/mL of LL-37. During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 1.6 mg/mL of LL-37 and active doses of 40 µg/cm2.

Arm type	Experimental
Investigational medicinal product name	LL-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The IMP was provided in glass syringes, which contained 0.4 mL solution. The diluent (13.1% polyvinyl alcohol [PVA]) was provided in a sealed glass vial, containing 5.0 mL solution. The IMP and diluent were shipped and stored temperature-controlled at +2 to +8°C. The syringes and vials provided were intended for single use.
The IMP was prepared by mixing 0.4 mL of the test product or placebo with 1.6 mL of diluent immediately before use. The ready-to-use product had to be used within 3 hours after preparation. The doses were selected based on the results of the phase I/II study LL-37001B, which demonstrated the most pronounced effect on early wound healing response for the doses of 0.5 and 1.6 mg/mL.
All patients, regardless of treatment group, also received standard ulcer care including appropriate dressing and compression bandaging.

Arm title	Placebo

Arm description:

Patients were allocated to receive placebo (reference product). The placebo was applied every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

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

Dosage and administration details:

The reference product, placebo, was identical to the composition of the test product with the exception that it contained no LL-37. The ready-to-use reference product was prepared by mixing the reference product with the diluent provided (13.1% PVA).
During the run-in period and the treatment period, the ready-to-use reference product was applied every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: One patient withdrew after randomisation and before treating. Therefore the total number of patints for whom baseline characteristics are reported is 148; 48 in the LL37 0.5 mg/mL group, 49 in the LL37 1.6 mg/mL group and 51 in the placebo group. By selecting Period 2-Ttreatment period as the baseline period, the correct number of patients is entered in the baseline characteristics report.

Number of subjects in period 2[2]	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo
Started	48	49	51
Completed	42	41	48
Not completed	6	8	3
Consent withdrawn by subject	2	4	2
Adverse event, non-fatal	-	4	-
Missing visits	1	-	-
Lost to follow-up	1	-	-

Protocol deviation	2	-	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient withdrew after randomisation and before treatment. Therefore the total number of patients for whom baseline characteristics are reported is 148; 48 in the LL37 0.5 mg/mL group, 49 in the LL37 1.6 mg/mL group and 51 in the placebo group. By selecting Period 2-Ttreatment period as the baseline period, the correct number of patients is entered in the baseline characteristics report.

Period 3

Period 3 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The blinding was broken for analysis of data when all patients completed the treatment period and the post-wound closure visits. To reduce the risk of bias, the blinding was maintained during the follow-up period among patients, site staff and other people not involved in the statistical analysis or writing of the clinical study report.

Arms

Are arms mutually exclusive?	Yes
Arm title	LL37 0.5 mg/mL group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	LL-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The IMP was provided in glass syringes, which contained 0.4 mL solution. The diluent (13.1% polyvinyl alcohol [PVA]) was provided in a sealed glass vial, containing 5.0 mL solution. The IMP and diluent were shipped and stored temperature-controlled at +2 to +8°C. The syringes and vials provided were intended for single use.
The IMP was prepared by mixing 0.4 mL of the test product or placebo with 1.6 mL of diluent immediately before use. The ready-to-use product had to be used within 3 hours after preparation. The doses were selected based on the results of the phase I/II study LL-37001B, which demonstrated the most pronounced effect on early wound healing response for the doses of 0.5 and 1.6 mg/mL.
All patients, regardless of treatment group, also received standard ulcer care including appropriate dressing and compression bandaging.

Arm title	LL37 1.6 mg/mL group

Arm description: -

Arm type	Experimental

Investigational medicinal product name	LL-37
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The IMP was provided in glass syringes, which contained 0.4 mL solution. The diluent (13.1% polyvinyl alcohol [PVA]) was provided in a sealed glass vial, containing 5.0 mL solution. The IMP and diluent were shipped and stored temperature-controlled at +2 to +8°C. The syringes and vials provided were intended for single use.
The IMP was prepared by mixing 0.4 mL of the test product or placebo with 1.6 mL of diluent immediately before use. The ready-to-use product had to be used within 3 hours after preparation. The doses were selected based on the results of the phase I/II study LL-37001B, which demonstrated the most pronounced effect on early wound healing response for the doses of 0.5 and 1.6 mg/mL.
All patients, regardless of treatment group, also received standard ulcer care including appropriate dressing and compression bandaging.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Sterile concentrate
Routes of administration	Cutaneous use

Dosage and administration details:

The reference product, placebo, was identical to the composition of the test product with the exception that it contained no LL-37. The ready-to-use reference product was prepared by mixing the reference product with the diluent provided (13.1% PVA).
During the run-in period and the treatment period, the ready-to-use reference product was applied every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

Number of subjects in period 3	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo
Started	42	41	48
8 weeks follow-up	31	26	35
16 weeks follow-up	26	25	27
Completed	26	25	27
Not completed	16	16	21
Physician decision	2	-	-
Consent withdrawn by subject	2	4	8
Other	1	3	1
Lost to follow-up	11	9	12

Baseline characteristics

Reporting groups	
Reporting group title	LL37 0.5 mg/mL group
Reporting group description:	
Patients were allocated to receive 0.5 mg/mL of LL-37. During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 0.5 mg/mL of LL-37 and active doses of 12.5 µg/cm2.	
Reporting group title	LL37 1.6 mg/mL group
Reporting group description:	
Patients were allocated to receive 1.6 mg/mL of LL-37. During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 1.6 mg/mL of LL-37 and active doses of 40 µg/cm2.	
Reporting group title	Placebo
Reporting group description:	
Patients were allocated to receive placebo (reference product). The placebo was applied every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.	

Reporting group values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo
Number of subjects	48	49	51
Age categorical			
Units: Subjects			
Adults (≥ 18 years)	48	49	51
Age continuous			
Units: years			
arithmetic mean	67.5	67.3	68.5
standard deviation	± 11.6	± 11.5	± 11.7
Gender categorical			
Units: Subjects			
Female	26	28	29
Male	22	21	22
Location of the target ulcer			
History of target ulcer.			
Units: Subjects			
Left leg back	1	3	3
Left leg front	4	3	5
Left leg inner aspect	14	17	12
Left leg outer aspect	8	7	8
Right leg back	0	1	0
Right leg front	8	3	5
Right leg inner aspect	9	5	11
Right leg outer aspect	4	10	7
Prior use of compression therapy			
History of target ulcer.			
Units: Subjects			
Yes	48	49	51
No	0	0	0

Prior use of ulcer dressing			
History of target ulcer.			
Units: Subjects			
Yes	44	46	47
No	4	3	4
Duration of the target ulcer			
History of target ulcer.			
Units: Days			
arithmetic mean	1590.8	1131.3	1984.7
standard deviation	± 2277.7	± 1388.3	± 2548.7
Ankle-brachial pressure index (ABPI)			
Units: No unit			
arithmetic mean	0.973	0.993	1.007
standard deviation	± 0.140	± 0.172	± 0.980

Reporting group values	Total		
Number of subjects	148		
Age categorical			
Units: Subjects			
Adults (≥ 18 years)	148		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	83		
Male	65		
Location of the target ulcer			
History of target ulcer.			
Units: Subjects			
Left leg back	7		
Left leg front	12		
Left leg inner aspect	43		
Left leg outer aspect	23		
Right leg back	1		
Right leg front	16		
Right leg inner aspect	25		
Right leg outer aspect	21		
Prior use of compression therapy			
History of target ulcer.			
Units: Subjects			
Yes	148		
No	0		
Prior use of ulcer dressing			
History of target ulcer.			
Units: Subjects			
Yes	137		
No	11		

Duration of the target ulcer			
History of target ulcer.			
Units: Days arithmetic mean standard deviation	- 		
Ankle-brachial pressure index (ABPI) Units: No unit arithmetic mean standard deviation	- 		

Subject analysis sets

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis set was defined as all patients who received at least one application of the study treatment.
Analysis on the safety analysis set was based on actual treatment (i.e. patients were analysed "as treated").

Subject analysis set title	Per-protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol analysis set (PPAS) was defined as the subset of patients in the FAS who completed the treatment period and for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified. The decision as to which protocol deviations were considered as reason for exclusion from the PPAS was made at the clean file meeting and documented in the clean file report. Analysis on the PPAS was based on the actual treatment (i.e. patients were analysed "as treated").

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set (FAS) was defined as all randomised patients who received at least one application of the study treatment and for whom at least one post-baseline ulcer assessment was made. Patients who were randomised in violation of eligibility criteria were excluded from the FAS. The blinding ensured that the decision of whether to begin treatment could not be influenced by knowledge of the assigned treatment, and thus the intention-to-treat principle was preserved despite the exclusion of patients who did not receive any application of the study treatment. The same rationale applied to the exclusion of patients with no post-baseline ulcer assessment, since the first such assessment was performed within a few days after baseline. Analysis on the FAS was based on the planned treatment (i.e. patients were analysed "as randomised").

Subject analysis set title	FAS, sub-group of patients who completed the treatment period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FAS, sub-group of patients who completed the treatment period

Subject analysis set title	FAS, patients with wound area < 10 cm² at randomisation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FAS, patients with wound area < 10 cm² at randomisation

Subject analysis set title	FAS, patients with wound area ≥ 10 cm² at randomisation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FAS, patients with wound area ≥ 10 cm² at randomisation

Reporting group values	Safety analysis set	Per-protocol analysis set	Full analysis set
Number of subjects	148	129	144
Age categorical			
Units: Subjects			
Adults (≥ 18 years)	148	129	144
Age continuous			
Units: years			
arithmetic mean	67.8	67.6	67.6
standard deviation	± 11.5	± 11.5	± 11.5
Gender categorical			
Units: Subjects			
Female	83	74	80
Male	65	55	64
Location of the target ulcer			
History of target ulcer.			
Units: Subjects			
Left leg back	7	7	7
Left leg front	12	11	12
Left leg inner aspect	43	36	42
Left leg outer aspect	23	22	23
Right leg back	1	0	0
Right leg front	16	12	14
Right leg inner aspect	25	24	25
Right leg outer aspect	21	17	21
Prior use of compression therapy			
History of target ulcer.			
Units: Subjects			
Yes	148	129	144
No	0	0	0
Prior use of ulcer dressing			
History of target ulcer.			
Units: Subjects			
Yes	137	120	134
No	11	9	10
Duration of the target ulcer			
History of target ulcer.			
Units: Days			
arithmetic mean	1574.4	1649.1	1577.9
standard deviation	± 2149.7	± 2225.0	± 2159.7
Ankle-brachial pressure index (ABPI)			
Units: No unit			
arithmetic mean	0.991	0.990	0.988
standard deviation	± 0.153	± 0.158	± 0.154

Reporting group values	FAS, sub-group of patients who completed the treatment period	FAS, patients with wound area < 10 cm² at randomisation	FAS, patients with wound area ≥ 10 cm² at randomisation
Number of subjects	131	78	66
Age categorical			
Units: Subjects			
Adults (≥ 18 years)			

Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Location of the target ulcer			
History of target ulcer.			
Units: Subjects			
Left leg back Left leg front Left leg inner aspect Left leg outer aspect Right leg back Right leg front Right leg inner aspect Right leg outer aspect			
Prior use of compression therapy			
History of target ulcer.			
Units: Subjects			
Yes No			
Prior use of ulcer dressing			
History of target ulcer.			
Units: Subjects			
Yes No			
Duration of the target ulcer			
History of target ulcer.			
Units: Days arithmetic mean standard deviation	±	±	±
Ankle-brachial pressure index (ABPI) Units: No unit arithmetic mean standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	LL37 0.5 mg/mL group

Reporting group description:

Patients were allocated to receive 0.5 mg/mL of LL-37
During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 0.5 mg/mL of LL-37 and active doses of 12.5 µg/cm2.

Reporting group title	LL37 1.6 mg/mL group

Reporting group description:

Patients were allocated to receive 1.6 mg/mL of LL-37 During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 1.6 mg/mL of LL-37 and active doses of 40 µg/cm2.

Reporting group title	Placebo

Reporting group description:

Patients were allocated to receive placebo (reference product) every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

Reporting group title	LL37 0.5 mg/mL group

Reporting group description:

Patients were allocated to receive 0.5 mg/mL of LL-37. During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 0.5 mg/mL of LL-37 and active doses of 12.5 µg/cm2.

Reporting group title	LL37 1.6 mg/mL group

Reporting group description:

Patients were allocated to receive 1.6 mg/mL of LL-37. During the treatment period, the test product was applied every third day (±1 day), but not more often than twice a week. The test product was applied on the wound bed, using 25 µL solution per cm2 ulcer area, at concentrations 1.6 mg/mL of LL-37 and active doses of 40 µg/cm2.

Reporting group title	Placebo

Reporting group description:

Patients were allocated to receive placebo (reference product). The placebo was applied every third day (±1 day), but not more often than twice a week. The ready-to-use reference product was applied on the wound bed, using 25 µL solution per cm2 ulcer area. The product was applied in the centre of the ulcer using a 1 mL graded syringe and distributed over the entire ulcer area.

Reporting group title	LL37 0.5 mg/mL group
Reporting group description: -	
Reporting group title	LL37 1.6 mg/mL group
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis set was defined as all patients who received at least one application of the study treatment.
Analysis on the safety analysis set was based on actual treatment (i.e. patients were analysed "as treated").

Subject analysis set title	Per-protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

Per-protocol analysis set (PPAS) was defined as the subset of patients in the FAS who completed the

treatment period and for whom no protocol deviation judged as having an impact on the primary efficacy analysis was reported or identified. The decision as to which protocol deviations were considered as reason for exclusion from the PPAS was made at the clean file meeting and documented in the clean file report. Analysis on the PPAS was based on the actual treatment (i.e. patients were analysed "as treated").

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full analysis set (FAS) was defined as all randomised patients who received at least one application of the study treatment and for whom at least one post-baseline ulcer assessment was made. Patients who were randomised in violation of eligibility criteria were excluded from the FAS. The blinding ensured that the decision of whether to begin treatment could not be influenced by knowledge of the assigned treatment, and thus the intention-to-treat principle was preserved despite the exclusion of patients who did not receive any application of the study treatment. The same rationale applied to the exclusion of patients with no post-baseline ulcer assessment, since the first such assessment was performed within a few days after baseline. Analysis on the FAS was based on the planned treatment (i.e. patients were analysed "as randomised").

Subject analysis set title	FAS, sub-group of patients who completed the treatment period
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FAS, sub-group of patients who completed the treatment period

Subject analysis set title	FAS, patients with wound area < 10 cm² at randomisation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FAS, patients with wound area < 10 cm² at randomisation

Subject analysis set title	FAS, patients with wound area ≥ 10 cm² at randomisation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

FAS, patients with wound area ≥ 10 cm² at randomisation

Primary: Confirmed complete wound closure of the target ulcer-estimated proportion of responders (FAS)

End point title	Confirmed complete wound closure of the target ulcer-estimated proportion of responders (FAS)

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure. The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. The wound closure was always to be documented by photography, both when first recorded and when confirmed 2 weeks later. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed. Post-wound closure visits could be conducted at any time point during the treatment period after the wound was assessed as closed.
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Primary

End point timeframe:

Results presented are from data collected from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[1]	48[2]	50[3]	
Units: percentage				
number (confidence interval 90%)				
Estimated proportion of subjects (%)	26.5 (17.1 to 38.7)	24.7 (15.8 to 36.4)	25.3 (16.4 to 36.9)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Confirmed complete wound closure. FAS

Statistical analysis description:

The primary efficacy variable, confirmed complete wound closure, was analysed using a logistic regression model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. For dichotomous efficacy variables, the missing equals failure approach was used for the analysis on the FAS, i.e. patients with missing values were considered as non-responders.

Comparison groups	LL37 1.6 mg/mL group v Placebo v LL37 0.5 mg/mL group
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[4] - LL37 0.5 mg/mL vs placebo: OR = 1.067 (95% CI: 0.492, -), p-value = 0.4453

LL37 1.6 mg/mL vs placebo: OR = 0.968 (95% CI: 0.446, -), p-value= 0.5274

Primary: Confirmed complete wound closure of the target ulcer- observed proportion of responders (FAS)

End point title	Confirmed complete wound closure of the target ulcer- observed proportion of responders (FAS)[5]

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure. The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed. Post-wound closure visits could be conducted at any time point during the treatment period after the wound was assessed as closed.
Note that the proportion of responders presented is the observed proportion in the study (i.e. number of responders divided by the total number of patients, for each treatment group).

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[6]	48[7]	50[8]	
Units: subjects				
Not achieved	33	35	37	
Achieved	13	13	13	

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: Confirmed complete wound closure of the target ulcer- estimated proportion of responders in the subgroup of patients that completed the treatment phase

End point title	Confirmed complete wound closure of the target ulcer- estimated proportion of responders in the subgroup of patients that completed the treatment phase

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure. The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. The wound closure was always to be documented by photography, both when first recorded and when confirmed 2 weeks later. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed. Post-wound closure visits could be conducted at any time point during the treatment period after the wound was assessed as closed.
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[9]	41[10]	48[11]	
Units: percentage				
number (confidence interval 90%)				
Estimated proportion	28.9 (18.7 to 41.9)	29.5 (19.0 to 42.6)	26.0 (16.8 to 38.0)	

Notes:

[9] - FAS, subgroup of patients who completed the treatment period

[10] - FAS, subgroup of patients who completed the treatment period

[11] - FAS, subgroup of patients who completed the treatment period

Statistical analyses

Statistical analysis title	Confirmed complete wound closure. Subgroup

Statistical analysis description:

The primary efficacy variable, confirmed complete wound closure, was analysed using a logistic regression model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. For dichotomous efficacy variables, the missing equals failure approach was used for the analysis on the FAS, i.e. patients with missing values were considered as non-responders.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[12] - LL37 0.5 mg/mL vs placebo: OR = 1.159 (0.527, -) , p-value = 0.3787

LL37 1.6 mg/mL vs placebo: OR = 1.189 (0.538, -), p-value = 0.3599

Primary: Confirmed complete wound closure of the target ulcer- observed proportion of responders in the subgroup of patients that completed the treatment phase

End point title	Confirmed complete wound closure of the target ulcer- observed proportion of responders in the subgroup of patients that completed the treatment phase[13]

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure. The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed. Post-wound closure visits could be conducted at any time point during the treatment period after the wound was assessed as closed.
Note that the proportion of responders presented is the observed proportion in the study (i.e. number of responders divided by the total number of patients, for each treatment group).

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[14]	41[15]	48[16]	
Units: subjects				
Not achieved	29	28	25	
Achieved	13	13	13	

Notes:

[14] - FAS, subgroup of patients who completed the treatment period

[15] - FAS, subgroup of patients who completed the treatment period

[16] - FAS, subgroup of patients who completed the treatment period

Statistical analyses

No statistical analyses for this end point

Primary: Confirmed complete wound closure of the target ulcer- estimated proportion of responders (PPAS)

End point title	Confirmed complete wound closure of the target ulcer- estimated proportion of responders (PPAS)[17]

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure. The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. The wound closure was always to be documented by photography, both when first recorded and when confirmed 2 weeks later. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed. Post-wound closure visits could be conducted at any time point during the treatment period after the wound was assessed as closed.
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[17] - 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: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	Placebo	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[18]	41[19]	47[20]	
Units: percentage				
number (confidence interval 90%)				
Estimated proportion	29.8 (19.3 to 43.0)	29.3 (18.9 to 42.4)	26.6 (17.2 to 38.8)	

Notes:

[18] - PPAS

[19] - PPAS

[20] - PPAS

Statistical analyses

Statistical analysis title	Confirmed complete wound closure. PPAS

Statistical analysis description:

The primary efficacy variable, confirmed complete wound closure, was analysed using a logistic regression model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. For dichotomous efficacy variables, the missing equals failure approach was used for the analysis on the FAS, i.e. patients with missing values were considered as non-responders.

Comparison groups	Placebo v LL37 0.5 mg/mL group v LL37 1.6 mg/mL group
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [21]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[21] - LL37 0.5 mg/mL vs placebo: OR = 1.168 (0.528, -), p-value = 0.3735

LL37 1.6 mg/mL vs placebo: OR = 1.140 (0.514, -), p-value = 0.3933

Primary: Confirmed complete wound closure of the target ulcer- observed proportion of responders (PPAS)

End point title	Confirmed complete wound closure of the target ulcer- observed proportion of responders (PPAS)[22]

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure. The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed. Post-wound closure visits could be conducted at any time point during the treatment period after the wound was assessed as closed.
Note that the proportion of responders presented is the observed proportion in the study (i.e. number of responders divided by the total number of patients, for each treatment group).

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[23]	41[24]	47[25]	
Units: subjects				
Not achieved	28	28	34	
Achieved	13	13	13	

Notes:

[23] - PPAS

[24] - PPAS

[25] - PPAS

Statistical analyses

No statistical analyses for this end point

Primary: Unconfirmed complete wound closure (FAS)

End point title	Unconfirmed complete wound closure (FAS)[26]

End point description:

The number of patients who achieved complete wound closure during the treatment period but for whom the wound closure status was not possible to assess at the post-wound closure visit after 2 weeks (i.e. for whom it is not known whether the wound reopened or remained closed).

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[26] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[27]	48[28]	50[29]	
Units: subjects				
Wound closure	15	13	15	
Unconfirmed closure	2	0	1	

Notes:

[27] - FAS

[28] - FAS

[29] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: Unconfirmed complete wound closure in the subgroup of patients who completed the treatment period

End point title	Unconfirmed complete wound closure in the subgroup of patients who completed the treatment period[30]

End point description:

The number of patients who achieved complete wound closure during the treatment period but for whom the wound closure status was not possible to assess at the post-wound closure visit after 2 weeks (i.e. for whom it is not known whether the wound reopened or remained closed)

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the

end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[30] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[31]	41[32]	48[33]	
Units: subjects				
Wound closure	14	13	15	
Unconfirmed closure	1	0	1	

Notes:

[31] - FAS, subgroup of patients who completed the treatment period

[32] - FAS, subgroup of patients who completed the treatment period

[33] - FAS, subgroup of patients who completed the treatment period

Statistical analyses

No statistical analyses for this end point

Primary: Unconfirmed complete wound closure (PPAS)

End point title	Unconfirmed complete wound closure (PPAS)[34]

End point description:

The number of patients who achieved complete wound closure during the treatment period but for whom the wound closure status was not possible to assess at the post-wound closure visit after 2 weeks (i.e. for whom it is not known whether the wound reopened or remained closed)

End point type	Primary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

Notes:

[34] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for this endpoint. Data is presented descriptively.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	41[35]	41[36]	47[37]	
Units: subjects				
Wound closure	13	13	14	
Unconfirmed wound closure	0	0	0	

Notes:

[35] - PPAS

[36] - PPAS

[37] - PPAS

Statistical analyses

No statistical analyses for this end point

Secondary: Wound healing rate of the target ulcer, FAS

End point title	Wound healing rate of the target ulcer, FAS

End point description:

The wound healing rate for each patient was estimated by fitting an exponential decay model with 2 parameters to the wound area measurements over time.
Only wound area measurements during the treatment period (including the baseline measurement at randomisation) were considered for the modelling. For patients for whom the wound reopened after complete wound closure, only measurements up to and including the first time of wound closure were included in the model. Patients with less than 4 measurements were excluded from the analysis.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).

End point type	Secondary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[38]	42[39]	48[40]	
Units: rate				
arithmetic mean (confidence interval 90%)				
Wound healing rate	0.0261 (0.0146 to 0.0375)	0.0112 (-0.003 to 0.0227)	0.0204 (0.0097 to 0.0312)	

Notes:

[38] - FAS

[39] - FAS

[40] - FAS

Statistical analyses

Statistical analysis title	Wound healing rate difference

Statistical analysis description:

The wound healing rate was analysed using an analysis of covariance (ANCOVA) model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. Each active treatment group was tested against placebo, and the null hypotheses that the least square mean difference in wound healing rate is equal to zero were tested against one-sided alternative hypotheses that the difference ≥ 0.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [41]
Method	ANCOVA
Parameter estimate	LS mean difference

Notes:

[41] - LL37 0.5 mg/mL vs placebo: difference in wound healing rate = 0.0057/day (95% CI: -0.0100, -), p-value = 0.2759
LL37 1.6 mg/mL vs placebo: difference in wound healing rate = -0.0092/day (95% CI: -0.0250, -) , p-value = 0.8326

Secondary: Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS

End point title	Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS

End point description:

Time to confirmed complete wound closure was analysed using a regression analysis to estimate the restricted mean survival time (RMST). The model included treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate.
For patients completing the treatment period or being prematurely withdrawn from the study without experiencing confirmed complete wound closure (including patients for whom the wound reopened during the post-wound closure visits), the time to event was right-censored at the date of end of treatment/ withdrawal.

End point type	Secondary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[42]	48[43]	50[44]	
Units: days				
arithmetic mean (confidence interval 90%)				
RMST	83.1 (76.3 to 89.8)	90.3 (86.2 to 94.3)	87.9 (83.3 to 92.6)	

Notes:

[42] - FAS

[43] - FAS

[44] - FAS

Statistical analyses

Statistical analysis title	Difference in RMST (FAS)

Statistical analysis description:

Each of the two active treatment groups were tested separately against placebo, and null hypotheses that the difference in RMST for confirmed complete wound closure is equal to zero were tested against one-sided alternative hypotheses that the difference in RMST is less than zero.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [45]
Method	RMST regression
Parameter estimate	RMST difference

Confidence interval	
level	95 %
sides	1-sided

Notes:

[45] - LL37 0.5 mg/mL vs placebo: difference in RMST = -4.9 (-, 3.3), p-value = 0.1644
LL37 1.6 mg/mL vs placebo: difference in RMST = 2.3 (-, 8.7), p-value = 0.7270

Secondary: Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS, subgroup of patients who completed the treatment period

End point title	Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS, subgroup of patients who completed the treatment period

End point description:

Time to confirmed complete wound closure was analysed using a regression analysis to estimate the restricted mean survival time (RMST). The model included treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate.
For patients completing the treatment period or being prematurely withdrawn from the study without experiencing confirmed complete wound closure (including patients for whom the wound reopened during the post-wound closure visits), the time to event was right-censored at the date of end of treatment/ withdrawal.

End point type	Secondary

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42[46]	41[47]	48[48]	
Units: days				
arithmetic mean (confidence interval 90%)				
RMST	82.0 (74.9 to 89.1)	89.6 (85.0 to 94.1)	87.8 (83.1 to 92.5)	

Notes:

[46] - FAS, subgroup of patients who completed the treatment period

[47] - FAS, subgroup of patients who completed the treatment period

[48] - FAS, subgroup of patients who completed the treatment period

Statistical analyses

Statistical analysis title	Difference in RMST, FAS completed treatment

Statistical analysis description:

Each of the two active treatment groups were tested separately against placebo, and null hypotheses that the difference in RMST for confirmed complete wound closure is equal to zero were tested against one-sided alternative hypotheses that the difference in RMST is less than zero.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [49]
Method	RMST regression
Parameter estimate	RMST difference
Confidence interval	
level	95 %
sides	1-sided

Notes:

[49] - LL37 0.5 mg/mL vs placebo: difference in RMST = -5.8 (-, 2.8), p-value = 0.1348
LL37 1.6 mg/mL vs placebo: difference in RMST = 1.8 (-, 8.4) p-value = 0.6677

Secondary: Attainment of target ulcer area reduction of at least 50% from baseline-estimated proportion of responders (FAS)

End point title	Attainment of target ulcer area reduction of at least 50% from baseline-estimated proportion of responders (FAS)

End point description:

Attainment of target ulcer area reduction of at least 50% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Secondary

End point timeframe:

Endpoint was asseesd at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[50]	48[51]	50[52]	
Units: percentage				
arithmetic mean (confidence interval 90%)				
Estimated proportion of reposnders	56.4 (44.2 to 67.8)	35.0 (24.6 to 47.0)	46.2 (34.9 to 57.9)	

Notes:

[50] - FAS

[51] - FAS

[52] - FAS

Statistical analyses

Statistical analysis title	Attainment ≥ 50%, OR vs placebo (FAS)

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the target ulcer (dichotomised as < or ≥ 10cm²) and duration of the target ulcer at baseline.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [53]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[53] - LL37 0.5 mg/mL vs placebo: OR = 1.507 (0.764, -), p-value = 0.1603
LL37 1.6 mg/mL vs placebo: OR = 0.627 (0.314, -) , p-value = 0.8666

Secondary: Attainment of target ulcer area reduction of at least 70% from baseline-estimated proportion of responders (FAS)

End point title	Attainment of target ulcer area reduction of at least 70% from baseline-estimated proportion of responders (FAS)

End point description:

Attainment of target ulcer area reduction of at least 70% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Secondary

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[54]	48[55]	50[56]	
Units: percentage				
arithmetic mean (confidence interval 90%)				
Estimated proportion of responders	43.1 (31.6 to 55.3)	34.6 (24.2 to 46.6)	34.0 (23.9 to 45.9)	

Notes:

[54] - FAS

[55] - FAS

[56] - FAS

Statistical analyses

Statistical analysis title	Attainment ≥ 70%, OR vs placebo (FAS)

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the target ulcer (dichotomised as < or ≥ 10cm²) and duration of the target ulcer at baseline.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [57]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[57] - LL37 0.5 mg/mL vs placebo: OR =1.465 (0.729, —) , p-value = 0.1839
LL37 1.6 mg/mL vs placebo: OR = 1.023 (0.503, —), p-value = 0.4788

Secondary: Attainment of target ulcer area reduction of at least 50% from baseline- Number of patients that achieved it or not (FAS)

End point title	Attainment of target ulcer area reduction of at least 50% from baseline- Number of patients that achieved it or not (FAS)

End point description:

Attainment of target ulcer area reduction of at least 50% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).

End point type	Secondary

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[58]	48[59]	50[60]	
Units: subjects				
Achieved	26	17	23	
Not achieved	20	31	27	
Missing	3	4	3	

Notes:

[58] - FAS

[59] - FAS

[60] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Attainment of target ulcer area reduction of at least 70% from baseline- Number of patients that achieved it or not (FAS)

End point title	Attainment of target ulcer area reduction of at least 70% from baseline- Number of patients that achieved it or not (FAS)

End point description:

Attainment of target ulcer area reduction of at least 70% at end-of-treatment compared to baseline was analysed using logistic regression models.

Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).

End point type	Secondary

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	46[61]	48[62]	50[63]	
Units: subjects				
Achieved	20	17	17	
Not achieved	26	31	33	
Missing	3	4	3	

Notes:

[61] - FAS

[62] - FAS

[63] - FAS

Statistical analyses

No statistical analyses for this end point

Post-hoc: Confirmed complete wound closure. FAS, subgroup of patients with wound area less than 10 cm² at randomisation.

End point title	Confirmed complete wound closure. FAS, subgroup of patients with wound area less than 10 cm² at randomisation.

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure.
The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. The wound closure was always to be documented by photography, both when first recorded and when confirmed 2 weeks later. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed.

End point type	Post-hoc

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[64]	27[65]	26[66]	
Units: percentage				
number (confidence interval 90%)				
Estimated proportion	26.0 (14.1 to 42.8)	31.4 (18.7 to 47.7)	44.2 (28.8 to 60.8)	

Notes:

[64] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[65] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[66] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Confirmed complete wound closure. Subgroup

Statistical analysis description:

The primary efficacy variable, confirmed complete wound closure, was analysed using a logistic regression model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. For dichotomous efficacy variables, the missing equals failure approach was used for the analysis on the FAS, i.e. patients with missing values were considered as non-responders.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [67]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[67] - LL37 0.5 mg/mL vs placebo: OR = 0.443 (0.160, -), p-value = 0.9062

LL37 1.6 mg/mL vs placebo: OR = 0.578 (0.220, -), p-value = 0.8252

Post-hoc: Confirmed complete wound closure of the target ulcer. FAS, subgroup of patients with wound area at least 10 cm² at randomisation.

End point title	Confirmed complete wound closure of the target ulcer. FAS, subgroup of patients with wound area at least 10 cm² at randomisation.

End point description:

The primary efficacy endpoint was a confirmed complete wound closure of the target ulcer, defined as skin re-epithelialisation without drainage or dressing requirements at any time up to the end-of-treatment visit at 13 weeks, which was sustained at the post-wound closure visit, 2 weeks after the first reported closure.
The Investigator assessed at each visit whether complete wound closure of the target ulcer had been achieved. The wound closure was always to be documented by photography, both when first recorded and when confirmed 2 weeks later. At the post-wound closure visits, 2 weeks after the complete wound closure was first reported, the Investigator assessed whether the complete wound closure was confirmed.

End point type	Post-hoc

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[68]	21[69]	24[70]	
Units: percentage				
number (confidence interval 90%)	28.1 (14.9 to 46.6)	19.6 (8.8 to 38.0)	8.1 (2.5 to 23.1)	

Notes:

[68] - FAS, patients with wound area ≥ 10 cm² at randomisation

[69] - FAS, patients with wound area ≥ 10 cm² at randomisation

[70] - FAS, patients with wound area ≥ 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Confirmed complete wound closure. Subgroup

Statistical analysis description:

The primary efficacy variable, confirmed complete wound closure, was analysed using a logistic regression model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. For dichotomous efficacy variables, the missing equals failure approach was used for the analysis on the FAS, i.e. patients with missing values were considered as non-responders.

Comparison groups	LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	superiority
P-value	> 0.05 [71]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[71] - LL37 1.6 mg/mL vs placebo: OR = 2.771 (0.590, -), p-value = 0.1393

Statistical analysis title	Confirmed complete wound closure. Subgroup

Statistical analysis description:

The primary efficacy variable, confirmed complete wound closure, was analysed using a logistic regression model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. For dichotomous efficacy variables, the missing equals failure approach was used for the analysis on the FAS, i.e. patients with missing values were considered as non-responders.

Comparison groups	Placebo v LL37 0.5 mg/mL group
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05 [72]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Confidence interval	
level	95 %
sides	1-sided

Notes:

[72] - LL37 0.5 mg/mL vs placebo: OR = 4.454 (1.038, -), p-value = 0.0458

Post-hoc: Wound healing rate. FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point title	Wound healing rate. FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point description:

The wound healing rate for each patient was estimated by fitting an exponential decay model with 2 parameters to the wound area measurements over time. Only wound area measurements during the treatment period (including the baseline measurement at randomisation) were considered for the modelling. For patients for whom the wound reopened after complete wound closure, only measurements up to and including the first time of wound closure were included in the model. Patients with less than 4 measurements were excluded from the analysis.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).

End point type	Post-hoc

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[73]	22[74]	24[75]	
Units: rate				
arithmetic mean (confidence interval 90%)				
Wound healing rate	0.0138 (0.0020 to 0.0256)	0.0076 (-0.0040 to 0.0191)	0.0324 (0.0213 to 0.0435)	

Notes:

[73] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[74] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[75] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Wound healing rate difference (subgroup analysis)

Statistical analysis description:

The wound healing rate was analysed using an analysis of covariance (ANCOVA) model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. Each active treatment group was tested against placebo, and the null hypotheses that the least square mean difference in wound healing rate is equal to zero were tested against one-sided alternative hypotheses that the difference ≥ 0.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [76]
Method	ANCOVA
Parameter estimate	LS mean difference

Notes:

[76] - LL37 0.5 mg/mL vs placebo: difference in wound healing rate = -0.0186/day (95% CI: -0.0348, -) , p-value = 0.9693
LL37 1.6 mg/mL vs placebo: difference in wound healing rate = -0.0248/day (95% CI: -0.0409, -) , p-value = 0.9939

Post-hoc: Wound healing rate. FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point title	Wound healing rate. FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point description:

The wound healing rate for each patient was estimated by fitting an exponential decay model with 2 parameters to the wound area measurements over time. Only wound area measurements during the treatment period (including the baseline measurement at randomisation) were considered for the modelling. For patients for whom the wound reopened after complete wound closure, only measurements up to and including the first time of wound closure were included in the model. Patients with less than 4 measurements were excluded from the analysis.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).

End point type	Post-hoc

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[77]	20[78]	24[79]	
Units: rate				
arithmetic mean (confidence interval 90%)				
Wound rate	0.0367 (0.0174 to 0.0559)	0.0159 (-0.0040 to 0.0358)	0.0093 (-0.0087 to 0.0274)	

Notes:

[77] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[78] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[79] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Wound healing rate difference (subgroup analysis)

Statistical analysis description:

The wound healing rate was analysed using an analysis of covariance (ANCOVA) model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. Each active treatment group was tested

against placebo, and the null hypotheses that the least square mean difference in wound healing rate is equal to zero were tested against one-sided alternative hypotheses that the difference ≥ 0.

Comparison groups	LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [80]
Method	ANCOVA
Parameter estimate	LS mean difference

Notes:

[80] - LL37 1.6 mg/mL vs placebo: difference in wound healing rate = 0.0066 (95% CI: -0.0204, -) , p-value = 0.3430

Statistical analysis title	Wound healing rate difference (subgroup...

Statistical analysis description:

The wound healing rate was analysed using an analysis of covariance (ANCOVA) model, including treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate. Each active treatment group was tested against placebo, and the null hypotheses that the least square mean difference in wound healing rate is equal to zero were tested against one-sided alternative hypotheses that the difference ≥ 0.

Comparison groups	Placebo v LL37 0.5 mg/mL group
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [81]
Method	ANCOVA
Parameter estimate	LS mean difference

Notes:

[81] - LL37 0.5 mg/mL vs placebo: OR = 3.252 (1.165, -) , p-value = 0.0294

Post-hoc: Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point title	Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point description:

Time to confirmed complete wound closure was analysed using a regression analysis to estimate the restricted mean survival time (RMST). The model included treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate.
For patients completing the treatment period or being prematurely withdrawn from the study without experiencing confirmed complete wound closure (including patients for whom the wound reopened during the post-wound closure visits), the time to event was right-censored at the date of end of treatment/ withdrawal.

End point type	Post-hoc

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[82]	27[83]	26[84]	
Units: days				
arithmetic mean (confidence interval 90%)				
RMST	77.9 (67.4 to 88.4)	86.1 (80.1 to 92.2)	77.2 (68.8 to 85.9)	

Notes:

[82] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[83] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[84] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Difference in RMST, FAS subgroup analysis

Statistical analysis description:

Each of the two active treatment groups were tested separately against placebo, and null hypotheses that the difference in RMST for confirmed complete wound closure is equal to zero were tested against one-sided alternative hypotheses that the difference in RMST is less than zero.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [85]
Method	RMST regression
Parameter estimate	RMST difference
Confidence interval	
level	95 %
sides	1-sided

Notes:

[85] - LL37 0.5 mg/mL vs placebo: difference in RMST = 0.7 (-, 14.1), p-value = 0.5333
LL37 1.6 mg/mL vs placebo: difference in RMST = 0,8.9 (-, 19.4) p-value = 0.9181

Post-hoc: Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point title	Time to confirmed complete wound closure- restricted mean survival time (RMST). FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point description:

Time to confirmed complete wound closure was analysed using a regression analysis to estimate the restricted mean survival time (RMST). The model included treatment group and the baseline area of the target ulcer (dichotomous stratification factor) as factors, and the duration of the target ulcer at baseline as a covariate.
For patients completing the treatment period or being prematurely withdrawn from the study without experiencing confirmed complete wound closure (including patients for whom the wound reopened during the post-wound closure visits), the time to event was right-censored at the date of end of treatment/ withdrawal.

End point type	Post-hoc

End point timeframe:

Results presented are from data collected during the study, from the start of the run-in period to the end of post-wound closure period at Visit 36 (Week 15). No efficacy evaluation was performed during the follow-up period.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[86]	21[87]	24[88]	
Units: days				
arithmetic mean (confidence interval 90%)				
RMST	87.4 (80.9 to 93.9)	92.6 (88.3 to 96.9)	97.5 (96.1 to 98.8)	

Notes:

[86] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[87] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[88] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Difference in RMST, FAS subgroup analysis

Statistical analysis description:

Each of the two active treatment groups were tested separately against placebo, and null hypotheses that the difference in RMST for confirmed complete wound closure is equal to zero were tested against one-sided alternative hypotheses that the difference in RMST is less than zero.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [89]
Method	RMST regression
Parameter estimate	RMST difference
Confidence interval	
level	95 %
sides	1-sided

Notes:

[89] - LL37 0.5 mg/mL vs placebo: difference in RMST = -10.1 (-, -3.4), p-value = 0.0066
LL37 1.6 mg/mL vs placebo: difference in RMST = -4.8 (-, 0.3),- p-value = 0.0407

Post-hoc: Attainment of target ulcer area reduction of at least 50% from baseline-estimated proportion of responders. FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point title	Attainment of target ulcer area reduction of at least 50% from baseline-estimated proportion of responders. FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point description:

Attainment of target ulcer area reduction of at least 50% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Post-hoc

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[90]	27[91]	26[92]	
Units: percentage				
arithmetic mean (confidence interval 90%)				
Estimated proportion of responders	51.6 (35.4 to 67.4)	32.8 (19.9 to 49.0)	58.7 (42.2 to 73.4)	

Notes:

[90] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[91] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[92] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Attainment ≥ 50% OR vs placebo (subgroup analysis)

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the target ulcer (dichotomised as < or ≥ 10cm²) and duration of the target ulcer at baseline.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [93]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[93] - LL37 0.5 mg/mL vs placebo: OR = 0.750 (0.292, -), p-value = 0.6920
LL37 1.6 mg/mL vs placebo: OR = 0.344 (0.133, -), p-value = 0.9669

Post-hoc: Attainment of target ulcer area reduction of at least 50% from baseline-estimated proportion of responders. FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point title	Attainment of target ulcer area reduction of at least 50% from baseline-estimated proportion of responders. FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point description:

Attainment of target ulcer area reduction of at least 50% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Post-hoc

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[94]	21[95]	24[96]	
Units: percentage				
arithmetic mean (confidence interval 90%)				
Estimated proportion of responders	61.9 (43.6 to 77.3)	38.2 (22.7 to 56.6)	33.3 (19.6 to 50.5)	

Notes:

[94] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[95] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[96] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Attainment ≥ 50% OR vs placebo (subgroup analysis)

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the target ulcer (dichotomised as < or ≥ 10cm²) and duration of the target ulcer at baseline.

Comparison groups	LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [97]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[97] - LL37 1.6 mg/mL vs placebo: OR = 1.240 (0.438,), p-value = 0.3669

Statistical analysis title	Attainment ≥ 50% OR vs placebo (subgrou...

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the target ulcer (dichotomised as < or ≥ 10cm²) and duration of the target ulcer at baseline.

Comparison groups	Placebo v LL37 0.5 mg/mL group
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [98]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[98] - LL37 0.5 mg/mL vs placebo: OR = 3.252 (1.165, -) , p-value = 0.0294

Post-hoc: Attainment of target ulcer area reduction of at least 70% from baseline-estimated proportion of responders FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point title	Attainment of target ulcer area reduction of at least 70% from baseline-estimated proportion of responders FAS, subgroup of patients with wound area less than 10 cm² at randomisation

End point description:

Attainment of target ulcer area reduction of at least 70% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Post-hoc

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[99]	27[100]	26[101]	
Units: percentage				
arithmetic mean (confidence interval 90%)				
Estimated proportion of responders	38.7 (24.2 to 55.6)	32.1 (19.3 to 48.3)	51.9 (35.8 to 67.7)	

Notes:

[99] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[100] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

[101] - FAS, subgroup of patients with wound area less than 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Attainment ≥ 70% OR vs placebo (subgroup analysis)

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the target ulcer (dichotomised as < or ≥ 10cm²) and duration of the target ulcer at baseline.

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority[102]
P-value	> 0.05 [103]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Confidence interval	
level	90 %
sides	1-sided

Notes:

[102] - One-sided tests of differences from placebo were performed for each of the two active treatment groups at the 0.05 significance level.
[103] - LL37 0.5 mg/mL vs placebo: OR = 0.586 (0.224, -), p-value = 0.8205
LL37 1.6 mg/mL vs placebo: OR = 0.438 (0.168, -), p-value = 0.9223

Post-hoc: Attainment of target ulcer area reduction of at least 70% from baseline-estimated proportion of responders. FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point title	Attainment of target ulcer area reduction of at least 70% from baseline-estimated proportion of responders. FAS, subgroup of patients with wound area at least 10 cm² at randomisation

End point description:

Attainment of target ulcer area reduction of at least 70% at end-of-treatment compared to baseline was analysed using logistic regression models.
Wound area measurements were performed at Visits 1, 3 and 6 (Run-in period), Visits 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32 (Treatment period) and at Visits 37 and 38 (follow-up period). Wound photography was performed at the same timepoints and at Visits 34 and 36 (post-wound closure period).
Note that the estimated proportion of responders is based on the statistical model (logistic regression analysis) and adjusted for covariates.

End point type	Post-hoc

End point timeframe:

Endpoint was assessed at the end of the treatment period and compared to the baseline.

End point values	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21[104]	21[105]	24[106]	
Units: percentage				
arithmetic mean (confidence interval 90%)				
Estimated proportion of responders	47.2 (30.3 to 64.8)	39.0 (23.3 to 57.5)	16.2 (7.2 to 32.5)	

Notes:

[104] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[105] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

[106] - FAS, subgroup of patients with wound area at least 10 cm² at randomisation

Statistical analyses

Statistical analysis title	Attainment ≥ 70%,OR vs placebo (subgroup analysis)

Statistical analysis description:

A logistic regression model was used. The model was adjusted for treatment, baseline area of the

Comparison groups	LL37 0.5 mg/mL group v LL37 1.6 mg/mL group v Placebo

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [107]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	1-sided

Notes:

[107] - LL37 0.5 mg/mL vs placebo: OR = 4.619 (1.450, -) , p-value = 0.0149
LL37 1.6 mg/mL vs placebo: OR = 3.307 (1.005, -), p-value = 0.0493

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Total study:
Screening and run-in period (Visits 1 to 6, Weeks -3 to -1)
Treatment period (Visits 7 to 32, Weeks 1 to 13)
Post-wound closure period (Visits 33 to 36, Weeks 14 to 15)
Follow-up period (Visits 37 and 38, Weeks 21 and 29)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	LL37 0.5 mg/mL group
Reporting group description: -	
Reporting group title	LL37 1.6 mg/mL group
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)	6 / 49 (12.24%)	1 / 51 (1.96%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 51 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 51 (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
Lower limb fracture			

subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 51 (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
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 48 (2.08%)	1 / 49 (2.04%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 51 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 48 (0.00%)	1 / 49 (2.04%)	0 / 51 (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			
Asthma			
subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 51 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 48 (0.00%)	0 / 49 (0.00%)	1 / 51 (1.96%)
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			
Erysipelas			
subjects affected / exposed	1 / 48 (2.08%)	1 / 49 (2.04%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 48 (2.08%)	0 / 49 (0.00%)	0 / 51 (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: 5 %

Non-serious adverse events	LL37 0.5 mg/mL group	LL37 1.6 mg/mL group	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 48 (31.25%)	14 / 49 (28.57%)	10 / 51 (19.61%)
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	6 / 48 (12.50%)	4 / 49 (8.16%)	3 / 51 (5.88%)
occurrences (all)	15	9	5
Underdose			
subjects affected / exposed	2 / 48 (4.17%)	3 / 49 (6.12%)	1 / 51 (1.96%)
occurrences (all)	5	5	2
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 48 (4.17%)	2 / 49 (4.08%)	3 / 51 (5.88%)
occurrences (all)	2	2	3
Infections and infestations			
Wound infection			
subjects affected / exposed	3 / 48 (6.25%)	2 / 49 (4.08%)	3 / 51 (5.88%)
occurrences (all)	4	2	3
Erysipelas			
subjects affected / exposed	2 / 48 (4.17%)	3 / 49 (6.12%)	0 / 51 (0.00%)
occurrences (all)	4	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2018	The first CSP version under which patients were included in the study was version 1.0 (dated 2018 03-01). After this, there was one protocol amendment in the study, resulting in CSP version 2.0 (dated 2018 06-11). Changes included sample time point correction, clarification of description of blinding and unblinding, as well as clarification that patients with missing data should be considered as non-responders in the main analysis on the full analysis set, upon request from the Swedish competent authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported