Clinical trial results:
Randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of “Lixim 70 mg wirkstoffhaltiges Pflaster” (etofenamate 70 mg medicated plaster) applied once daily (every 24 hours) or twice daily (every 12 hours) vs. matching placebo in the short-term symptomatic treatment of local pain in acute uncomplicated ankle sprains in adults

Summary

EudraCT number	2020-001032-99
Trial protocol	DE
Global end of trial date	04 May 2021

Results information

Result version number	v1 (current)
This version publication date	23 September 2022
First version publication date	23 September 2022

Trial information

Trial identification

Sponsor protocol code	DRO-200-III-20-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Drossapharm AG
Sponsor organisation address	Birsweg 1, Arlesheim, Switzerland, 4144
Public contact	Prof. Dr. Bruno Giannetti, Clinsearch GmbH, 41 417116376, info@clinsearch.ch
Scientific contact	Prof. Dr. Bruno Giannetti, Clinsearch GmbH, 41 417116376, info@clinsearch.ch

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	15 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the Lixim plaster applied once every 24 hours is superior to matching placebo plasters, in particular with regard to pain relief.

Protection of trial subjects:

This clinical trial was designed and was implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including applicable European Directives, AMG and GCP-V), and with the ethical principles laid down in the Declaration of Helsinki.

Every patient was informed verbally and also in writing, with a patient information leaflet explaining the nature of the study, its objectives, the study medication and potential risks, the rights and obligations of the participant and the fact that he was free to withdraw his consent at any time without giving any reason. Details of indemnity and insurance were also stated. All questions about the trial were answered to the satisfaction of the patient.

Women of child bearing potential had to be informed that taking the IMP may involve unknown risks to the fetus if pregnancy occurred during the clinical trial and agree that in order to participate in the clinical trial, they must adhere to the contraception requirement for the duration of the clinical trial.

Prior to the participation in the trial, a written informed consent form had to be signed and personally dated by the subject and by the person who conducted the informed consent. The patient’s information and informed consent form were available in the local language.

The final trial protocol together with the patient information sheet, the informed consent form and the Investigator’s drug brochure were submitted to the involved Ethics Committees and were constituted to fulfil regulatory laws. The study was approved by all Ethics Committees before clinical trial start.

Background therapy:

Not applicable.

Evidence for comparator:

None.

List of abbreviations:
ADR - Adverse Drug Reaction
AE - Adverse event
AMG - Arzneimittelgesetz, German Medicinal Products Act
ANOVA - Analysis of Variance
ATC - Anatomical Therapeutic Chemical Classification System
AUC - Area under the Curve
BID - twice daily, from Latin "bis in die"
BMI - Body-Mass Index
C - Concentration
FAS - Full Analysis Set
FDA - Food and Drug Administration
GCP - Good Clinical Practice
GLP - Good Laboratory Practice
GMP - Good Manufacturing Practice
h - hours
ICF - Informed Consent Form

ICH - International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP - Investigational Medicinal Product
kg - kilogram
l/L - Litre
LC-MS/MS - Liquid Chromatography Hyphenated with Tandem Mass Spectrometry
MedDRA - Medical Dictionary for Regulatory Activities
mg - milligram
min - Minutes
ml - millilitres
N - Number of subjects
PK - Pharmacokinetic
PPS - Per Protocol Set
PPSLT - Per Protocol Set Local Tolerability
PPSPA - Per Protocol Set Plaster Adhesion
PPSPK - Per Protocol Set Pharmacokinetic
PT - Preferred Term
PTAE - Pre-Treatment Adverse Event
R - Reference
SAE - Serious Adverse Event
SD - Standard Deviation
SOC - System Organ Class
t - time
T - Test
TEAE - Treatment-Emergent Adverse Event
WHO - World Health Organisation

Actual start date of recruitment	01 September 2020
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	Germany: 223
Worldwide total number of subjects	223
EEA total number of subjects	223

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)	223
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 223 male and female adult patients with local pain in acute uncomplicated ankle sprains and aged on average 36.0 years were enrolled from four study centers in Germany between November 2020 and May 2021.

Pre-assignment

Screening details:

Subjects were eligible for enrollment according to the trial inclusion and exclusion criteria.

Period 1

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

Blinding implementation details:

The clinical trial was double-blind with respect to allocation to active and placebo plasters from the time of randomization until database lock, using the following methods:
(1) randomization data were kept strictly confidential, accessible only to authorized persons, until the time of unblinding;
(2) the identity of the treatments was concealed by the use of IMPs that were all identical in packaging, labeling, schedule of administration, appearance and odor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Lixim plaster applied once daily (o.d.)

Arm description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Arm type	Experimental
Investigational medicinal product name	Lixim 70 mg wirkstoffhaltiges Pflaster
Investigational medicinal product code	
Other name	etofenamate 70 mg medicated plaster
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical

Dosage and administration details:

One plaster of Lixim 70 mg wirkstoffhaltiges Pflaster applied topically once daily (morning or evening) to the affected side of the injured ankle for 7 (±1) days.

Arm title	Lixim plaster applied twice daily (b.i.d.)

Arm description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Arm type	Active comparator

Investigational medicinal product name	Lixim 70 mg wirkstoffhaltiges Pflaster
Investigational medicinal product code	
Other name	etofenamate 70 mg medicated plaster
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical

Dosage and administration details:

One plaster of Lixim 70 mg wirkstoffhaltiges Pflaster applied topically twice daily (morning and evening) to the affected side of the injured ankle for 7 (±1) days.

Arm title	Placebo applied once daily (o.d.)

Arm description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Arm type	Placebo
Investigational medicinal product name	Placebo plaster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical

Dosage and administration details:

The placebo plaster was identical in composition to the Lixim plaster, without the active ingredient.
One placebo plaster was applied topically once daily (morning or evening) to the affected side of the injured ankle for 7 (±1) days.

Arm title	Placebo applied twice daily (b.i.d.)

Arm description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Arm type	Placebo
Investigational medicinal product name	Placebo plaster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous patch
Routes of administration	Topical

Dosage and administration details:

The placebo plaster was identical in composition to the Lixim plaster, without the active ingredient.
One placebo plaster was applied topically twice daily (morning and evening) to the affected side of the injured ankle for 7 (±1) days.

Number of subjects in period 1	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)
Started	80	80	31
Completed	80	80	31

Number of subjects in period 1	Placebo applied twice daily (b.i.d.)
Started	32
Completed	32

Baseline characteristics

Reporting groups	
Reporting group title	Lixim plaster applied once daily (o.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Reporting group title	Lixim plaster applied twice daily (b.i.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Reporting group title	Placebo applied once daily (o.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Reporting group title	Placebo applied twice daily (b.i.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Reporting group values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)
Number of subjects	80	80	31
Age categorical Units: Subjects			
Adults (18-64 years)	80	80	31
Age continuous Units: years			
median	36.2	35.3	36.5
standard deviation	± 11.5	± 11.6	± 12.7
Gender categorical Units: Subjects			
Female	36	39	11
Male	44	41	20

Reporting group values	Placebo applied twice daily (b.i.d.)	Total	

Number of subjects	32	223	
Age categorical Units: Subjects			
Adults (18-64 years)	32	223	
Age continuous Units: years			
median	36.6		
standard deviation	± 11.0	-	
Gender categorical Units: Subjects			
Female	16	102	
Male	16	121	

End points

End points reporting groups

Reporting group title	Lixim plaster applied once daily (o.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Reporting group title	Lixim plaster applied twice daily (b.i.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Reporting group title	Placebo applied once daily (o.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Reporting group title	Placebo applied twice daily (b.i.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Primary: Ankle pain-on-movement (POM) - change from baseline at Visit 5

End point title	Ankle pain-on-movement (POM) - change from baseline at Visit 5

End point description:

The primary efficacy outcome was change from baseline of ankle POM assessed by Visual Analogue Scale (VAS) at Visit 5 (72 hours after initiating treatment).

End point type	Primary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-47.8 (± 12.6)	-45.8 (± 12.6)	-29.8 (± 17.9)	-29.6 (± 19.1)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.

Statistical analysis description:

For quantitative outcomes assessed at the clinical trial site (POM, PAR, ankle swelling) and derived outcomes (change from baseline, AUC) null hypothesis was to be tested with an analysis of covariance (ANCOVA) model with baseline value as covariate and site as fixed factor. The least square mean for each treatment and the corresponding difference between least square means (Lixim plaster - placebo) with the p-value and 95 % confidence interval were to be presented from the model.

Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	-14
Variability estimate	Standard error of the mean
Dispersion value	2.6

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.8
upper limit	-11.7

Variability estimate	Standard error of the mean
Dispersion value	2.8

Statistical analysis title	o.d. vs. b.i.d.

Statistical analysis description:

Once-vs-twice-daily-comparison of (once daily active) group C vs. (twice daily active) group A: H0: μC = μA - Δ; Non-Inferiority test (by superiority test against the shifted alternative: C better than A - Δ, or analogously by assessment of the two-sided 95-confidence interval for the mean differences) at two-sided level α = 5 %; based on PP population. However, the PP population was equal to the FAS population according to the decisions taken at the BDRM.

Comparison groups	Lixim plaster applied once daily (o.d.) v Lixim plaster applied twice daily (b.i.d.)
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	LS Means treatment effect
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	1.6

Secondary: Ankle POM - change from baseline at V3

End point title	Ankle POM - change from baseline at V3

End point description:

Change from baseline of ankle POM on VAS at Visit 3 (24 hours after initiating treatment).

End point type	Secondary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-25.2 (± 15.2)	-23.6 (± 12.7)	-13.5 (± 11.5)	-15.5 (± 15.8)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once

	daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3
upper limit	-8.2
Variability estimate	Standard error of the mean
Dispersion value	2.3

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.6
upper limit	-4.2
Variability estimate	Standard error of the mean
Dispersion value	2.4

Secondary: Ankle POM - change from baseline at V4	
End point title	Ankle POM - change from baseline at V4
End point description:	
Change from baseline of ankle POM on VAS at Visit 4 (48 hours after initiating treatment).	
End point type	Secondary
End point timeframe:	
POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit	

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-37.9 (± 14.4)	-34.5 (± 13.0)	-21.6 (± 17.2)	-21.7 (± 17.8)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-17.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	-12.1
Variability estimate	Standard error of the mean
Dispersion value	2.6

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-13.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	-8.5
Variability estimate	Standard error of the mean
Dispersion value	2.6

Secondary: Ankle POM - change from baseline at V6	
End point title	Ankle POM - change from baseline at V6
End point description: Change from baseline of ankle POM on VAS at Visit 6 (96 hours after initiating treatment).	
End point type	Secondary
End point timeframe: POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit	

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-55.8 (± 11.0)	-54.6 (± 12.8)	-36.6 (± 18.6)	-37.1 (± 20.6)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.2
upper limit	-15.6
Variability estimate	Standard error of the mean
Dispersion value	2.4

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-18.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	-13.1
Variability estimate	Standard error of the mean
Dispersion value	2.8

Secondary: Ankle POM - change from baseline at V7

End point title	Ankle POM - change from baseline at V7
End point description:	
The changes in POM on VAS from baseline to Visit 7.	
End point type	Secondary
End point timeframe:	
POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit	

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-64.1 (± 10.6)	-62.1 (± 12.8)	-48.5 (± 16.2)	-49.8 (± 17.6)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-17.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	-12.8
Variability estimate	Standard error of the mean
Dispersion value	2.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.2
upper limit	-9
Variability estimate	Standard error of the mean
Dispersion value	2.3

Secondary: Pain-at-rest (PAR) - change from baseline at V5

End point title	Pain-at-rest (PAR) - change from baseline at V5

End point description:

The patient was asked to sit down on a chair with the injured leg touching the ground. After five minutes of sitting in this position, the extent of ankle pain was evaluated by the patient in answer to the question: "How would you describe your ankle pain right now?" ("Wie würden Sie Ihre Schmerzen in Ihrem Sprunggelenk in diesem Moment beschreiben?"). The patient drew a perpendicular line on a 100 mm Visual Analogue Scale (VAS) with anchors at 0 = "no pain (keine Schmerzen)" and 100 = "Extreme pain (extreme Schmerzen)" to reflect the pain intensity at rest.

End point type	Secondary

End point timeframe:

Pain-at-rest (PAR) was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-17.2 (± 10.8)	-15.6 (± 12.1)	-14.8 (± 10.7)	-12.9 (± 9.9)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Placebo applied once daily (o.d.) v Lixim plaster applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0768
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0071
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	-0.9
Variability estimate	Standard error of the mean
Dispersion value	1.2

Secondary: AUC of POM VAS over the 0-24 hour interval	
End point title	AUC of POM VAS over the 0-24 hour interval

End point description:

The areas-under-the-curve (AUCs) over time between baseline (0 h) and the first 24 hours after initiating treatment were calculated by means of the trapezoidal rule for pain-on-movement measured by VAS as secondary efficacy variables. Lower AUC values represent less pain and therefore a better clinical outcome.

End point type	Secondary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm*h				
arithmetic mean (standard deviation)	1369.4 (± 234.9)	1371.2 (± 276.2)	1551.8 (± 229.1)	1477.7 (± 239.9)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-161.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-223.7
upper limit	-99.3
Variability estimate	Standard error of the mean
Dispersion value	31.4

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-83.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-152.8
upper limit	-13.4
Variability estimate	Standard error of the mean
Dispersion value	35.2

Secondary: AUC of POM VAS over the 0-48 hour interval

End point title	AUC of POM VAS over the 0-48 hour interval

End point description:

The areas-under-the-curve (AUCs) over time between baseline (0 h) and the first 48 hours after initiating treatment were calculated by means of the trapezoidal rule for pain-on-movement measured by VAS as secondary efficacy variables. Lower AUC values represent less pain and therefore a better clinical outcome.

End point type	Secondary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm*h				
arithmetic mean (standard deviation)	2259.6 (± 561.0)	2323.1 (± 536.3)	2787.4 (± 535.0)	2706.8 (± 618.3)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-493.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-647.6
upper limit	-339.4
Variability estimate	Standard error of the mean
Dispersion value	77.7

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-351.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-520.7
upper limit	-183.2
Variability estimate	Standard error of the mean
Dispersion value	85.1

Secondary: AUC of POM VAS over the 0-72 hour interval

End point title	AUC of POM VAS over the 0-72 hour interval

End point description:

The areas-under-the-curve (AUCs) over time between baseline (0 h) and the first 72 hours after initiating treatment were calculated by means of the trapezoidal rule for pain-on-movement measured by VAS as secondary efficacy variables. Lower AUC values represent less pain and therefore a better clinical outcome.

End point type	Secondary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm*h				
arithmetic mean (standard deviation)	2890.9 (± 857.8)	3018.3 (± 786.2)	3863.8 (± 973.3)	3779.1 (± 1048.1)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-927
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1187.8
upper limit	-666.2
Variability estimate	Standard error of the mean
Dispersion value	131.5

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-723.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1007.4
upper limit	-439
Variability estimate	Standard error of the mean
Dispersion value	143.3

Secondary: AUC of POM VAS over the 0-96 hour interval

End point title	AUC of POM VAS over the 0-96 hour interval

End point description:

The areas-under-the-curve (AUCs) over time between baseline (0 h) and the first 96 hours after initiating treatment were calculated by means of the trapezoidal rule for pain-on-movement measured by VAS as secondary efficacy variables. Lower AUC values represent less pain and therefore a better clinical outcome.

End point type	Secondary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm*h				
arithmetic mean (standard deviation)	3306.7 (± 1078.9)	3472.7 (± 979.0)	4760.4 (± 1416.1)	4666.9 (± 1490.2)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-1399.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1759.5
upper limit	-1039.6
Variability estimate	Standard error of the mean
Dispersion value	181.5

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-1153.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1554.5
upper limit	-751.7
Variability estimate	Standard error of the mean
Dispersion value	202.5

Secondary: Ankle swelling V2 (12h)

End point title	Ankle swelling V2 (12h)

End point description:

Ankle swelling was evaluated by the Figure-of-eight-method. The Figure-of-eight-method was reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the Figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling. Each ankle was measured three times and the average was calculated. The difference in this average between ankles tracked the natural course of disease. The differences between the active groups and the placebo group were a measure of treatment efficacy.

End point type	Secondary

End point timeframe:

Ankle swelling was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: cm				
arithmetic mean (standard deviation)	1.1 (± 0.8)	1.1 (± 0.6)	1.1 (± 0.9)	1.1 (± 0.7)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1027
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4738
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Ankle swelling V3 (24h)

End point title	Ankle swelling V3 (24h)

End point description:

Ankle swelling was evaluated by the Figure-of-eight-method. The Figure-of-eight-method was reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the Figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling. Each ankle was measured three times and the average was calculated. The difference in this average between ankles tracked the natural course of disease. The differences between the active groups and the placebo group were a measure of treatment efficacy.

End point type	Secondary

End point timeframe:

Ankle swelling was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: cm				
arithmetic mean (standard deviation)	0.9 (± 0.7)	0.8 (± 0.5)	1.0 (± 0.9)	0.7 (± 0.5)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Placebo applied once daily (o.d.) v Lixim plaster applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0901
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8652
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2

Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Ankle swelling V4 (48h)

End point title	Ankle swelling V4 (48h)

End point description:

Ankle swelling was evaluated by the Figure-of-eight-method. The Figure-of-eight-method was reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the Figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling. Each ankle was measured three times and the average was calculated. The difference in this average between ankles tracked the natural course of disease. The differences between the active groups and the placebo group were a measure of treatment efficacy.

End point type	Secondary

End point timeframe:

Ankle swelling was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: cm				
arithmetic mean (standard deviation)	0.7 (± 0.7)	0.6 (± 0.5)	0.9 (± 0.8)	0.7 (± 0.5)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0176
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2618
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Ankle swelling V5 (72h)

End point title	Ankle swelling V5 (72h)

End point description:

Ankle swelling was evaluated by the Figure-of-eight-method. The Figure-of-eight-method was reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the Figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling. Each ankle was measured three times and the average was calculated. The difference in this average between ankles tracked the natural course of disease. The differences between the active groups and the placebo group were a measure of treatment efficacy.

End point type	Secondary

End point timeframe:

Ankle swelling was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: cm				
arithmetic mean (standard deviation)	0.6 (± 0.6)	0.5 (± 0.4)	0.8 (± 0.7)	0.6 (± 0.5)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0175
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1461
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Ankle swelling V6 (96h)

End point title	Ankle swelling V6 (96h)

End point description:

Ankle swelling was evaluated by the Figure-of-eight-method. The Figure-of-eight-method was reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the Figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling. Each ankle was measured three times and the average was calculated. The difference in this average between ankles tracked the natural course of disease. The differences between the active groups and the placebo group were a measure of treatment efficacy.

End point type	Secondary

End point timeframe:

Ankle swelling was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: cm				
arithmetic mean (standard deviation)	0.4 (± 0.5)	0.4 (± 0.4)	0.6 (± 0.7)	0.4 (± 0.4)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0153
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4646
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Ankle swelling V7 (7d)

End point title	Ankle swelling V7 (7d)

End point description:

Ankle swelling was evaluated by the Figure-of-eight-method. The Figure-of-eight-method was reproduced by using bony landmarks about the ankle. Common sites of ankle sprain swelling are the anterior talofibular ligament, calcaneofibular ligament, and anterior tibiofibular ligament. Because the tape spans each of these anatomical areas, the Figure-of-eight-method may offer a more accurate clinical assessment of ankle swelling. Each ankle was measured three times and the average was calculated. The difference in this average between ankles tracked the natural course of disease. The differences between the active groups and the placebo group were a measure of treatment efficacy.

End point type	Secondary

End point timeframe:

Ankle swelling was evaluated at Visits 1-7.

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: cm				
arithmetic mean (standard deviation)	0.3 (± 0.5)	0.3 (± 0.4)	0.5 (± 0.6)	0.3 (± 0.4)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0112
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6261
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Sum of Pain Intensity Differences (SPID) 0-24 h

End point title	Sum of Pain Intensity Differences (SPID) 0-24 h
End point description:	
SPID was calculated using following equation: Σ PIDi x (ti+1 – ti), with PIDi=[POM on VAS at Visit i] - [POM on VAS at Visit 1 (BL)] and t=time of Visit i. A higher score indicated less pain.	
End point type	Secondary
End point timeframe:	
POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit	

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-417.1 (± 282.2)	-382.4 (± 246.0)	-256.5 (± 264.4)	-275.8 (± 278.4)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-178
Confidence interval	
level	95 %
sides	2-sided
lower limit	-265.3
upper limit	-90.8
Variability estimate	Standard error of the mean
Dispersion value	44

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0046
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-120.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-203.6
upper limit	-38.1
Variability estimate	Standard error of the mean
Dispersion value	41.7

Secondary: SPID 0-48 h

End point title	SPID 0-48 h

End point description:
SPID was calculated using following equation: Σ PIDi x (ti+1 – ti), with PIDi=[POM on VAS at Visit i] - [POM on VAS at Visit 1 (BL)] and t=time of Visit i. A higher score indicated less pain.

End point type	Secondary

End point timeframe:
POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-1322 (± 601.8)	-1203 (± 527.1)	-730.7 (± 580.3)	-794.6 (± 682.8)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-633.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-817.6
upper limit	-449.5
Variability estimate	Standard error of the mean
Dispersion value	92.8

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-445

Confidence interval	
level	95 %
sides	2-sided
lower limit	-639
upper limit	-251
Variability estimate	Standard error of the mean
Dispersion value	97.9

Secondary: SPID 0-72 h

End point title	SPID 0-72 h

End point description:

SPID was calculated using following equation: Σ PIDi x (ti+1 – ti), with PIDi=[POM on VAS at Visit i] - [POM on VAS at Visit 1 (BL)] and t=time of Visit i. A higher score indicated less pain.

End point type	Secondary

End point timeframe:

POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-2467 (± 856.1)	-2301 (± 783.5)	-1443 (± 979.1)	-1502 (± 1121.9)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Lixim plaster applied once daily (o.d.) v Placebo applied once daily (o.d.)
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-1093.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1381.5
upper limit	-804.7
Variability estimate	Standard error of the mean
Dispersion value	145.5

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-859.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1175
upper limit	-543.6
Variability estimate	Standard error of the mean
Dispersion value	159.2

Secondary: SPID 0-96 h

End point title	SPID 0-96 h
End point description:	
SPID was calculated using following equation: Σ PIDi x (ti+1 – ti), with PIDi=[POM on VAS at Visit i] - [POM on VAS at Visit 1 (BL)] and t=time of Visit i. A higher score indicated less pain.	
End point type	Secondary
End point timeframe:	
POM was assessed at 24, 48, 72, 96, and 168 hours measured by 100 mm VAS – clinic visit	

End point values	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)	Placebo applied twice daily (b.i.d.)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	80	31	32
Units: mm				
arithmetic mean (standard deviation)	-3804 (± 1070.0)	-3615 (± 1015.0)	-2321 (± 1394.2)	-2321 (± 1581.3)

Statistical analyses

Statistical analysis title	Test vs. placebo o.d.
Comparison groups	Placebo applied once daily (o.d.) v Lixim plaster applied once daily (o.d.)

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-1581.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1968.5
upper limit	-1195.3
Variability estimate	Standard error of the mean
Dispersion value	195

Statistical analysis title	Test vs. placebo b.i.d.
Comparison groups	Lixim plaster applied twice daily (b.i.d.) v Placebo applied twice daily (b.i.d.)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean treatment effect
Point estimate	-1311.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1743.1
upper limit	-879.3
Variability estimate	Standard error of the mean
Dispersion value	217.9

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded throughout the clinical trial from randomization on.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Lixim plaster applied once daily (o.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Reporting group title	Lixim plaster applied twice daily (b.i.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Reporting group title	Placebo applied once daily (o.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 24 hours (in the morning or the evening, depending on time of first plaster application) for the following 7 days.

Reporting group title	Placebo applied twice daily (b.i.d.)

Reporting group description:

All patients were randomly assigned (allocation ratio 5:2:5:2) to double-blind treatment (Lixim plaster once daily, placebo once daily, Lixim plaster twice daily , placebo twice daily).

All patients received in total two packs containing 7 plasters each of IMP drug. The first plaster was applied at the clinical trial site by the investigator or the designee.
In this arm patients were instructed to apply a plaster approximately every 12 hours (in the morning and in the evening) for the following 7 days.

Serious adverse events	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo applied twice daily (b.i.d.)		

Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Lixim plaster applied once daily (o.d.)	Lixim plaster applied twice daily (b.i.d.)	Placebo applied once daily (o.d.)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 80 (0.00%)	0 / 80 (0.00%)	0 / 31 (0.00%)

Non-serious adverse events	Placebo applied twice daily (b.i.d.)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: During the course of the clinical trial no adverse events were reported for any patient of any of the treatment groups.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported