Clinical trial results:
Randomized, controlled, multi-center trial to evaluate the efficacy and safety of a Flurbiprofen 40 mg cutaneous hydrogel medicated plaster vs. placebo and vs. a marketed active comparator in the local symptomatic and short-term treatment of pain in acute strains, sprains or bruises of the soft tissues following blunt trauma, e.g. sports injuries

Summary

EudraCT number	2020-005217-41
Trial protocol	DE
Global end of trial date	16 August 2022

Results information

Result version number	v1 (current)
This version publication date	11 October 2023
First version publication date	11 October 2023

Trial information

Trial identification

Sponsor protocol code	51-03FPAEU

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Lead Chemical Company
Sponsor organisation address	77-3 Himata, Toyama-city Toyama, Japan, 930-0912
Public contact	Ilias Zontiros, Dr. Regenold GmbH, +49 76328226270, ilias.zontiros@regenold.com
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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	12 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine efficacy and safety of a flurbiprofen 40 mg cutaneous hydrogel medicated plaster (Test) compared to placebo and to a marketed active comparator in patients with acute strains, sprains or bruises (contusions) of the soft tissues following blunt trauma, e.g. sports injuries.
To demonstrate that the Test plaster is superior to placebo, is comparable to the active comparator, and that the Test plaster has acceptable local tolerability.

Protection of trial subjects:

This clinical study was designed and was implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice E6 (R2) [European Medicines Agency 2016], with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities. Subjects were monitored for adverse events throughout participation in the trial.

Background therapy:

Concomitant therapies allowed during the study:
• Rescue medication (paracetamol, 500 mg tablets) except for the 6 hours prior to visit 5 (72 h).
• Standard care by rest, ice, compression (non-occlusive bandage), or elevation (RICE) could have been considered following discussion with the Investigator.

Concomitant therapies prohibited during the study:
• Use of systemic or topical NSAIDs, analgesics (other than paracetamol), opioids, corticosteroids (except for topical treatment of bronchial asthma), heparin, or psychotropic agents.

The Investigator instructed the patient to notify the study center about any new medications and significant non-drug therapies (i.e. RICE) he/she took after the start of the study drug. All medications and significant non-drug therapies taken during the 30 days prior to Visit 1 (0h, Day 1) (including physical therapy and blood transfusions) or administered after the patient started treatment with study drug were listed on the Concomitant medications/Significant nondrug therapies CRF page. An AE CRF page was also completed, if appropriate.

Evidence for comparator: -

Actual start date of recruitment	09 November 2021
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: 312
Worldwide total number of subjects	312
EEA total number of subjects	312

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)	3
Adults (18-64 years)	303
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 312 healthy (151 female and 161 male) subjects were randomised. In total 310 out of 312 study participants (99.36 %) were Caucasian.
The trial was performed in 5 centers in Germany.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

Double-blind with respect to flurbiprofen and placebo formulations. Patients, investigator staff, persons performing the assessments, monitors, data analysts blinded until data base close. With respect to the active comparator, full blinding of patients and investigators could not be completely assured due to slight differences between Test and the Diclofenac-ratiopharm Schmerzpflaster. Measures were put in place to ensure that the opportunity was limited to become aware of treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Flurbiprofen (Test)

Arm description:

Flurbiprofen 40 mg cutaneous hydrogel medicated plaster was applied topically to the injury side once every 12 hours.

Arm type	Experimental
Investigational medicinal product name	Flurbiprofen 40 mg cutaneous hydrogel medicated plaster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Cutaneous use, Local use , Transdermal use

Dosage and administration details:

The Test product `Flurbiprofen 40 mg cutaneous hydrogel medicated plaster´ was applied topically to the injured site twice daily (i.e., every 12 hours) for 7 days.
Overall, subjects were exposed to 560 mg Flurbiprofen (7*2*40 mg).

Arm title	Placebo

Arm description:

The placebo plaster that did not contain the active ingredient but the excipients used in the placebo formulation were identical to the ones used in the Test formulation.
The placebo plaster was applied topically to the injury side once every 12 hours.

Arm type	Placebo
Investigational medicinal product name	Placebo plaster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Cutaneous use, Local use , Transdermal use

Dosage and administration details:

A single placebo plaster was applied topically to the injured site twice daily (i.e., every 12 hours) for 7 days.

Arm title	Active comparator

Arm description:

Diclofenac-ratiopharm Schmerzpflaster containing 140 mg of diclofenac sodium were used as marketed active comparator and had been purchased from the German market. Samples originated from normal production batches. No modifications were made to the authorized product other than clinical re-packaging and labelling. There was complete over-labelling of the sachets in order to conceal the branded labelling.
The active comparator plaster was applied topically to the injury side once every 12 hours.

Arm type	Experimental
Investigational medicinal product name	Diclofenac-ratiopharm Schmerzpflaster
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Transdermal patch
Routes of administration	Cutaneous use, Transdermal use, Local use

Dosage and administration details:

A single Diclofenac-ratiopharm plaster (diclofenac sodium 140 mg) was applied topically to the injured site
twice daily (i.e., every 12 hours) for 7 days.

Overall, subjects were exposed to 1960 mg Diclofenac (7*2*140 mg).

Number of subjects in period 1	Flurbiprofen (Test)	Placebo	Active comparator
Started	156	78	78
Completed	156	78	78

Baseline characteristics

Reporting groups

Reporting group title	Intervention

Reporting group description: -

Reporting group values	Intervention	Total	
Number of subjects	312	312	
Age categorical Units: Subjects			
Adolescents (12-17 years)	3	3	
Adults (18-64 years)	303	303	
From 65-84 years	6	6	
Age continuous Units: years			
arithmetic mean	36.6		
standard deviation	± 13.3	-	
Gender categorical Units: Subjects			
Female	151	151	
Male	161	161	

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was all randomized patients who received at least one dose of study drug. The FAS population was primary population for the analysis of efficacy. Any exclusions from the FAS population were made and documented before unblinding (e.g., never used study medication, randomized twice). Additional secondary populations could have been defined before unblinding

Reporting group values	Full Analysis Set (FAS)		
Number of subjects	312		
Age categorical Units: Subjects			
Adolescents (12-17 years)	3		
Adults (18-64 years)	303		
From 65-84 years	6		
Age continuous Units: years			
arithmetic mean	36.6		
standard deviation	± 13.3		
Gender categorical Units: Subjects			
Female	151		
Male	161		

End points

End points reporting groups

Reporting group title	Flurbiprofen (Test)

Reporting group description:

Flurbiprofen 40 mg cutaneous hydrogel medicated plaster was applied topically to the injury side once every 12 hours.

Reporting group title	Placebo

Reporting group description:

The placebo plaster that did not contain the active ingredient but the excipients used in the placebo formulation were identical to the ones used in the Test formulation.
The placebo plaster was applied topically to the injury side once every 12 hours.

Reporting group title	Active comparator

Reporting group description:

Diclofenac-ratiopharm Schmerzpflaster containing 140 mg of diclofenac sodium were used as marketed active comparator and had been purchased from the German market. Samples originated from normal production batches. No modifications were made to the authorized product other than clinical re-packaging and labelling. There was complete over-labelling of the sachets in order to conceal the branded labelling.
The active comparator plaster was applied topically to the injury side once every 12 hours.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) was all randomized patients who received at least one dose of study drug. The FAS population was primary population for the analysis of efficacy. Any exclusions from the FAS population were made and documented before unblinding (e.g., never used study medication, randomized twice). Additional secondary populations could have been defined before unblinding

Primary: Pain-on-movement (POM)

End point title	Pain-on-movement (POM)

End point description:

The primary efficacy outcome was pain-on-movement on VAS (using a 100 mm VAS from 0 = "no pain" to 100 = "extreme pain") at 72 hours (±4 h) after initiating treatment in the Full Analysis Set (FAS) population.
POM was induced by the same subject-specific standardised passive movement, and/or investigator-derived manipulation of the nearest joint. To standardize the procedure for the assessment of POM a special movement could have been performed by the patient, where possible, either for the upper limb or the lower limb depending on which limb was injured.

End point type	Primary

End point timeframe:

72 hours after initiating treatment (visit 5)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	14.1 (± 13.1)	30.1 (± 18.0)	14.4 (± 12.6)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Comparison groups	Active comparator v Flurbiprofen (Test)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8304
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3592
upper limit	4.1805

Statistical analysis title	Treatment comparison - Test vs. placebo
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7516
upper limit	-12.2702

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.7851
upper limit	-12.058

Secondary: Pain-on-movement (POM) at visit 1	
End point title	Pain-on-movement (POM) at visit 1

End point description:

As secondary endpoints POM measured by VAS at baseline.

End point type	Secondary

End point timeframe:

Visit 1

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	69.1 (± 7.3)	69.0 (± 7.5)	70.7 (± 8.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pain-on-movement (POM) at visit 2

End point title	Pain-on-movement (POM) at visit 2

End point description:

End point type	Secondary

End point timeframe:

Visit 2 (12 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	56.4 (± 11.9)	59.9 (± 11.3)	57.3 (± 14.5)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Comparison groups	Flurbiprofen (Test) v Active comparator

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6328
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8162
upper limit	2.9825

Statistical analysis title	Treatment comparison - Test vs. placebo
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1233
upper limit	-1.3617

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1028
upper limit	-1.5485

Secondary: Pain-on-movement (POM) at visit 3

End point title	Pain-on-movement (POM) at visit 3

End point description:

End point type	Secondary

End point timeframe:

Visit 3 (24 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	44.1 (± 15.3)	52.8 (± 15.9)	45.9 (± 17.0)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9006
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5159
upper limit	3.0957

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.0788
upper limit	-5.5184

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4149
upper limit	-4.7621

Secondary: Pain-on-movement (POM) at visit 4	
End point title	Pain-on-movement (POM) at visit 4
End point description:	
End point type	Secondary
End point timeframe:	
Visit 4 (48 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	26.8 (± 15.4)	41.3 (± 16.7)	27.8 (± 15.5)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.99
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.0998
upper limit	4.0479

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7044
upper limit	-10.6197

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3515
upper limit	-9.9207

Secondary: Pain-on-movement (POM) at visit 6

End point title	Pain-on-movement (POM) at visit 6

End point description:

End point type	Secondary

End point timeframe:

Visit 6 (96 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	7.1 (± 10.0)	19.8 (± 16.7)	6.6 (± 9.6)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.563
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2394
upper limit	4.1067

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description:

Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.852
upper limit	-9.555

Statistical analysis title	Treatment comparison - Comparator vs. placebo

Statistical analysis description:

Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3099
upper limit	-9.9645

Secondary: Pain-on-movement (POM) at visit 7

End point title	Pain-on-movement (POM) at visit 7

End point description:

End point type	Secondary

End point timeframe:

Visit 7 (168 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	1.2 (± 4.4)	8.1 (± 12.9)	1.6 (± 5.8)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as

covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7804
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3616
upper limit	1.7751

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description:

Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9704
upper limit	-4.8656

Statistical analysis title	Treatment comparison - Comparator vs. placebo

Statistical analysis description:

Pain-on-movement VAS - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.0189
upper limit	-4.2306

Secondary: AUC for POM on VAS - visit 3

End point title	AUC for POM on VAS - visit 3
End point description:	
For POM on VAS, partial AUCs were calculated based on the raw VAS values and actual times of scheduled visits.	
End point type	Secondary
End point timeframe:	
Visit 3 (24 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: mm*h				
arithmetic mean (standard deviation)	1358.24893160 (± 233.62331908)	1444.68322650 (± 235.21685419)	1387.33440170 (± 306.75795742)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7287
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.967
upper limit	52.8055

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-134.4
upper limit	-45.3194

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-149.73
upper limit	-45.8228

Secondary: AUC for POM on VAS - visit 4	
End point title	AUC for POM on VAS - visit 4
End point description:	

End point type	Secondary
End point timeframe:	
Visit 4 (48 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: mm*h				
arithmetic mean (standard deviation)	2178.71554490 (± 525.38989828)	2528.70192310 (± 553.90662209)	2235.73664530 (± 634.90203041)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8854
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-112.8
upper limit	130.64

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-477.26
upper limit	-235.71

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Confidence interval	
level	95 %
sides	2-sided
lower limit	-506.29
upper limit	-224.52

Secondary: AUC for POM on VAS - visit 5

End point title	AUC for POM on VAS - visit 5
End point description:	
End point type	Secondary
End point timeframe:	
Visit 5 (72 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: mm*h				
arithmetic mean (standard deviation)	2672.786859000 (± 806.58571556)	3393.589743600 (± 931.53411720)	2746.617521400 (± 931.50009354)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9012
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-191.65
upper limit	217.49

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-931.97
upper limit	-526

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Comparison groups	Active comparator v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-978.68
upper limit	-505.12

Secondary: AUC for POM on VAS - visit 6	
End point title	AUC for POM on VAS - visit 6
End point description:	
End point type	Secondary
End point timeframe:	
Visit 6 (hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: mm*h				
arithmetic mean (standard deviation)	2927.68750000 (± 1019.64577700)	3992.62446580 (± 1288.80139820)	2997.72115380 (± 1141.10623940)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8306
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-243.89
upper limit	303.45

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1344.89
upper limit	-801.78

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement AUC - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1419.89
upper limit	-786.35

Secondary: POM - Time to meaningful reduction (30%)

End point title	POM - Time to meaningful reduction (30%)

End point description:

End point type	Secondary

End point timeframe:

Time to meaningful (30 %) reduction of pain was calculated as 30 % reduction of baseline POM respectively, based on the VAS values measured for POM at the study visits.

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: hour				
arithmetic mean (standard deviation)	34.0 (± 20.5)	53.4 (± 28.3)	33.7 (± 16.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: POM - Time to optimal reduction (50%)

End point title	POM - Time to optimal reduction (50%)

End point description:

End point type	Secondary

End point timeframe:

Time to optimal (50 %) reduction of pain was calculated as 50 % reduction of baseline POM respectively, based on the VAS values measured for POM at the study visits.

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	72	78	
Units: hour				
arithmetic mean (standard deviation)	53.7 (± 28.1)	83.0 (± 44.8)	51.8 (± 25.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: POM - Time to complete resolution of pain

End point title	POM - Time to complete resolution of pain

End point description:

End point type	Secondary

End point timeframe:

Time to complete (100 %) resolution of pain was calculated as 100 % reduction of baseline POM, based on the VAS values measured for POM at the study visits.

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	42	59	
Units: hour				
arithmetic mean (standard deviation)	122.1 (± 45.3)	130.3 (± 43.4)	118.4 (± 46.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pain-at-rest (PAR) - visit 2

End point title	Pain-at-rest (PAR) - visit 2

End point description:

The patients' pain-at-rest (PAR) was assessed at baseline, V2 (12 h), V3 (24 h), V4 (48 h), V5 (72 h) and V6 (96 h) using a 100 mm VAS from 0 = "no pain" to 100 = "extreme pain" in response to the question:
"How would you describe the pain in the injured area at rest?"
From the assessments of PAR at baseline (screening visit) vs. all later visits the change from baseline was calculated as pain intensity difference (PID).

End point type	Secondary

End point timeframe:

Visit 2 (12 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-5.2 (± 5.5)	-3.0 (± 3.2)	-4.6 (± 4.5)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3229
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5102
upper limit	0.4992

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.0523
upper limit	-1.0475

Statistical analysis title	Treatment comparison - Comparator vs. placebo

Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Active comparator v Flurbiprofen (Test)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7078
upper limit	-0.381

Secondary: Pain-at-rest (PAR) - visit 3

End point title	Pain-at-rest (PAR) - visit 3
End point description:	
The patients' pain-at-rest (PAR) was assessed at baseline, V2 (12 h), V3 (24 h), V4 (48 h), V5 (72 h) and V6 (96 h) using a 100 mm VAS from 0 = "no pain" to 100 = "extreme pain" in response to the question: "How would you describe the pain in the injured area at rest?" From the assessments of PAR at baseline (screening visit) vs. all later visits the change from baseline was calculated as pain intensity difference (PID).	
End point type	Secondary
End point timeframe:	
Visit 3 (24 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: hour				
arithmetic mean (standard deviation)	-9.5 (± 7.1)	-6.1 (± 5.3)	-9.5 (± 7.1)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8666
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.0727
upper limit	1.2731

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3931
upper limit	-2.0526

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.6812
upper limit	-1.9648

Secondary: Pain-at-rest (PAR) - visit 4

End point title	Pain-at-rest (PAR) - visit 4

End point description:

The patients' pain-at-rest (PAR) was assessed at baseline, V2 (12 h), V3 (24 h), V4 (48 h), V5 (72 h) and V6 (96 h) using a 100 mm VAS from 0 = "no pain" to 100 = "extreme pain" in response to the question:
"How would you describe the pain in the injured area at rest?"
From the assessments of PAR at baseline (screening visit) vs. all later visits the change from baseline was calculated as pain intensity difference (PID).

End point type	Secondary

End point timeframe:

Visit 4 (48 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-13.6 (± 6.9)	-9.2 (± 5.6)	-13.1 (± 6.6)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4581
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3767
upper limit	0.6221

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.195
upper limit	-3.2007

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Active comparator v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9778
upper limit	-2.6632

Secondary: Pain-at-rest (PAR) - visit 5

End point title	Pain-at-rest (PAR) - visit 5

End point description:

The patients' pain-at-rest (PAR) was assessed at baseline, V2 (12 h), V3 (24 h), V4 (48 h), V5 (72 h) and V6 (96 h) using a 100 mm VAS from 0 = "no pain" to 100 = "extreme pain" in response to the question:
"How would you describe the pain in the injured area at rest?"
From the assessments of PAR at baseline (screening visit) vs. all later visits the change from baseline was calculated as pain intensity difference (PID).

End point type	Secondary

End point timeframe:

Visit 5 (72 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-15.1 (± 6.8)	-12.1 (± 6.4)	-15.1 (± 6.6)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7393
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6497
upper limit	0.9144

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4906
upper limit	-1.9299

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Active comparator v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7483
upper limit	-1.937

Secondary: Pain-at-rest (PAR) - visit 6

End point title	Pain-at-rest (PAR) - visit 6

End point description:

The patients' pain-at-rest (PAR) was assessed at baseline, V2 (12 h), V3 (24 h), V4 (48 h), V5 (72 h) and V6 (96 h) using a 100 mm VAS from 0 = "no pain" to 100 = "extreme pain" in response to the question:
"How would you describe the pain in the injured area at rest?"
From the assessments of PAR at baseline (screening visit) vs. all later visits the change from baseline was calculated as pain intensity difference (PID).

End point type	Secondary

End point timeframe:

Visit 6 (96 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-16.0 (± 6.7)	-13.8 (± 6.3)	-15.8 (± 6.6)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5641
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7271
upper limit	0.3972

Statistical analysis title	Treatment comparison - Comparator vs. placebo

Statistical analysis description:

Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS

Comparison groups	Active comparator v Placebo

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4747
upper limit	-1.1728

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-at-rest PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5495
upper limit	-1.4278

Secondary: POM - responder rate - visit 5

End point title	POM - responder rate - visit 5
End point description:	
The responder rate was defined as the number of patients achieving at least 50% reduction from baseline in the VAS score for POM at 72 hours.	
End point type	Secondary
End point timeframe:	
Visit 5 (72 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: Yes	142	43	73	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

POM Responder - response at Visit 5 (72 h) stratified by center - frequency analysis including 95% CI and CMH test of general association, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4982
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description:

POM Responder - response at Visit 5 (72 h) stratified by center - frequency analysis including 95% CI and CMH test of general association, FAS

Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Treatment comparison - Comparator vs. placebo

Statistical analysis description:

POM Responder - response at Visit 5 (72 h) stratified by center - frequency analysis including 95% CI and CMH test of general association, FAS

Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: POM - Pain Intensity Difference (PID) - visit 2

End point title	POM - Pain Intensity Difference (PID) - visit 2

End point description:

PID (Pain Intensity Difference calculated as reduction in VAS for POM from baseline) was a derived parameter calculated from POM data and used as secondary endpoint. Negative PID values indicate pain reduction.

End point type	Secondary

End point timeframe:

Visit 2 (12 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-12.8 (± 10.7)	-9.1 (± 9.1)	-13.4 (± 11.3)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.6328
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8162
upper limit	2.9825

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1233
upper limit	-1.3617

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1028
upper limit	-1.5485

Secondary: POM - Pain Intensity Difference (PID) - visit 3

End point title	POM - Pain Intensity Difference (PID) - visit 3
End point description:	
PID (Pain Intensity Difference calculated as reduction in VAS for POM from baseline) was a derived parameter calculated from POM data and used as secondary endpoint. Negative PID values indicate pain reduction.	
End point type	Secondary
End point timeframe:	
Visit 3 (24 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-25.0 (± 14.4)	-16.3 (± 13.7)	-24.8 (± 13.4)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9006
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5159
upper limit	3.0957

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.0788
upper limit	-5.5184

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.4149
upper limit	-4.7621

Secondary: POM - Pain Intensity Difference (PID) - visit 4

End point title	POM - Pain Intensity Difference (PID) - visit 4

End point description:

PID (Pain Intensity Difference calculated as reduction in VAS for POM from baseline) was a derived parameter calculated from POM data and used as secondary endpoint. Negative PID values indicate pain reduction.

End point type	Secondary

End point timeframe:

Visit 4 (48 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-42.3 (± 16.2)	-27.7 (± 15.1)	-42.8 (± 13.0)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.99
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.0998
upper limit	4.0479

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description:

Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Placebo

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7044
upper limit	-10.6197

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.3515
upper limit	-9.9207

Secondary: POM - Pain Intensity Difference (PID) - visit 5

End point title	POM - Pain Intensity Difference (PID) - visit 5
End point description:	
PID (Pain Intensity Difference calculated as reduction in VAS for POM from baseline) was a derived parameter calculated from POM data and used as secondary endpoint. Negative PID values indicate pain reduction.	
End point type	Secondary
End point timeframe:	
Visit 5 (72 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-55.0 (± 14.7)	-38.9 (± 16.8)	-56.3 (± 11.4)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8304
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.3592
upper limit	4.1805

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7516
upper limit	-12.2702

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.7851
upper limit	-12.058

Secondary: POM - Pain Intensity Difference (PID) - visit 6

End point title	POM - Pain Intensity Difference (PID) - visit 6
End point description:	
End point type	Secondary
End point timeframe:	
Visit 6 (96 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-62.0 (± 12.2)	-49.2 (± 16.7)	-64.1 (± 10.2)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.563
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2394
upper limit	4.1067

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.852
upper limit	-9.555

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement PID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Active comparator v Placebo
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.3099
upper limit	-9.9645

Secondary: POM - SPID (Sum of Pain Intensity Differences) - visit 3

End point title	POM - SPID (Sum of Pain Intensity Differences) - visit 3
End point description:	
SPID (Sum of Pain Intensity Differences) was derived parameter calculated from POM data and used as secondary endpoint. Negative SPID values indicate pain reduction. SPID was calculated as the time-weighted sum of pain intensity differences.	
End point type	Secondary
End point timeframe:	
Visit 3 (24 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-300.52029910 (± 195.36163866)	-211.62446580 (± 171.29802329)	-308.97329060 (± 205.46802941)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7287
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.967
upper limit	52.8055

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-134.4
upper limit	-45.3194

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-149.73
upper limit	-45.8228

Secondary: POM - SPID (Sum of Pain Intensity Differences) - visit 4	
End point title	POM - SPID (Sum of Pain Intensity Differences) - visit 4
End point description:	
SPID (Sum of Pain Intensity Differences) was derived parameter calculated from POM data and used as secondary endpoint. Negative SPID values indicate pain reduction. SPID was calculated as the time-weighted sum of pain intensity differences.	
End point type	Secondary
End point timeframe:	
Visit 4 (48 hours)	

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-1138.82291700 (±	-783.91346150 (± 456.89601944)	-1156.87873900 (±	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8854
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-112.8
upper limit	130.64

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-477.26
upper limit	-235.71

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-506.29
upper limit	-224.52

Secondary: POM - SPID (Sum of Pain Intensity Differences) - visit 5

End point title	POM - SPID (Sum of Pain Intensity Differences) - visit 5

End point description:

SPID (Sum of Pain Intensity Differences) was derived parameter calculated from POM data and used as secondary endpoint. Negative SPID values indicate pain reduction. SPID was calculated as the time-weighted sum of pain intensity differences.

End point type	Secondary

End point timeframe:

Visit 5 (72 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-2303.52083300 (±	-1575.33333300 (±	-2342.30555600 (±	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9012
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-191.65
upper limit	217.49

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description:

Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Flurbiprofen (Test) v Placebo

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-931.97
upper limit	-526

Statistical analysis title	Treatment comparison - Comparator vs. placebo

Statistical analysis description:

Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS

Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-978.68
upper limit	-505.12

Secondary: POM - SPID (Sum of Pain Intensity Differences) - visit 6

End point title	POM - SPID (Sum of Pain Intensity Differences) - visit 6

End point description:

SPID (Sum of Pain Intensity Differences) was derived parameter calculated from POM data and used as secondary endpoint. Negative SPID values indicate pain reduction. SPID was calculated as the time-weighted sum of pain intensity differences.

End point type	Secondary

End point timeframe:

Visit 6 (96 hours)

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	78	78	
Units: millimetre(s)				
arithmetic mean (standard deviation)	-3707.38942300 (± 1083.2468793	-2632.60630300 (± 1143.5024923	-3787.50961500 (±	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8306
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-243.89
upper limit	303.45

Statistical analysis title	Treatment comparison - Test vs. placebo
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1344.89
upper limit	-801.78

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description:	
Pain-on-movement SPID - treatment comparison by Visit – ANCOVA considering baseline value as covariate including type-III tests of fixed effects, FAS	
Comparison groups	Placebo v Active comparator

Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1419.89
upper limit	-786.35

Secondary: Time to resolution of tissue injury/contusion in days

End point title	Time to resolution of tissue injury/contusion in days

End point description:

End point type	Secondary

End point timeframe:

Resolution of soft tissue injury/contusion was assessed by the Investigator at the final study visit. The date was documented and used to derive the time span between "date of visit V1" and "date of resolution".

End point values	Flurbiprofen (Test)	Placebo	Active comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	78	77	
Units: day				
arithmetic mean (standard deviation)	5.9 (± 1.9)	7.9 (± 2.9)	6.1 (± 2.5)	

Statistical analyses

Statistical analysis title	Treatment comparison - Test vs. comparator

Statistical analysis description:

Resolution of tissue injury – Time to resolution by treatment – log-rank test stratified by center, FAS

Comparison groups	Flurbiprofen (Test) v Active comparator
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7691
Method	Logrank

Statistical analysis title	Treatment comparison - Test vs. placebo

Statistical analysis description: Resolution of tissue injury – Time to resolution by treatment – log-rank test stratified by center, FAS	
Comparison groups	Flurbiprofen (Test) v Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Statistical analysis title	Treatment comparison - Comparator vs. placebo
Statistical analysis description: Resolution of tissue injury – Time to resolution by treatment – log-rank test stratified by center, FAS	
Comparison groups	Placebo v Active comparator
Number of subjects included in analysis	155
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events (AEs) were evaluated at every visit (except randomisation visit).	
Adverse event reporting additional description:	
The Safety Analysis Set (SAF) was used for the evaluation of adverse events. The SAF included all randomized patients who received at least one dose of the study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Flurbiprofen (Test)
Reporting group description:	
Flurbiprofen 40 mg cutaneous hydrogel medicated plaster was applied topically to the injury side once every 12 hours.	
Reporting group title	Placebo
Reporting group description:	
The placebo plaster was applied topically to the injury side once every 12 hours.	
Reporting group title	Active comparator
Reporting group description:	
The active comparator plaster was applied topically to the injury side once every 12 hours.	

Serious adverse events	Flurbiprofen (Test)	Placebo	Active comparator
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 156 (0.00%)	0 / 78 (0.00%)	0 / 78 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Flurbiprofen (Test)	Placebo	Active comparator
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 156 (0.64%)	1 / 78 (1.28%)	5 / 78 (6.41%)
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	0 / 156 (0.00%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	0	0	1
Application site joint erythema			

subjects affected / exposed	0 / 156 (0.00%)	0 / 78 (0.00%)	2 / 78 (2.56%)
occurrences (all)	0	0	2
Application site rash			
subjects affected / exposed	0 / 156 (0.00%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	0	0	1
Immune system disorders			
Immunisation reaction			
subjects affected / exposed	0 / 156 (0.00%)	1 / 78 (1.28%)	0 / 78 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Asymptomatic COVID-19			
subjects affected / exposed	1 / 156 (0.64%)	0 / 78 (0.00%)	0 / 78 (0.00%)
occurrences (all)	1	0	0
Coronavirus infection			
subjects affected / exposed	0 / 156 (0.00%)	0 / 78 (0.00%)	1 / 78 (1.28%)
occurrences (all)	0	0	1

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