# EU Clinical Trials Register

## Clinical trial results:
**Randomized, controlled, double-blind, multi-center trial to evaluate the efficacy and safety of a Loxoprofen sodium 60 mg tape medicated plaster vs. placebo in the local symptomatic and short-term treatment of pain in acute strains, sprains or bruises of the extremities following blunt trauma, e.g. sports injuries**

### Summary

| EudraCT number | 2019-001038-32 |
|---|---|
| Trial protocol | DE |
| Global end of trial date | 19 March 2020 |

### Results information

| Result version number | v1 (current) |
|---|---|
| This version publication date | 04 April 2021 |
| First version publication date | 04 April 2021 |

### Trial information

### Trial identification

| Sponsor protocol code | 48-03LXPU |
|---|---|

### Additional study identifiers

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

Notes:

### Sponsors

| Sponsor organisation name | Lead Chemical Co. Ltd. |
|---|---|
| Sponsor organisation address | 77-3 Himata, Toyama, Japan, 930-0912 |
| Public contact | Dr. Regenold GmbH, Dr. Regenold GmbH, +49 763282260, info@regenold.com |
| Scientific contact | Dr. Regenold GmbH, Dr. Regenold GmbH, +49 763282260, info@regenold.com |

Notes:

### Paediatric regulatory details

| Is trial part of an agreed paediatric investigation plan (PIP) | No |
|---|---|
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 28 September 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 19 March 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Evaluate the efficacy of a loxoprofen sodium 60 mg tape medicated plaster, applied once a day, compared with placebo for up to 7 days, in male and female subjects with acute blunt, soft tissue injuries of the limbs (i.e. sports injuries). The study had a double-blind, randomized, multi-center, placebo-controlled, parallel group design.

Patients were randomized soon after the injury (from injury to initial treatment not >6 h). After the randomization Visit (V) 1 = Baseline, Day (D) 1, patients returned to the study center for post-baseline visits. Patients applied the plaster approximately every 24 hours for the following 7 days witnessed by clinical trial staff at the trial center for the first 5 days, then alone at home.

Patients assessed pain-on-movement (POM) and spontaneous pain-at-rest (PAR), as well as efficacy and safety of the treatment at each study visit i.e. V1 (D1), V2 (D1 or D2), V3 (D2), V4 (D3), V5 (D4), V6 (D5), and Final visit V7 (D7 ± 1D).

Protection of trial subjects:

The clinical trial protocol and amendments were approved by local ethics committees/Institutional Review Boards and Competent Authorities. The clinical trial was conducted in accordance with good clinical practice (GCP) and the Declaration of Helsinki. Informed consent was obtained in writing prior to any trial-related activities.
Patients were monitored for adverse events throughout participation in the study.

Background therapy:

Standard care by rest, ice, compression (non-occlusive bandage), or elevation (RICE) at the discretion of the Investigator.
Rescue medication (paracetamol) except for the 6 hours immediately preceding Visit 5 (72 h).

Evidence for comparator:

None.

Abbreviations used in this study entry
AE=Adverse event
ANCOVA=Analysis of covariance
AUC=Area under the curve
CI=Confidence interval
D=Day
GCP=Good Clinical Practice
h=hour
LSMeans = Least Square Means
PAR=Pain-at-rest
POM=Pain-on-movement
V=Visit
VAS=Visual Analogue Scale

| Actual start date of recruitment | 15 November 2019 |
|---|---|
| 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: 127 |
|---|---|
| Worldwide total number of subjects | 127 |
| EEA total number of subjects | 127 |

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) | 127 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

# Subject disposition

## Recruitment

Recruitment details:

Overall 127 adult male and female patients were recruited. All patients had acute blunt, soft-tissue injury or contusion (such as sports injuries) of the upper or lower limb. The trial was performed in 3 study centers in Germany.

## Pre-assignment

Screening details:

Patients were eligible for enrollment according to the trial inclusion and exclusion criteria. The size of injury was measured by the Investigator at randomisation  (V1). The size had to be at least 25 cm2 and at most 120 cm2, based on the largest perpendicular diameters.

## Period 1

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

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration, appearance, and odor.

### Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Loxoprofen sodium |

Arm description:

Patients received Loxoprofen sodium 60 mg tape medicated plaster applied once a day for up to 7 days.

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Loxoprofen sodium |
| Investigational medicinal product code | |
| Other name | Loxoprofen sodium hydrate |
| Pharmaceutical forms | Medicated plaster |
| Routes of administration | Transdermal use |

Dosage and administration details:

Loxoprofen sodium 60 mg tape medicated plaster was applied once a day, for up to 7 days.

Active ingredient: Loxoprofen sodium hydrate 68 mg (60 mg as anhydrate).

| **Arm title** | Placebo |
|---|---|

Arm description:

Patients received placebo plasters that were applied once a day for up to 7 days.

| Arm type | Placebo |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Medicated plaster |
| Routes of administration | Transdermal use |

Dosage and administration details:

Placebo plaster applied once a day, for up to 7 days.

Placebo plaster did not contain the active ingredient but was otherwise indistinguishable from the investigational drug tape medicated plaster.

| Number of subjects in period 1 | Loxoprofen sodium | Placebo |
|---|---|---|
| Started | 65 | 62 |
| Completed | 65 | 61 |
| Not completed | 0 | 1 |
|    Adverse event, non-fatal | - | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Loxoprofen sodium |
|---|---|
| Reporting group description: | |
| Patients received Loxoprofen sodium 60 mg tape medicated plaster applied once a day for up to 7 days. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients received placebo plasters that were applied once a day for up to 7 days. | |

| Reporting group values | Loxoprofen sodium | Placebo | Total |
|---|---|---|---|
| Number of subjects | 65 | 62 | 127 |
| Age categorical | | | |
| Units: Subjects | | | |
|     Adults (18-64 years) | 65 | 62 | 127 |
| Age continuous | | | |
| Units: years | | | |
|     arithmetic mean | 31.1 | 35.6 | |
|     standard deviation | ± 10.1 | ± 10.6 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
|     Female | 30 | 26 | 56 |
|     Male | 35 | 36 | 71 |
| Race | | | |
| Units: Subjects | | | |
|     Asian | 1 | 0 | 1 |
|     Caucasian | 64 | 61 | 125 |
|     Other | 0 | 1 | 1 |
| Height | | | |
| Units: cm | | | |
|     arithmetic mean | 176.0 | 177.0 | |
|     standard deviation | ± 10.2 | ± 10.3 | - |
| Weight | | | |
| Units: kg | | | |
|     arithmetic mean | 80.7 | 83.5 | |
|     standard deviation | ± 14.4 | ± 19.2 | - |
| Pain-on-movement at baseline | | | |
| Pain-on-movement at baseline. | | | |
| Units: mm | | | |
|     arithmetic mean | 75.8 | 75.7 | |
|     standard deviation | ± 8.2 | ± 8.6 | - |
| Pain-at-rest at baseline | | | |
| Pain-at-rest at baseline | | | |
| Units: mm | | | |
|     arithmetic mean | 27.9 | 28.9 | |
|     standard deviation | ± 21.2 | ± 22.4 | - |
| Size of injury at baseline | | | |
| Size of injury at baseline. | | | |
| Units: cm2 | | | |

| | | | |
|---|---|---|---|
| arithmetic mean | 42.3 | 44.3 | |
| standard deviation | ± 12.3 | ± 11.8 | - |

## End points

### End points reporting groups

| Reporting group title | Loxoprofen sodium |
|---|---|
| Reporting group description: | |
| Patients received Loxoprofen sodium 60 mg tape medicated plaster applied once a day for up to 7 days. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Patients received placebo plasters that were applied once a day for up to 7 days. | |

### Primary: 1_Pain-on-movement (POM) -- post treatment at 72 h

| End point title | 1_Pain-on-movement (POM) -- post treatment at 72 h |
|---|---|
| End point description: | |

Pain-on-movement (POM) at injured site in mm, measured using a 100 mm Visual Analogue Scale (VAS) at Visit 5 (Day 4, 72 h after start of the treatment).

POM was assessed in mm on a 100 mm VAS, where 0 mm = 'no pain', and 100 mm = 'extreme pain'.

Results are expressed as absolute change from baseline (baseline values minus post-baseline values).

| End point type | Primary |
|---|---|
| End point timeframe: | |
| Baseline (pre treatment Day 1), post treatment at 72 h (Day 4). | |

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[1] | 62[2] | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | 59.5 (± 16.7) | 36.5 (± 19.7) | | |

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

### Statistical analyses

| Statistical analysis title | POM Visit 5 (72 h post treatment) |
|---|---|
| Statistical analysis description: | |

Pain-on-movement at Visit 5 (72 h post treatment).

ANCOVA – Analysis-of-covariance with the factors treatment group, center, and baseline VAS pain-on-movement, as covariate.

LS Means treatment effect at V5 (72h post treatment), [Placebo minus Loxoprofen] in (mm).

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 [3] |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 23.1 |
| Confidence interval | |
|    level | 95 % |
|    sides | 2-sided |
|    lower limit | 18 |
|    upper limit | 28.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.6 |

Notes:

[3] - ANCOVA= Analysis-of-covariance with the factors treatment group, center, and baseline.

### Secondary: 2_AUC for pain-on-movement (POM) -- post treatment at 24, 48, 72, 96, and 168 h

| | |
|---|---|
| End point title | 2_AUC for pain-on-movement (POM) --  post treatment at 24, 48, 72, 96, and 168 h |

End point description:

Area under the curve (AUC) over time between baseline and the first 24, 48, 72, 96, and 168 h of treatment, for POM, as measured by visual analogue scale (VAS).

POM was assessed in mm on a 100 mm VAS, where 0 mm = 'no pain', and 100 mm = 'extreme pain'.

AUC was presented as ordinate = POM score in mm, abscissa = time after treatment.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Baseline (pre treatment, Day 1), post treatment at 24, 48, 72, 96, and 168 h.

| **End point values** | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[4] | 62[5] | | |
| Units: mm*h | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC (0-24 h) | 1433.2 (± 206.1) | 1587.2 (± 198.3) | | |
| AUC (0-48 h) | 2291.5 (± 489.2) | 2868.5 (± 461.2) | | |
| AUC (0-72 h) | 2850.3 (± 776.8) | 3958.0 (± 761.4) | | |
| AUC (0-96 h) | 3147.9 (± 1008.2) | 4770.2 (± 1063.2) | | |
| AUC (0-168 h) | 3578.1 (± 1509.6) | 6272.0 (± 1879.2) | | |

Notes:

[4] - Full Analysis Set

[5] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | 1_AUC (0-24 h) for POM |
|---|---|

Statistical analysis description:

Results shown represent the LS Mean difference for [Placebo minus Loxoprofen sodium], in mm*h.

AUC=Area-under-the-curve; ANCOVA=Analysis-of-covariance with the factors treatment group, center, and baseline as covariate.

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 156.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 99.4 |
| upper limit | 213.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 28.8 |

| Statistical analysis title | 2_AUC (0-48 h) for POM |
|---|---|

Statistical analysis description:

Results shown represent the LS Mean difference for [Placebo minus Loxoprofen sodium], in mm*h.

AUC=Area-under-the-curve; ANCOVA=Analysis-of-covariance with the factors treatment group, center, and baseline as covariate.

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 582.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 427.8 |
| upper limit | 736.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 78.1 |

| Statistical analysis title | 3_AUC (0-72 h) for POM |
|---|---|

Statistical analysis description:

Results shown represent the LS Mean difference for [Placebo minus Loxoprofen sodium], in mm*h.

AUC=Area-under-the-curve; ANCOVA=Analysis-of-covariance with the factors treatment group, center, and baseline as covariate.

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 1115.2 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 852.6 |
|     upper limit | 1377.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 132.7 |

| **Statistical analysis title** | 4_AUC (0-96 h) for POM |
|---|---|

Statistical analysis description:

Results shown represent the LS Mean difference for [Placebo minus Loxoprofen sodium], in mm*h.

AUC=Area-under-the-curve; ANCOVA=Analysis-of-covariance with the factors treatment group, center, and baseline as covariate.

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 1632.6 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 1274.6 |
|     upper limit | 1990.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 180.8 |

| **Statistical analysis title** | 5_AUC (0-168 h) for POM |
|---|---|

Statistical analysis description:

Results shown represent the LS Mean difference for [Placebo minus Loxoprofen sodium], in mm*h.

AUC=Area-under-the-curve; ANCOVA=Analysis-of-covariance with the factors treatment group, center, and baseline as covariate.

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 2711.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2136.8 |
| upper limit | 3285.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 290.2 |

### Secondary: 3_Pain-on-movement (POM) -- post treatment at 24, 48, 96, and 168 h

| End point title | 3_Pain-on-movement (POM) -- post treatment at 24, 48, 96, and 168 h |
|---|---|

End point description:

Pain-on-movement (POM) at injured site in mm, measured using a 100 mm Visual Analogue Scale (VAS).

POM was assessed in mm on a 100 mm VAS, where 0 mm = 'no pain', and 100 mm = 'extreme pain'.

Results are expressed as absolute change from baseline (baseline values minus post-baseline values).

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (pre treatment Day 1), post treatment at 24, 48, 96, and 168 h.

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[6] | 62[7] | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | | | | |
| POM (0-24 h) | 31.6 (± 14.5) | 15.6 (± 12.8) | | |
| POM (0-48 h) | 45.5 (± 15.8) | 24.2 (± 16.5) | | |
| POM (0-96 h) | 67.2 (± 14.1) | 47.3 (± 21.7) | | |
| POM (0-168 h) | 72.4 (± 12.8) | 62.8 (± 19.9) | | |

Notes:

[6] - Full Analysis Set

[7] - Full Analysis Set

### Statistical analyses

| Statistical analysis title | 1_POM (0-24 h) |
|---|---|

Statistical analysis description:

ANCOVA – Analysis-of-covariance with the factors treatment group, center, and baseline VAS pain-on-

movement, as covariate.

LS Means treatment effect at respective visit, [Placebo minus Loxoprofen] in (mm).

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 15.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.4 |
| upper limit | 20.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.3 |

| **Statistical analysis title** | 2_POM (0-48 h) |
|---|---|

Statistical analysis description:

ANCOVA – Analysis-of-covariance with the factors treatment group, center, and baseline VAS pain-on-movement, as covariate.

LS Means treatment effect at respective visit, [Placebo minus Loxoprofen] in (mm).

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 21.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 16.2 |
| upper limit | 26.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.6 |

| **Statistical analysis title** | 3_POM (0-96 h) |
|---|---|

Statistical analysis description:

ANCOVA – Analysis-of-covariance with the factors treatment group, center, and baseline VAS pain-on-movement, as covariate.

LS Means treatment effect at respective visit, [Placebo minus Loxoprofen] in (mm).

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 20 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 15.5 |
|     upper limit | 24.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.2 |

| Statistical analysis title | 4_POM (0-168 h) |
|---|---|

Statistical analysis description:

ANCOVA – Analysis-of-covariance with the factors treatment group, center, and baseline VAS pain-on-movement, as covariate.

LS Means treatment effect at respective visit, [Placebo minus Loxoprofen] in (mm).

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 9.6 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 6.4 |
|     upper limit | 12.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.6 |

## Secondary: 4_Pain-at-rest (PAR)

| End point title | 4_Pain-at-rest (PAR) |
|---|---|

End point description:

Pain-at-rest (PAR) at injured site at 24, 48, and 72 h post treatment.

PAR was assessed in mm on a 100 mm visual analogue scale (VAS), where 0 mm = 'no pain', and 100 mm = 'extreme pain'.

Results are expressed as absolute change from baseline (baseline values minus post-baseline values).

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Baseline (pre treatment, Day 1), post treatment at 24, 48, 72 h. | |

| **End point values** | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[8] | 62[9] | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | | | | |
| PAR (0-24 h) | 10.1 (± 13.9) | 5.1 (± 7.8) | | |
| PAR (0-48 h) | 16.3 (± 16.1) | 9.5 (± 11.8) | | |
| PAR (0-72 h) | 21.4 (± 18.4) | 14.5 (± 15.6) | | |

Notes:

[8] - Full Analysis Set

[9] - Full Analysis Set

## Statistical analyses

| **Statistical analysis title** | 1_PAR (0-24 h) |
|---|---|

Statistical analysis description:

LSMeans and p-values from ANCOVA with treatment and site as fixed effects and baseline PAR assessment as a covariate.

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0002 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 5.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.9 |
| upper limit | 8.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.5 |

| **Statistical analysis title** | 2_PAR (0-48 h) |
|---|---|

Statistical analysis description:

LSMeans and p-values from ANCOVA with treatment and site as fixed effects and baseline PAR

assessment as a covariate.

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 7.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5 |
| upper limit | 10.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.4 |

| **Statistical analysis title** | 3_PAR (0-72 h) |
|---|---|

Statistical analysis description:

LSMeans and p-values from ANCOVA with treatment and site as fixed effects and baseline PAR assessment as a covariate.

LSMeans = Least Square Means

| Comparison groups | Loxoprofen sodium v Placebo |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | ANCOVA |
| Parameter estimate | LS Means Difference |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 5.6 |
| upper limit | 10.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.2 |

## Secondary: 5_Time to meaningful reduction (30%) of pain-on-movement (POM)

| End point title | 5_Time to meaningful reduction (30%) of pain-on-movement (POM) |
|---|---|

End point description:

Time to meaningful (30%) reduction of POM.

A meaningful reduction of pain was defined as a reduction of 30% from baseline, measured on a visual analogue scale (VAS) for POM.

POM was assessed in mm on a 100 mm VAS, where 0 mm = 'no pain', and 100 mm = 'extreme pain'.

Results are expressed as the number of patients reaching a meaningful (30%) reduction of POM during the respective time interval.

Time to meaningful (30%) reduction of pain in hours (h):
Loxoprofen sodium, Median:  23.5 h, 95% CI: (23.1, 24.0)
Placebo, Median:  69.1 h, 95% CI: (48.5, 71.7)

| End point type | Secondary |
| --- | --- |
| End point timeframe: | |
| Baseline (pre treatment, Day 1), post treatment at 12, 24, 48, 72, 96, and 192 h. | |

| End point values | Loxoprofen sodium | Placebo | | |
| --- | --- | --- | --- | --- |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[10] | 62[11] | | |
| Units: subjects | | | | |
| Not achieved | 0 | 1 | | |
| < 12 h | 2 | 0 | | |
| 12 to < 24 h | 44 | 10 | | |
| 24 to < 48 h | 12 | 13 | | |
| 48 to < 72 h | 4 | 18 | | |
| 72 to < 96 h | 3 | 14 | | |
| 96 to < 192 h | 0 | 6 | | |

Notes:

[10] - Full Analysis Set

[11] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Time to meaningful reduction (30%) of POM |
| --- | --- |
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |

## Secondary: 6_Time to optimal reduction (50%) of pain-on-movement (POM)

| End point title | 6_Time to optimal reduction (50%) of pain-on-movement (POM) |
| --- | --- |
| End point description: | |

Time to optimal (50%) reduction  of POM.

An optimal reduction of pain was defined as a reduction of 50% from baseline, measured on a visual analogue scale (VAS) for POM.

POM was assessed in mm on a 100 mm VAS, where 0 mm = 'no pain', and 100 mm = 'extreme pain'.

Results are expressed as the number of patients reaching an optimal (50%) reduction of POM during the

respective time interval.

Time to optimal (50%) reduction of pain in hours (h):
Loxoprofen sodium, Median:  47.3 h, 95% CI: (44.8, 47.8)
Placebo, Median:  95.6 h, 95% CI: (71.9, 166.6)

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (pre treatment, Day 1), post treatment at 12, 24, 48, 72, 96, and 192 h.

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[12] | 62[13] | | |
| Units: subjects | | | | |
| Not achieved | 1 | 4 | | |
| < 12 h | 1 | 0 | | |
| 12 to < 24 h | 16 | 3 | | |
| 24 to < 48 h | 27 | 8 | | |
| 48 to < 72 h | 15 | 13 | | |
| 72 to < 96 h | 4 | 10 | | |
| 96 to < 192 h | 1 | 24 | | |

Notes:

[12] - Full Analysis Set

[13] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Time to optimal reduction (50%) of POM |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Logrank |

## Secondary: 7_Responder rate -- at least 50% reduction of POM at 72 h

| End point title | 7_Responder rate -- at least 50% reduction of POM at 72 h |
|---|---|

End point description:

Responder rate.

The responder rate is defined as the proportion of patients achieving at least 50% reduction of POM on Day 4 (72 h), compared with baseline.

Results are expressed as the number of responders reaching that level of POM reduction.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (pre treatment, Day 1), post treatment at 72 h (Day 4).

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[14] | 62[15] | | |
| Units: subjects | 34 | 22 | | |

Notes:

[14] - Full Analysis Set

[15] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Responder rate on Day 4 (72 h) |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0444 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 8_Clinical global assessment of efficacy -- 48 h -- (Investigator)

| End point title | 8_Clinical global assessment of efficacy -- 48 h -- (Investigator) |
|---|---|

End point description:

Clinical global assessment of efficacy at V4 (48 h post treatment), assessed by the Investigator

The investigator's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the investigator had to answer was:
Considering all the ways this treatment has affected the patient since he/she started in the study, how well is he/she doing?
The response options were: 'very good', 'good', 'fair', 'poor',  or 'very poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
|---|---|

End point timeframe:

Visit 4 (48 h post treatment)

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[16] | 62[17] | | |
| Units: subjects | | | | |
| Very good | 16 | 5 | | |
| Good | 39 | 13 | | |
| Fair | 8 | 32 | | |

| | | | | |
|---|---|---|---|---|
| Poor | 2 | 12 | | |
| Very poor | 0 | 0 | | |

Notes:

[16] - Full Analysis Set

[17] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Visit 4 (48 h) -- Investigator |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 9_Clinical global assessment of efficacy -- 72 h -- (Investigator)

| End point title | 9_Clinical global assessment of efficacy -- 72 h -- (Investigator) |
|---|---|

End point description:

Clinical global assessment of efficacy at V5 (72 h post treatment), assessed by the Investigator.

The investigator's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the investigator had to answer was:
Considering all the ways this treatment has affected the patient since he/she started in the study, how well is he/she doing?
The response options were: 'very good', 'good', 'fair', 'poor',  or 'very poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
|---|---|

End point timeframe:

Visit 5 (72 h post treatment)

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[18] | 62[19] | | |
| Units: subjects | | | | |
| Very good | 30 | 5 | | |
| Good | 26 | 15 | | |
| Fair | 6 | 27 | | |
| Poor | 3 | 15 | | |
| Very poor | 0 | 0 | | |

Notes:

[18] - Full Analysis Set

[19] - Full Analysis Set

**Statistical analyses**

| Statistical analysis title | Visit 5 (72 h) -- Investigator |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

**Secondary: 10_Clinical global assessment of efficacy -- 168 h -- (Investigator)**

| End point title | 10_Clinical global assessment of efficacy -- 168 h -- (Investigator) |
|---|---|

End point description:

Clinical global assessment of efficacy at V7 (168 h post treatment), assessed by the Investigator.

The investigator's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the investigator had to answer was:
Considering all the ways this treatment has affected the patient since he/she started in the study, how well is he/she doing?
The response options were: 'very good', 'good', 'fair', 'poor',  or 'very poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
|---|---|

End point timeframe:

Visit 7 (168 h post treatment)

| **End point values** | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[20] | 62[21] | | |
| Units: subjects | | | | |
| Very good | 34 | 9 | | |
| Good | 23 | 16 | | |
| Fair | 6 | 21 | | |
| Poor | 2 | 16 | | |
| Very poor | 0 | 0 | | |

Notes:

[20] - Full Analysis Set

[21] - Full Analysis Set

**Statistical analyses**

| Statistical analysis title | Visit 7 (168 h) -- Investigator |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 11_Clinical global assessment of efficacy -- 48 h -- (Patient)

| | |
|---|---|
| End point title | 11_Clinical global assessment of efficacy -- 48 h -- (Patient) |

End point description:

Clinical global assessment of efficacy at V4 (48 h post treatment), assessed by the patient.

The patient's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the patient had to answer was:
Considering all the ways this treatment has affected you since you started in the clinical trial, how well are you doing?
The response options were: 'very good', 'good', 'fair', 'poor', or 'very poor'.

The results are shown as the number of patients per response category.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Visit 4 (48 h post treatment)

| **End point values** | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[22] | 62[23] | | |
| Units: subjects | | | | |
| Very good | 14 | 3 | | |
| Good | 39 | 15 | | |
| Fair | 11 | 38 | | |
| Poor | 1 | 6 | | |
| Very poor | 0 | 0 | | |

Notes:

[22] - Full Analysis Set

[23] - Full Analysis Set

## Statistical analyses

| **Statistical analysis title** | Visit 4 (48 h) -- Patient |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 12_Clinical global assessment of efficacy -- 72 h -- (Patient)

| End point title | 12_Clinical global assessment of efficacy -- 72 h -- (Patient) |
|---|---|

End point description:

Clinical global assessment of efficacy at V5 (72 h post treatment), assessed by the patient.

The patient's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the patient had to answer was:
Considering all the ways this treatment has affected you since you started in the clinical trial, how well are you doing?
The response options were: 'very good', 'good', 'fair', 'poor',  or 'very poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
|---|---|

End point timeframe:

Visit 5 (72 h post treatment)

| **End point values** | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[24] | 62[25] | | |
| Units: subjects | | | | |
| Very good | 31 | 5 | | |
| Good | 26 | 23 | | |
| Fair | 6 | 21 | | |
| Poor | 2 | 13 | | |
| Very poor | 0 | 0 | | |

Notes:

[24] - Full Analysis Set

[25] - Full Analysis Set

### Statistical analyses

| **Statistical analysis title** | Visit 5 (72 h) -- Patient |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 13_Clinical global assessment of efficacy -- 168 h -- (Patient)

| End point title | 13_Clinical global assessment of efficacy -- 168 h -- (Patient) |
|---|---|

End point description:

Clinical global assessment of efficacy at V7 (168 h post treatment), assessed by the patient.

The patient's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the patient had to answer was:
Considering all the ways this treatment has affected you since you started in the clinical trial, how well are you doing?
The response options were: 'very good', 'good', 'fair', 'poor', or 'very poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
| --- | --- |
| End point timeframe: | |
| Visit 7 (168 h post treatment) | |

| End point values | Loxoprofen sodium | Placebo | | |
| --- | --- | --- | --- | --- |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64[26] | 62[27] | | |
| Units: subjects | | | | |
| Very good | 32 | 10 | | |
| Good | 23 | 18 | | |
| Fair | 8 | 25 | | |
| Poor | 1 | 9 | | |
| Very poor | 0 | 0 | | |

Notes:

[26] - Full Analysis Set

[27] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Visit 7 (168 h) -- Patient |
| --- | --- |
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 14_Treatment assessment -- 48 h -- (Patient)

| End point title | 14_Treatment assessment -- 48 h -- (Patient) |
| --- | --- |

End point description:

Treatment assessment at V4 (48 h post treatment), assessed by the patient.

The patient's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the patient had to answer was:
How do you rate this medication as a treatment for the pain of your soft tissue injury/contusion?
The response options were: 'excellent', 'very good', 'good', 'fair', or 'poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
| --- | --- |

End point timeframe:

Visit 4 (48 h post treatment)

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[28] | 62[29] | | |
| Units: subjects | | | | |
| Excellent | 5 | 1 | | |
| Very good | 22 | 8 | | |
| Good | 30 | 13 | | |
| Fair | 7 | 32 | | |
| Poor | 1 | 8 | | |

Notes:

[28] - Full Analysis Set

[29] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Visit 4 (48 h) -- Patient |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 15_Treatment assessment -- 72 h -- (Patient)

| End point title | 15_Treatment assessment -- 72 h -- (Patient) |
|---|---|

End point description:

Treatment assessment at V5 (72 h post treatment), assessed by the patient.

The patient's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the patient had to answer was:
How do you rate this medication as a treatment for the pain of your soft tissue injury/contusion?"
The response options were: 'excellent', 'very good', 'good', 'fair', or 'poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
|---|---|

End point timeframe:

Visit 5 (72 h post treatment)

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65[30] | 62[31] | | |
| Units: subjects | | | | |
| Excellent | 10 | 2 | | |
| Very good | 32 | 10 | | |
| Good | 13 | 14 | | |
| Fair | 8 | 26 | | |
| Poor | 2 | 10 | | |

Notes:

[30] - Full Analysis Set

[31] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Visit 5 (72 h) -- Patient |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 127 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

## Secondary: 16_Treatment assessment -- 168 h -- (Patient)

| End point title | 16_Treatment assessment -- 168 h -- (Patient) |
|---|---|

End point description:

Treatment assessment at V7 (168 h post treatment), assessed by the patient.

The patient's opinion on the global efficacy assessment of the IMP on the following 5-point Likert scale was documented.

The question that the patient had to answer was:
How do you rate this medication as a treatment for the pain of your soft tissue injury/contusion?"
The response options were: 'excellent', 'very good', 'good', 'fair', or 'poor'.

The results are shown as the number of patients per response category.

| End point type | Secondary |
|---|---|

End point timeframe:

Visit 7 (168 h post treatment)

| End point values | Loxoprofen sodium | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 64[32] | 62[33] | | |
| Units: subjects | | | | |
| Excellent | 8 | 5 | | |
| Very good | 32 | 8 | | |
| Good | 16 | 15 | | |
| Fair | 7 | 26 | | |

| | | | | |
|---|---|---|---|---|
| Poor | 1 | 8 | | |

Notes:

[32] - Full Analysis Set

[33] - Full Analysis Set

## Statistical analyses

| Statistical analysis title | Visit 7 (168 h) -- Patient |
|---|---|
| Comparison groups | Loxoprofen sodium v Placebo |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Cochran-Mantel-Haenszel |

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

From the time of signing the informed consent form and to trial completion or discontinuation.

Adverse event reporting additional description:

Safety analysis set was used to evaluate the adverse events.

Safety analysis set = Full analysis set, defined as all randomized patients who received at least one dose of study drug.

| Assessment type | Systematic |
|---|---|

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 22.0 |

## Reporting groups

| Reporting group title | Loxoprofen sodium |
|---|---|

Reporting group description:

Patients received Loxoprofen sodium 60 mg tape medicated plaster applied once a day for up to 7 days.

| Reporting group title | Placebo |
|---|---|

Reporting group description:

Patients received placebo plasters that were applied once a day for up to 7 days.

| Serious adverse events | Loxoprofen sodium | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 0 / 62 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

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

| Non-serious adverse events | Loxoprofen sodium | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 2 / 62 (3.23%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | 0 / 62 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |

| | | |
|---|---|---|
| Application site irritation | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| | | |
| Application site pain | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 0 | 1 |
| | | |
| Application site swelling | | |
| subjects affected / exposed | 0 / 65 (0.00%) | 1 / 62 (1.61%) |
| occurrences (all) | 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| None. |

Notes: