2. SYNOPSIS

Sponsor/Company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier**	(for National Regulatory Authority use only)
Finished product: Not applicable	**Volume:**	
Active ingredient: Ibuprofen	**Page**	

Study code: 0028022

Study title: A randomised, multicentre, two-arm, parallel group, double-blind, placebo-controlled, comparative efficacy and safety clinical study of ibuprofen 5% roll-on gel in adult human patients with pain related to uncomplicated ankle injuries

Investigators and study centres: The study was conducted in 5 centres in total: in Finland (1 centre), Lithuania (3 centres), and Poland (1 centre). In addition, there were 4 non-recruiting centres (3 in Finland, 1 in Poland).
Study coordinating investigator: Juha-Pekka Kaukonen, Lahti, Finland

Development phase: III	**Study period**: 02 March 2012 to 05 October 2012

Objectives: The objective of the study was to evaluate the efficacy and safety of the Ibuprofen 5% roll-on gel versus Placebo roll-on gel in human adult subjects for the treatment of pain related to uncomplicated ankle injuries.

Methodology: This was a randomised, multicentre, two-arm, parallel group, double-blind, placebo-controlled, phase III clinical study in subjects with pain related to uncomplicated ankle injuries.

Each patient was to attend 3 visits over a period of 7 days. After randomisation and after all baseline assessments (including baseline pain assessments) the subjects were given their study medication and were instructed how to apply it. The rolled-on gel was to be applied all over the cleaned injured ankle in order to cover the area with a thin film during each administration. The rolled-on gel was to be gently rubbed on the injured area twice with a 1 minute interval between applications.

The rolled-on gel was to be applied 3 times a day (at 8 a.m., 3 p.m., and 10 p.m. [± 2 hours]) on the injured area, from day 1 to day 6. On day 0 (enrolment day), only 2 treatments were given, with the first treatment being applied at the study centre under the supervision of an investigator and/or trained study personnel and the second treatment applied at home at 10 p.m.

Pain assessment was done using a visual analogue scale (VAS; score 0-100 mm) and several verbal rating scale (VRS) parameters. Subjects were instructed to complete the VAS assessment at home every morning and evening just before application of the study treatment. Subjects were instructed to maintain a record of the VAS score in the subject diary. In the morning of day 3 and day 7, when the subject came to the centre, the VAS and VRS assessments were done at the study centre. The investigator examined the joint and the skin and reviewed the subject diary at every visit.

Sample size: The planned number of study subjects was 62 subjects (31 in each group), in order to have at least 28 subjects in each treatment group in the final analyses.

62 subjects were randomised (30 Ibuprofen 5% roll-on gel; 32 Placebo roll-on gel)

61 subjects were included in the per protocol analysis for the primary endpoint (29 Ibuprofen 5% roll-on gel; 32 Placebo roll-on gel)

62 subjects were included in the modified intention-to treat analysis for the primary endpoint (30 Ibuprofen 5% roll-on gel; 32 Placebo roll-on gel)

62 subjects were analysed for safety (30 Ibuprofen 5% roll-on gel; 32 Placebo roll-on gel)

Diagnosis and main criteria for inclusion:

1. Written informed consent obtained.
2. Male and female subjects, age in the range of 18-45 years (inclusive).

3. Subjects with pain related to uncomplicated ankle injuries (in case of doubt whether it was complicated an X-ray was to be taken).
4. Pain related to ankle injuries was scored as moderate or severe by the subject and the injury was less than 24 hours old.
5. Subjects with normal or clinically non-significant findings as determined by baseline history, physical examination, and vital signs (blood pressure, heart rate and axillary temperature).
6. Comprehension of the nature and purpose of the study and compliance with the protocol requirements.
7. Negative urine pregnancy test (for females only).

Investigational product, dose and mode of administration, batch number:

Ibuprofen 5% roll-on gel (each 1 g contains 50 mg Ibuprofen). Manufactured by Farmasierra, Spain.

Patients were instructed to clean the surface of the skin before application. They were instructed to rub the roll-on gel gently on the injured area of the ankle twice with a 1 minute interval between each administration. Each dose was approximately 2 - 2.5 g of gel, equivalent to 100 - 125 mg of ibuprofen.

Batch number: 2011-108

Duration of treatment:

7 days. The roll-on gel was applied 2 times a day on day 0, and 3 times a day from day 1 to day 6.

Reference product, dose and mode of administration, batch number:

Placebo roll-on gel manufactured by Farmasierra, Spain.

Patients were instructed to clean the surface of the skin before application. They were instructed to rub the roll-on gel gently on the injured area of the ankle twice with a 1 minute interval between each administration.

Each dose was approximately 2 - 2.5 g of gel.

Batch number: 2011-72

Variables and methods of assessments:

Primary efficacy variable:

- VAS pain score change over time from baseline (day 0 before treatment administration) to day 7.

Secondary efficacy variables:

- Percentage VAS pain score change from baseline separately to days 3 and 7.
- Area under VAS curve according to study visit measurements and subject diary from baseline separately to days 3 and 7 morning assessment.
- Proportions of responders separately at day 3 and day 7 (patient was considered as a responder if the reduction from baseline VAS pain score was at least 50%).
- Time to reduction of 50% in pain score from baseline.
- Proportion of subjects who needed rescue medication during the study.
- Change in VRS scores from baseline separately to days 3 and 7.
  - Functional impotence (absent, slight, moderate, severe).
  - Single leg load-bearing on the injured foot (possible without pain, possible with pain, impossible).
  - Assessment of pain (absent, slight, moderate, severe) by the investigator: pain at rest, pain under passive tension, pain under active tension, and pain on palpation.
- Overall assessment of efficacy (excellent, good, poor) separately at day 3 and day 7 by the subject.
- Overall assessment of efficacy (excellent, good, poor) separately at day 3 and day 7 by the investigator.
- Change in peri-articular oedema (difference in perimeter between the injured and healthy ankle) over time from baseline to day 7.

Tolerability assessments:

- Condition of the skin (normal, abnormal) at days 0, 3 and 7.
- Overall assessment of tolerability by subject (excellent, good, acceptable, poor) at days 3 and 7.
- Overall assessment of tolerability by investigator (excellent, good, acceptable, poor) at days 3 and 7.

Safety assessments:

- Physical examination including general and systemic examination and vital signs monitoring (blood pressure, heart rate, and axillary temperature in sitting posture) at days 0, 3, and 7.
- Adverse event (AE) monitoring at every visit. Subjects maintained a subject diary to record AEs and concomitant medications.

Statistical methods:

Evaluation of primary efficacy variable. The difference in VAS pain score change over time from baseline to day 7 between the treatment groups was analysed using repeated measures analysis of covariance. Only measurements from the study visits (day 0, 3, and 7) were included in the analysis. The analysis of covariance model included factors for baseline VAS level, treatment, time, treatment*time, and country. The difference in VAS pain score change over time between the treatment groups was considered statistically significant if the probability of the difference was at least 95%, i.e. 2-sided significance level of 5% was considered the level of statistical significance.

Evaluation of secondary efficacy variables related to VAS assessments. The difference in % change in VAS scores from baseline between the treatment groups was analysed using repeated measures analysis of covariance with a similar model as for the primary variable.

The difference between area under the VAS curves from baseline to the day 3 morning assessment between the treatment groups was analysed using an analysis of covariance model including factors for baseline VAS level, treatment, and country. The difference between the area under the VAS curves from baseline to the day 7 morning assessment was analysed similarly.

The analysis of the proportion of responders at day 3 between the treatment groups was performed using a generalised linear mixed model including factors for baseline level, treatment, and country. The analysis for proportion of responders at day 7 was analysed similarly.

Time to 50% reduction in pain score from baseline was evaluated as a time to event analysis. Measurements from the study visits and from the subject diaries were included in the analysis. Nonparametric log rank test was used for the analysis of treatment effect.

Evaluation of secondary efficacy variables related to VRS variables. For the overall assessments at days 3 and 7 the actual proportions were compared between the treatment groups. Chi-square was applied for the analysis of the overall assessments between the treatment groups at days 3 and 7.

For the other VRS assessments the changes from baseline to days 3 and 7 were evaluated and compared between the treatment groups. Changes in pain were categorised as no change, improved, and worsened. If for some variable there was no pain at baseline and it remained as no pain then an additional class “No pain” for the change was to be used. Chi-square test or Fisher’s exact test (in case of small cell frequencies) was applied for the analysis of the change in VRS scores from baseline to days 3 and 7 between the treatment groups.

Evaluation of other secondary efficacy variables. The change in peri-articular oedema over time from baseline to day 7 between the treatment groups was analysed using repeated measures analysis of covariance. The analysis of covariance model included factors for baseline difference in perimeter, treatment, time, treatment*time and country.

The proportion of subjects who needed rescue medication during the study period was compared between the treatment groups using generalised linear mixed model including factors for baseline VAS level, treatment, and country.

Evaluation of tolerability. The overall assessments of tolerability by subject and by investigator based on VRS (excellent, good, acceptable, poor) were compared between the treatment groups at day 3 and 7 using Chi-square test. Condition of the skin (normal, abnormal) was not analysed since it stayed normal during the whole study.

Safety variables were evaluated descriptively.

Summary-Conclusions

An abbreviated report was produced for this trial because there was no statistically significant difference between the active product ibuprofen and placebo and hence the project was discontinued.

Efficacy and tolerability results: No significant difference was found between the Ibuprofen 5% roll-on gel and Placebo roll-on gel treatment groups with regard to the primary efficacy variable or any of the secondary efficacy variables.

Safety results: Adverse events were reported infrequently and the incidences were comparable in the 2 treatment groups. In total, AEs were reported for 5 (16.7%) subjects in the ibuprofen group (arthralgia [3 subjects], headache and pyrexia [1 subject each]) and 4 (12.5%) subjects in the placebo group (arthralgia [3 subjects] and headache [1 subject]). None of the AEs were considered to be related to study medication. No deaths, other serious AEs, or significant AEs were reported for subjects in either treatment group. All AEs were of mild or moderate intensity. There were no noteworthy changes in vital signs or physical examination findings in either treatment group.

Conclusion: The efficacy of Ibuprofen 5% roll-on gel did not differ significantly from Placebo roll-on gel in the treatment of pain related to uncomplicated ankle injuries. The Ibuprofen 5% roll-on gel was well tolerated; safety findings for subjects treated with Ibuprofen 5% roll-on gel were comparable with those for subjects treated with Placebo roll-on gel.

Date of report: 12 Dec 2012