2. SYNOPSIS

Name of Sponsor: Gedeon Richter Plc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: RGH-507 (Gedeon Richter) Fastum (Belin Chemie/A. Menarini Srl.)	Volume:	
Name of Active Ingredient: 15% tolperisone containing gel, 25 mg ketoprofen containing gel	Page:	

Title of study:	A randomized, multicenter, double-blind, parallel study to compare the efficacy and safety profile of RGH-507 (tolperisone-containing) gel versus a ketoprofen-containing gel in the treatment of patients with soft tissue injuries.
Principal Investigators and study centers:	[redacted]

[redacted]

[redacted]

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Time of clinical part:	First subject in: 31 MAR 2010 Last subject out: 25 OCT 2010	**Phase of development:** Phase 3

Objective:

Primary objective:
To prove the non-inferiority in efficacy between RGH-507 (tolperisone-containing) gel and a ketoprofen-containing gel in the treatment of patients with acute, mild soft tissue injury.

Secondary objective:
To compare the safety profile of the two different gel preparations.

Methodology (study design): Multicenter, double-blind, randomized, parallel study with 2 treatment arms

Number of subjects:

Planned: 300 enrolled patients (150/tretatment group)
240 evaluated patients (120/treatment group)

Screened: 385 patients

Randomized: 384 patients

Safety population: 383 patients

ITT population: 369 patients

PP population: 343 patients

Drop outs/withdrawals: 7 patients

	RGH-507	Ketoprofen
Randomized	**193**	**191**
Safety	**192**	**191**
ITT	**184**	**185**
PP	**169**	**174**
Withdrawal	**5**	**2**
Adverse event	2	1
Protocol violation	1	0
Non-compliance	0	1
Other	2	0

Diagnosis and main criteria for inclusion: Acute (within 24 hours), mild soft tissue injury (traumatism or contusion) accompanied by signs of inflammation and pain in one of the extermeties, with or without functional loss, with intact skin that requires local treatment only.

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Test drug	Treatment Group 1: RGH-507 (15% tolperisone-containing gel)
Reference drug	Treatment Group 2: Fastum gel (containing 25 mg ketoprofen)
Treatment A:	Patients applied 3-5 cm or more RGH-507 (tolperisone containing) gel (Gedeon Richter Plc.), twice daily in a thin layer, for 7 days.
Treatment B:	Patients applied 3-5 cm or more Fastum (ketoprofen containing) gel (Berlin Chemie/A. Menarini Srl.), twice daily in a thin layer, for 7 days.
Duration of treatment:	1 week: Screening visit, Visit 1 (baseline: same day as screening), Visit 2 (+3 days±1 day after visit 1), Visit 3 (+8 days±1 day after visit 1).
Evaluation criteria:	***Efficacy parameters:*** *Primary:* Spontaneous average pain for the last 24 hours by VAS. *Secondary:* Spontaneous maximal pain for the last 24 hours by VAS. Spontaneous actual pain by VAS. Proveked pain on pressure and on passive movement by a semi-quantitative scale. Oedema or inflammation by a semi-quantitative scale. Functional incapacity by a semiquantitative scale. CGIC-PGIC ***Safety parameters:*** Medical history, physical examination, 12-lead ECG, vital signs (blood pressure, heart rate), lab examinations (haematology, biochemistry, urinalysis, pregnancy test), adverse events.

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Statistical methods:

Efficacy parameters:

For assessment of non-inferiority a confidence interval approach was used. Non-inferiority between the test and reference preparation can be concluded if the lower limit of 95% confidence interval (equivalent to a one-sided 97.5% confidence interval) of their differences in the primary outcome measure is above the non-inferiority margin of -10 mm at the end of the study (Visit 3) in both efficacy populations (PP and ITT).

Secondary efficacy parameters were summarized by treatment groups using descriptive statistics. Spontaneous maximal and actual pain were analyzed the same way as the primary parameter. For the analysis of the semi-quantitative secondary scales and CGIC-PGIC scores the Mann-Whitney test was used.

Safety parameters:

The safety parameters were evaluated using descriptive statistics and summarized by treatment group and time points. For the laboratory safety data out of range values were flagged in the data listings and a list of clinically significant abnormal values were presented.

Adverse events were tabulated and summarized according to the Medical Dictionary for Regulatory Activities (MedDRA).

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RESULTS:

Efficacy:

The primary efficacy parameter was the average severity of spontaneous pain level for the last 24 hours prior to assessment and it was rated by the patient using Visual Analogue Scale (VAS). For assessment of non-inferiority a confidence interval approach was used. The lower limits of the calculated confidence intervals for the treatment difference were -3.81 mm in the ITT population and -3.38 mm in the PP set. Since these values were above the non-inferiority margin of -10 mm in both efficacy populations, the statistical analysis had proved the non-inferiority of the RGH-507 gel compared with the Fastum gel. Furthermore, because the calculated confidence intervals were entirely within the [-10 mm, 10 mm] range, the therapeutic equivalence criterion was also fulfilled.

The maximal severity of spontaneous pain for the last 24 hours prior to assessment and the actual spontaneous pain were rated with the same method as the primary efficacy variable. The lower limits of the calculated confidence intervals were -3.74 mm (ITT) and -3.25 mm (PP) in case of maximal pain and -3.66 mm (ITT) and -3.15 mm (PP) in case of actual pain. So, the non-inferiority and therapeutic equivalence criteria were fulfilled for these parameters in both efficacy sets also.

The severity of provoked pain on pressure and on passive movement was assessed by the investigator using a four-degree semiquantitative scale. The difference between the treatment groups was not statistically significant. The severity of oedema or inflammation was assessed by the investigator using a five-degree semiquantitative scale. The difference between the treatment groups was not statistically significant for the ITT population, however in case of the PP population a statistically significant difference was observed ($p=0.040$). The mean score of the rank sum test indicated a slightly higher improvement in the RGH-507 group. The severity of functional incapacity was assessed by the investigator using a four-degree semiquantitative scale. The difference between the treatment groups was not statistically significant. The Clinician and Patient Global Impression of Change were used to evaluate the overall improvement by both the investigator and the patient. There were no significant differences between the treatment groups regarding the CGIC/PGIC evaluation.

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Safety:
A total of 18 adverse events occurred during the study and 7 of them was assessed as related or possibly related with the treatment. There were 10 adverse events in the RGH-507 group (6 of them was related or possibly related) and 8 adverse events in the Fastum group (1 of them was related). The adverse events were assessed as mild in 13 cases, moderate in 4 cases and severe in 1 case in intensity.

There was 1 serious adverse event in the Fastum group (hospitalisation and surgery due to rupture of ligament of left knee), but it was not drug related.

The most frequent adverse event (related or possibly related to study medication) was skin irritation in 5 cases (27.8% of the events) and all events were observed in the RGH-507 group.

From general safety aspect, there were no clinically significant change in the medical history, in the physical examination parameter, in the vital signs or in the ECG measurements during the whole study period in both treatment group.

Conclusion
In summary, the non-inferiority was proved considering both the primary and the secondary parameters. Therefore, it can be deduced that RGH-507 (15% tolperisone-containing) gel is at least as effective as the ketoprofen-containing Fastum gel in patients with pain and inflammation caused by acute, mild soft tissue injury.

Both treatment was well tolerated from general or local safety aspect, however the occurrence of skin irritation was a slightly higher in the RGH-507 group.

According to the result of this phase 3 study we can deduce that the 15% tolperisone-containing RGH-507 gel has at least such efficacy as the 25 mg ketoprofen-containing Fastum gel in patients with acute mild soft tissue injury and has a good local and general safety profile as well.