2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
ratiopharm GmbH</td><td colspan="4">TABULAR FORMAT
Ref. To Part IV B.1</td></tr>
<tr><td>Name of Finished Products:
Diclofenac-ratiopharm® Gel 1 %,
Diclofenac-ratiopharm® Gel 3 %,
Diclofenac-ratiopharm® Gel 5 %</td><td colspan="4">Volume:</td></tr>
<tr><td>Name of Active Ingredient:
Diclofenac-Na</td><td colspan="4">Page:</td></tr>
<tr><td>Title of Study</td><td colspan="4">Randomised, double-blind, multi-centre, placebo-controlled clinical dose-finding study in four parallel groups comparing

▪ Diclofenac-ratiopharm® Gel 1 %,
▪ Diclofenac-ratiopharm® Gel 3 %,
▪ Diclofenac-ratiopharm® Gel 5 %, and
▪ Placebo Gel

in patients with traumatic blunt soft tissue injury/contusion.</td></tr>
<tr><td rowspan="4">Investigators/Study Centres</td><td colspan="4">Multi-centre study with 4 study centres in Germany</td></tr>
<tr><td colspan="4">Centre</td></tr>
<tr><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>Prof. Dr. med. [redacted]
Cologne</td><td>Dr. med. [redacted]
Gilching</td><td>Dr. med. [redacted]
Bergisch Gladbach</td><td>Facharzt [redacted]
Grünwald</td></tr>
<tr><td colspan="4">See Appendix 16.1.4 for more details</td></tr>
<tr><td>Publication</td><td colspan="4">Planned</td></tr>
<tr><td>Studied Period</td><td colspan="4">4 months</td></tr>
<tr><td>Date of First Enrolment</td><td colspan="4">15 January 2006</td></tr>
<tr><td>Date of Last Completed</td><td colspan="4">29 May 2006</td></tr>
<tr><td>Phase of Development</td><td colspan="4">Clinical Phase II</td></tr>
<tr><td>Date of Report</td><td colspan="4">27 November 2006/Final version</td></tr>
</table>

Name of Sponsor/Company: ratiopharm GmbH	TABULAR FORMAT Ref. To Part IV B.1	
Name of Finished Products: **Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 %, Diclofenac-ratiopharm® Gel 5 %**	Volume:	
Name of Active Ingredient: Diclofenac-Na	Page:	
Objectives	The primary objective of this Phase II study was to investigate the dose response relationship of Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 % and Diclofenac-ratiopharm® Gel 5 % in patients with traumatic blunt soft tissue injury/contusion in comparison with placebo as assessed by speed of decrease in pain intensity. The following null hypotheses were tested in an a priori ordering: Step 1: $H_{01}: F_{X_1} \le F_{X_2} \le F_{X_3} \le F_{X_4}$ *vs.* $H_{11}: F_{X_1} \ge F_{X_2} \ge F_{X_3} \ge F_{X_4}$ with at least one of the inequalities being strict, Step 2: $H_{02}: F_{X_1} \le F_{X_4}$ *vs.* $H_{12}: F_{X_1} > F_{X_4}$ Step 3: $H_{03}: F_{X_1} \le F_{X_3}$ *vs.* $H_{13}: F_{X_1} > F_{X_3}$ Step 4: $H_{04}: F_{X_1} \le F_{X_2}$ *vs.* $H_{14}: F_{X_1} > F_{X_2}$ Step 5: $H_{05}: F_{X_2} \le F_{X_4}$ *vs.* $H_{15}: F_{X_2} > F_{X_4}$ Step 6: $H_{06}: F_{X_2} \le F_{X_3}$ *vs.* $H_{16}: F_{X_2} > F_{X_3}$ Step 7: $H_{07}: F_{X_3} \le F_{X_4}$ *vs.* $H_{17}: F_{X_3} > F_{X_4}$. The Jonckheere-Terpstra test was used for the first null hypothesis. All other hypothesis were tested by means of Wilcoxon-Mann-Whitney U tests. Because of the a priori ordering, if a local type I error level α=5 % was applied in each step, this multiple test procedure also guaranteed control of the experiment wise error rate α=5 %. Tenderness was determined by the pressure, at which the subject reports the first pain reaction, as measured by calibrated callipers at the centre of the injury. First pain reaction was defined as the first communication by the patient that the exerted pressure caused an unpleasant feeling.	

Name of Sponsor/Company: ratiopharm GmbH	TABULAR FORMAT Ref. To Part IV B.1	
Name of Finished Products: **Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 %, Diclofenac-ratiopharm® Gel 5 %**	Volume:	
Name of Active Ingredient: Diclofenac-Na	Page:	
	The secondary objectives of this study were the investigation of the: - dose-response relationship, - time to resolution of pain, - pain assessment by patient at rest and on movement by means of Visual Analogue Scales (VAS), - ratio of tenderness values (injured site/contralateral site). - algometric pain-measurement (pain-time curve; AUC) over the whole time (7 days). - consumption of rescue medication (paracetamol). - global assessment of efficacy by investigator and patient. - sum of pain intensity difference (SPID).	
Methodology	Multi-centre, double blind, randomised, placebo-controlled dose-finding trial comprising four treatment arms (parallel group design).	

<table>
<tr><td>Name of Sponsor/Company:
ratiopharm GmbH</td><td colspan="5">TABULAR FORMAT
Ref. To Part IV B.1

Volume:

Page:</td></tr>
<tr><td>Name of Finished Products:
Diclofenac-ratiopharm® Gel 1 %,
Diclofenac-ratiopharm® Gel 3 %,
Diclofenac-ratiopharm® Gel 5 %</td><td colspan="5"></td></tr>
<tr><td>Name of Active Ingredient:
Diclofenac-Na</td><td colspan="5"></td></tr>
<tr><td rowspan="6">Number of Patients</td><td colspan="5">Planned</td></tr>
<tr><td colspan="3">Diclofenac-ratiopharm® Gel</td><td rowspan="2">Placebo</td><td>Total</td></tr>
<tr><td>1 %</td><td>3 %</td><td>5 %</td><td></td></tr>
<tr><td>30</td><td>30</td><td>30</td><td>30</td><td>120</td></tr>
<tr><td colspan="5">Analysed (ITT/PP)</td></tr>
<tr><td colspan="3">Diclofenac-ratiopharm® Gel</td><td rowspan="2">Placebo</td><td rowspan="2">Total</td></tr>
<tr><td>1 %</td><td>3 %</td><td>5 %</td></tr>
<tr><td>34/29</td><td>34/32</td><td>34/29</td><td>34/30</td><td>136/120</td></tr>
<tr><td>Patient Population</td><td colspan="5">Ambulant patients (age range 18-60 years) suffering from fresh impact injuries (traumatic blunt soft tissue injury/contusion). Time elapse between traumatic event and inclusion did not have to be longer than 3 hours.</td></tr>
<tr><td>Diagnosis and Main Criteria for Inclusion</td><td colspan="5">Traumatic blunt soft tissue injury/contusion.

Inclusion criteria:

- age range 18 - 60 years,
- normal general health,
- injury not older than 3 h prior treatment,
- written informed consent,
- the basic value of the algometric measurement on the injured site did not exceed 50 % of the respective value of the contralateral site,
- the absolute sensitivity to pain on contralateral site was at least 2.5 N/cm²,
- the size of the traumatisation had to be at least 50 cm^2 and maximal 150 cm^2.</td></tr>
</table>

Name of Sponsor/Company: ratiopharm GmbH	TABULAR FORMAT Ref. To Part IV B.1	
Name of Finished Products: **Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 %, Diclofenac-ratiopharm® Gel 5 %**	Volume:	
Name of Active Ingredient: Diclofenac-Na	Page:	

Test Products	Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 %, and Diclofenac-ratiopharm® Gel 5 %
Dose	2-4 g (twice daily)
Mode of Administration	Day 1 to Day 3: topical treatment with the study medication by the investigator on every visit after the algometric measurement. Day 4 to Day 6: topical treatment with the study medication twice daily by the patient. Day 7: topical treatment with the study medication by the patient only in the morning.
Batch Nos.	Diclofenac-ratiopharm® Gel 1 %: F20450001, Diclofenac-ratiopharm® Gel 3 %: F20457001, Diclofenac-ratiopharm® Gel 5 %: F18598001.
Duration of Treatment	The study duration was 7 (± 1) days per patient.
Reference Therapy	Placebo Gel
Dose	2-4 g (twice daily)
Mode of Administration	Day 1 to Day 3: topical treatment with the study medication by the investigator on every visit after the algometric measurement. Day 4 to Day 6: topical treatment with the study medication twice daily by the patient. Day 7: topical treatment with the study medication by the patient only in the morning.
Batch No.	F20458001

Name of Sponsor/Company: ratiopharm GmbH	TABULAR FORMAT Ref. To Part IV B.1	
Name of Finished Products: **Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 %, Diclofenac-ratiopharm® Gel 5 %**	Volume:	
Name of Active Ingredient: Diclofenac-Na	Page:	
Criteria for Evaluation/ Efficacy	The primary variable was the area under the curve (AUC) where the y-axis was the pressure, at which there was the first tenderness reaction by patients and the x-axis was time after first treatment, restricted to the first three days (Days 1, 2 and 3) (ITT analysis). The tenderness reactions were measured by calibrated callipers in an area of 1 cm² at the centre of the injured area. Exact position of measurement was marked on patients' skin to ensure constant measuring points. The measurement was performed between time of injury and 3 hours thereafter. Measurement was performed with covered scale and evaluated after measurement.	
Safety	The following variables were recorded to assess the safety of the trial drug: • adverse events, • serious adverse events, • laboratory examinations (haemoglobin, erythrocytes, thrombocytes, GPT, γ-GT, serum creatinine, sodium, potassium), • vital signs, • physical examinations, • global assessment of tolerability by patient and investigator.	
Statistical Methods	A confirmatory one-sided Jonckheere-Terpstra test and one-sided Mann-Whitney-tests had been carried out in an a priori ordering (level of significance α=2.5 %). The treatment effects were estimated by means of corresponding Hodges-Lehmann estimators and 95 % confidence intervals. Furthermore, descriptive and exploratory statistical methods were used.	

Name of Sponsor/Company: ratiopharm GmbH	TABULAR FORMAT Ref. To Part IV B.1	
Name of Finished Products: **Diclofenac-ratiopharm® Gel 1 %, Diclofenac-ratiopharm® Gel 3 %, Diclofenac-ratiopharm® Gel 5 %**	Volume:	
Name of Active Ingredient: Diclofenac-Na	Page:	

Summary – Conclusions **Efficacy Results:**	A significant monotone dose-response relationship could be shown for the primary variable AUC of tenderness values over 3 days (Jonckheere-Terpstra test: p=0.0000). All of the three active treatments were superior to placebo. Between the active treatments no significant treatment differences were observed with regard to the primary variable. The results of the secondary efficacy variables supported the results for the primary variable. The ratio of tenderness values (injured/contralateral site) improved faster in the three active treated groups compared to placebo. The time to resolution of pain was shorter in the active treatments compared to placebo. A monotone dose-response relationship was also found for the AUC of tenderness values over 7 days. The global assessments of efficacy by the investigators and patients documented a superiority of the active preparations in comparison to placebo, too.
Safety Results:	A total of 4 patients (2.9 %) experienced AEs in the course of the clinical trial, 2 (5.9 %) in the Diclofenac-ratiopharm® Gel 1 % group [AEs: dry skin at concerned area; strain thigh right], 1 (2.9 %) in the Diclofenac-ratiopharm® Gel 3 % [AE: small pustules with slight pruritus at application site], and 1 (2.9 %) in the placebo group [AE: hidrosis]. All AEs were of a mild or moderate intensity and non-serious. The evaluation of the laboratory variables and the vital signs did not reveal any relevant safety concerns. The observed, rare deviations in some laboratory variables can be attributed to artefacts caused by the sampling situation. Furthermore, the analysis of the physical examinations revealed no safety concerns, too.
Conclusion:	The Diclofenac-ratiopharm® Gel 1 %, 3 %, and 5 % are effective and safe in the treatment of fresh blunt impact injuries. They produced a rapid pain reduction or resolution. Treated patients had statistically significant and clinically relevant reductions in pain scores and were free of pain significantly earlier than patients on placebo. Moreover, they can easily be administered by the patients.