SYNOPSIS

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Title of the study:	Pharmacokinetics, pharmacodynamics and safety of intra-articular multiple doses of 500 µg icatibant in an uncontrolled 13-week multi-center study in patients with symptomatic knee osteoarthritis. PKM6746 (TRICAPEKA)		
Coordinating investigator:	[redacted]		
Study center(s):	2 centers in Lithuania		
Publications (reference):	Not applicable		
Study period: Date first patient enrolled: 12JUL2006 Date last patient completed: 31OCT2006			**Phase of development:** Phase II (Pharmacokinetics in patients)
Objectives:	Primary ● To assess the systemic exposure of icatibant after intra-articular injection Secondary ● To evaluate the pharmacodynamic effect of icatibant via the Western Ontario McMaster Universities osteoarthritis pain questionnaire (WOMAC pain sub-score) and patient's global assessment (PGA) ● To evaluate the safety of icatibant after intra-articular injection of a dose of 3 x 500 µg		
Methodology:	This was an uncontrolled, multicenter, pharmacokinetic (PK) study with one treatment arm. The study comprised a screening period, 2-week treatment period, and 11-week follow-up period.		
Number of patients: **Evaluated:**	Planned: 12 Pharmacodynamics: 12	Randomized: NA Safety: 12	Treated: 12 Pharmacokinetics: 12
Diagnosis and criteria for inclusion:	Patients with symptomatic knee osteoarthritis (OA) (Kellgren & Lawrence stage II-IV)		
Investigational product: Dose: Administration: Batch number(s):	Icatibant solution for injection (100 µg/mL) 500 µg per week, 3 injections in total intra-articular (IA) injection [redacted]		
Duration of treatment: 2 weeks with a total of 3 injections	**Duration of observation:** Total of 14 weeks (screening period: 4-7 days; treatment period: 2 weeks; follow-up period: 11 weeks)		
Reference therapy:	Not applicable		

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Criteria for evaluation:		
Pharmacodynamics:	● Change in PGA from baseline to Weeks 1, 2, 5, 9, 13, and endpoint; ● Change in WOMAC pain sub-score from baseline to Weeks 1, 2, 5, 9, 13, and endpoint.	
Safety:	● Adverse events (AEs); ● Clinical laboratory data; ● Vital signs (blood pressure and heart rate); ● 12-lead electrocardiogram (ECG).	
Pharmacokinetics:	<u>Primary PK variable:</u> Concentrations of icatibant in the systemic circulation, measured over 48 h following each IA injection. <u>Secondary PK variables:</u> ● Concentrations of icatibant metabolites M1 and M2 in blood, measured over 48 h following each IA injection; ● Concentrations of icatibant and its metabolites in urine, measured over 48 h following each IA injection; ● Concentrations of icatibant in synovial fluid, measured prior to the 2nd and 3rd IA injections.	
Pharmacokinetic sampling times and bioanalytical methods:	Blood samples for PK were collected pre-dose and 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 h after each IA injection. Urine samples for PK were collected pre-dose and in intervals of 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 h after each IA injection. Synovial fluid samples for PK were collected just before the 2nd and 3rd IA injections.	

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Statistical methods:	Pharmacokinetic analysis Systemic exposure of icatibant and its 2 metabolites M1 and M2 in systemic blood were assessed. Plasma PK parameters for icatibant and its metabolites M1 and M2 (eg, t_{max}, C_{max}) were to be derived from the plasma concentration-time profiles using non-compartmental analysis. PK parameters were to be summarized separately using descriptive statistics; the differences between the injections were to be compared using the paired t-test and 95% confidence intervals to assess possible accumulation of icatibant after repeated injection. Descriptive statistics were to be used to summarize concentrations of icatibant and its metabolites M1 and M2 in plasma, icatibant concentrations in synovial fluid pre-dose, urine concentrations of icatibant and its metabolites M1 and M2 per collection interval, and icatibant and icatibant metabolites excreted per collection interval, per 24 h period and overall. Pharmacodynamic analysis Change from baseline in WOMAC pain sub-score assessed at each visit was summarized using descriptive statistics, and was presented using a plot over time. This was based on the intention-to-treat (ITT) population, which included all patients who received at least 1 injection of icatibant. PGA analysis was performed using an approach similar to WOMAC analysis. Safety analysis Safety was analyzed descriptively based on the ITT population, which included all patients who received at least one injection of icatibant.	
Summary: Pharmacodynamic results:	For combined analysis of patients in the two study centers, the WOMAC pain sub-score decreased from a mean of 60.3 at baseline to 32.8 at Week 1, and this decrease was maintained until the end of the follow-up period (mean at Week 13: 32.4). Similarly, the PGA decreased from a mean of 66.3 at baseline to 41.1 at Week 1, and this decrease was maintained until the end of the follow-up period (mean at Week 13: 41.0). For both the PGA and the WOMAC pain sub-score, the decrease was largest after the 1st injection and was less pronounced at Weeks 5 and 9. Comparison of WOMAC pain subscores and PGA scores for the two study centers showed large differences in baseline scores and in the change in scores over the course of the study. For both of these analytes, mean and median baseline scores were substantially worse for subjects at Center 1 as compared to those at Center 2. For the WOMAC pain sub-score, both groups of patients showed large improvements from baseline to Visit 3. However, whereas the group of patients at Center 1 showed a continuous improvement from baseline until Visit 7, the group of patients at Center 2 showed an improvement at Visit 3, a return to baseline values at Visit 4, and worse-than-baseline values at Visits 5 and 6. A very similar pattern of results was observed for the two centers for PGA scores.	

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Safety results	None of the 12 patients in this study had a treatment-emergent adverse event (TEAE), serious TEAE, or TEAE leading to death, and no patients were withdrawn from the study due to a TEAE. Two patients had non-treatment emergent adverse events, both of which were considered not related to study medication. Mean and median values for most biochemistry and hematology parameters showed only minor variations throughout the treatment and follow-up periods, with no apparent relationship to icatibant treatment. Three patients had potentially clinically significant abnormalities (PCSAs) for laboratory values at post-treatment time-points; for one of these patients the value was already classified as a PCSA at pre-treatment. No trends with regard to icatibant treatment could be detected. Mean and median values for vital sign parameters showed only minor variations throughout the treatment and follow-up periods, with no apparent relationship to icatibant treatment. Three patients had ECG abnormalities, but there was no apparent systematic relationship to icatibant.	

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Pharmacokinetic results:	All 12 patients had detectable levels of icatibant in plasma at 0.5 h after each of the three injections, and 11 of the 12 patients had detectable levels at 1 h after each of the three injections. However, very few patients had a measurable level of icatibant in plasma at any time-point more than 2 h after injection. Because little or no icatibant could be detected in plasma at most time-points, only a limited set of PK parameters could be derived. After each of the three injections, median T_{max} was 0.5 h, median T_{last} was 2 h, and median T_{lag} was 0 h. Mean C_{max} for icatibant in plasma was around 7.5 ng/mL after each of the three injections, and variability was low. Median AUC was 8.4, 8.2 and 10.6 ng*h/mL after the 1st, 2nd, and 3rd injection, respectively. All or most patients had detectable levels of M2 in plasma at all time-points from 0.5 h until 4 h after injection, and no patients had detectable levels of M2 in plasma at any time-point >12 h after injection. The median T_{max} for M2 in plasma was 1.5 h or 2 h after the three injections. The mean C_{max} for M2 in plasma ranged from 3.76 to 4.34 ng/mL after the three injections. Most patients had no detectable levels of M1 in plasma at all time-points. M1 could be quantified in only 5 out of 324 samples. The major proportion of icatibant was excreted renally within 4 h after injection; no icatibant was detected in urine more than 8 h after injection. The variability between patients was large with respect to the amount of icatibant excreted but not with respect to the time of excretion. There was no accumulation of icatibant in urine; after each of the three injections, the cumulative amount in urine for the time period from 24 h to 48 h was 0. The urinary excretion of metabolites M1 and M2 extended for at least 48 h after injection. The highest amounts of M1 and M2 were excreted within the first 8 h after injection. There were no notable differences between the three injections with respect to amount or timing of urinary excretion of M1 and M2. The percentage of unchanged icatibant excreted in urine was low after each injection (<1%). Mean total amount excreted in urine for M1 was in the range of 32% to 37%, and for M2 it was in the range of 24% to 26%.	

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Conclusions:	[redacted]	
Date of report:	10-Aug-2007	