SYNOPSIS

Name of company: sanofi-aventis **Name of finished product: Not applicable** **Name of active substance(s):HOE140**	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** **Volume:** **Page:**	**(For National Authority Use only)**
Title of the study:	Efficacy and safety of intra-articular multiple doses of 500 µg icatibant including 40 mg triamcinolone as calibrator in a randomized, double-blind, parallel-group, placebo-controlled 13-week[a] multi-centre study in patients with symptomatic knee osteoarthritis [a] After the clinical start of the study, a 26-week double-blind extension of the follow-up period was approved according to the Protocol Amendment no. 2, thus the overall study duration was 39 weeks for patients who participated in the extension period. Results from the extension period are included in this clinical study report.	
Coordinating investigator:	[redacted]	
Study center(s):	43 centers were initiated in Europe and the U.S.; 41 of these centers were active	
Publications (reference):	Not applicable	
Study period: Date first patient enrolled: 27/FEB/2006 Date last patient completed first part of study: 29/JAN/2007 Date last patient completed extension period: 31/JUL/2007		**Phase of development:** Phase IIb
Objectives:	Primary ● To compare the overall treatment effect on pain relief in the affected knee joint between icatibant and placebo in terms of average of daily general knee pain VAS score. Secondary ● To assess the efficacy of icatibant in terms of onset, extent and duration of pain relief relative to triamcinolone (used as calibrator); ● To evaluate the safety of icatibant versus placebo and triamcinolone; ● To evaluate overall conditions of daily life (reflected by patient's global assessment [PGA] and the Western Ontario McMaster Universities osteoarthritis questionnaire [WOMAC]) after treatment with icatibant versus placebo and triamcinolone; ● To assess systemic exposure of icatibant following intra-articular injection.	
Methodology:	This was a multi-center, double-blind, placebo-controlled, randomized, placebo- and corticosteroid-controlled 3-arm parallel group study. The study comprised a 4 to 7 day screening period, 2-week treatment period, an 11-week follow-up period, and a 26-week extension of the follow-up period (added according to Protocol Amendment no. 2). The 3 study periods are referred to as the "primary study period" (first 3 months), the "extension period" (last 6 months), and the "whole study period (all 9 months).	

<table>
<tr><td>Name of company: sanofi-aventis
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<tr><td rowspan="3">Number of patients:

Evaluated:</td><td colspan="2"><u>Planned</u>:
Placebo: 110
Icatibant: 220
Triamcinolone: 220</td><td colspan="2"><u>Randomized and treated</u>
Placebo: 118
Icatibant: 236
Triamcinolone: 236</td></tr>
<tr><td><u>Efficacy (ITT)</u>:
Placebo: 118
Icatibant: 236
Triamcinolone: 236</td><td><u>Safety</u>:
Placebo: 118
Icatibant: 236
Triamcinolone: 236</td><td><u>Pharmacokinetics</u>:
Placebo: 0
Icatibant: 234
Triamcinolone: 0</td></tr>
<tr><td colspan="2"><u>Efficacy (Patients who completed extension period)</u>:
Placebo: 90
Icatibant: 167
Triamcinolone: 153</td><td colspan="2"><u>Safety (Patients who entered extension period)</u>:
Placebo: 94
Icatibant: 177
Triamcinolone: 165</td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td colspan="4">Patients with symptomatic knee osteoarthritis (OA) (Kellgren & Lawrence stage II-IV), pain ≥ 40 mm on a visual analogue scale (VAS) at baseline, with or without flare after washout of OA-directed medication in the screening phase</td></tr>
<tr><td>Investigational product:
Dose:
Administration:
Batch number(s):</td><td colspan="4">Icatibant solution for injection (100 µg/mL)
500 µg in 5.0 mL vehicle, 1 injection per week, 3 injections total
intra-articular (IA) injection
[redacted]</td></tr>
<tr><td>Duration of treatment: 3 injections, administered over a 2-week treatment period</td><td colspan="4">Duration of observation: 39-40 weeks
(screening period: 4-7 days; treatment period: 2 weeks; follow-up period: 11 weeks; follow-up extension period [according to Protocol Amendment no. 2]: 26 additional weeks without any further treatment)</td></tr>
<tr><td>Reference therapy:
Dose:

Administration:
Batch number(s):</td><td colspan="2">Placebo
5.0 mL acetic acid-buffered saline, 1 injection per week, 3 injections total
intra-articular injection
<u>1554</u>
[redacted]</td><td colspan="2">Calibrator: triamcinolone acetonide
1.0 mL saline containing 40 mg triamcinolone acetonide as suspension, 1 injection followed by 2 placebo injections (1 mL each) in weekly intervals
intra-articular injection
[redacted]</td></tr>
</table>

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Criteria for evaluation:		
Efficacy:	Primary efficacy variable ● The primary efficacy variable was the average change from baseline over the primary study period (first 3 months) in general knee pain score, which comprised pain during activity, pain at rest and pain at night in a ratio of 1 : 1 : 1. Secondary efficacy variables Key secondary variables: ● Weighted average change from baseline over the primary study period in WOMAC pain sub-score; ● Weighted average change from baseline over the primary study period in WOMAC function sub-score; ● Average change from baseline over the primary study period in PGA; Other secondary variables: ● Weighted average change from baseline over the primary study period in WOMACstiffness sub-score, and WOMAC total score separately; ● Time to onset of general knee pain relief; ● Average change from baseline over the primary study period, determined separately for pain during activity, at rest, and at night; ● Osteoarthritis Research Society International (OARSI) responder rates; ● Intake of rescue medication.	
Safety: Pharmacokinetics:	Safety ● Adverse events (AEs); ● Clinical laboratory data; ● Vital signs (blood pressure and heart rate); ● 12-lead electrocardiogram (ECG). Bioanalytics ● Icatibant concentrations in pre- and post-injection blood samples; ● Icatibant concentrations in synovial fluid prior to subsequent injections. Pharmacokinetics (PK) Population kinetic approach	

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Pharmacokinetic sampling times and bioanalytical methods:	At Visits 2, 3 and 4, a PK blood sample was taken immediately prior to injection. After the intra-articular injections at Visits 2, 3 and 4, patients remained at the site for at least 1 h, with the option to remain for up to 6 h or to revisit the site within this extension period, if appropriate. As PK samples were used according to a population kinetic approach, the time-points for collection of blood samples were not pre-specified. For each of the three injections, three or more blood samples for PK were to be collected during the first hour after administration of icatibant, giving a total of nine or more samples after injection (taken up to 6 h post-dose) samples for each patient. As in the extension period no additional study drug was administered, no PK analysis was performed for this observation period. Synovial fluid was collected via aspiration prior to the 2nd and 3rd injections of investigational product at Visits 3 and 4 respectively, and was stored for subsequent analysis of drug concentration.	

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Statistical methods:	Efficacy analysis The primary efficacy endpoint (ie, the average change from baseline over the primary study period in general knee score) was calculated as follows: First, a simple daily mean score was calculated for each pain component (during activity, at rest and at night). Then, the mean of these three VAS scores on each day was used to determine a daily general knee pain score. Finally, the baseline general knee pain score was subtracted from the average of the daily general knee pain score to obtain the average change from baseline in general knee pain score. The primary analysis of the average change from baseline in general knee pain score was based on an analysis of covariance (ANCOVA) model including terms for treatment and pooled centers, and baseline score as a covariate. The analyses based on this model were used for statistical inference, for comparisons of icatibant versus placebo treatment and triamcinolone versus placebo treatment. Analyses of the other secondary efficacy variables were performed using an ANCOVA approach similar to that used for the primary analysis. The use of rescue medication was summarized by descriptive analysis. All efficacy analyses were based on the intention-to-treat (ITT) population, which consisted of all randomized patients. All patients were analyzed according to the treatment to which they were randomized. For the primary study period, baseline values were those collected at Visit 2, prior to the first injection of study medication. Because patients did not receive additional injections of study medication in the extension period, and because the purpose of the extension period was to investigate possibly long-term effects of icatibant, the same baseline values were also used for analysis of results from the extension period. For the extension period, the defined populations were: (1) patients who fulfilled criteria to enter the extension period, (2) patients who entered the extension period, (3) patients who completed the extension period, and (4) PP for the extension period. By-visit analyses were performed for the last 3 of these populations. At Visit 7, summary statistics were analyzed separately for the e-diary assessments and the paper assessments. Safety analysis Safety was analyzed descriptively on the basis of the safety population, which was defined as all patients exposed to study medication, regardless of the amount of treatment administered. Safety analyses were performed separately for the 3-month primary study period, the 6-month extension period, and the 9-month whole study period. Pharmacokinetic analysis Systemic icatibant exposure in peripheral blood was to be assessed using a stand-alone population kinetic approach.

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Summary: Study demographics:	A total of 590 patients were randomized in the study, among which 118 in the placebo group, 236 in the icatibant group and 236 in the triamcinolone group. All randomized patients were exposed to the study medication. Demographics, knee OA and baseline general knee pain score were generally comparable among the 3 treatment groups, with the following exceptions: the placebo group included a higher percentage of females (73.7%) as compared to the other treatment groups (70.8% for icatibant and 66.9% for triamcinolone), and the percentage of patients <65 years of age was slightly lower in the placebo group (57.6%) than the other groups (58.9% for icatibant and 60.2% for triamcinolone). The percentage of patients with BMI ≥25 kg/m^2 was higher in the triamcinolone group (92.8%) than in the other treatment groups (88.1% for both placebo and icatibant groups). The mean duration of OA at baseline was shorter in the placebo group than the other groups (49.1 months for placebo versus 59.3 months and 57.0 months for the icatibant and triamcinolone groups respectively). The percentage of patients with a Kellgren & Lawrence grade of IV was lowest in the triamcinolone group (6.4%) as compared to the other groups (8.5% for the placebo group and 9.7% for the icatibant group). Intake of previous medications showed a lower incidence of corticosteroid use among placebo patients as compared to the other treatment groups, whereas patients in the icatibant group showed a lower incidence of analgesic use and a higher incidence of viscosupplementation as compared to the other treatment groups.	

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Efficacy results:	*Primary study period* The primary efficacy variable was the change from baseline averaged over the primary study period (3 months) in the general knee pain score. Clinically relevant improvements from baseline were observed in all three treatment groups. The greatest mean and median changes from baseline were observed in the triamcinolone group, but there was no statistically significant difference between the triamcinolone and placebo groups (p=0.4627); the icatibant group showed statistically significantly less improvement than the placebo group (p=0.0407) but still a clinically relevant mean pain relief of > 20 VAS units. Treatment compliance was very high for all groups; > 97% of patients in each group received all 3 injections. There were no relevant differences between the groups with respect to compliance rate for EPD reporting during the screening phase and during the primary study period. For most primary and secondary efficacy parameters, including sub-group analyses, the triamcinolone group showed the greatest change (ie, improvement) from baseline, the placebo group showed a similar but numerically less change from baseline, and the icatibant group showed the least change from baseline. In general, neither of the active treatment groups was statistically significantly different from the placebo group; however, statistical analyses of some secondary efficacy parameters and some subgroups showed minor variations to this generalized conclusion. Intake of rescue medication showed even less consistent differences among the three treatment groups. Mean total intake of rescue medication was similar among the groups, but a higher percentage of patients in the placebo group required rescue medication, and the time until the first intake of rescue medication was much shorter in the placebo group (20 days) as compared to the icatibant (37 days) and triamcinolone (45 days) groups. The mean and median percentage of days with general knee pain relief as defined by a reduction from baseline of at least 20 VAS units was greatest for the triamcinolone group (mean: 58%, median 75%) and was lowest for the icatibant group (mean: 48%, median: 51%). *Extension period (observation period without further treatment)* The fraction of patients who entered the extension period was not notably different in its average characteristics from those in the primary study period (ITT population) with regard to demographic characteristics, protocol deviations, previous or concomitant medications, or baseline efficacy variables, and there were no relevant differences between the three treatment groups. For patients who completed the extension period, all treatment groups showed continued improvements in general knee pain score over the full 9-month study period. The mean change from baseline was similar for the triamcinolone and placebo groups, and was slightly less among the icatibant patients but exceeded 25 VAS units in all 3 treatment groups.	

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Safety results:	*Primary study period* Although similar percentages of patients in the three treatment groups (ie, 20 to 23%) experienced AEs during the primary study period, the percentage of patients with AEs during the on-treatment period (ie, treatment-emergent AEs; TEAEs) was higher among patients in the two active treatment groups (about 12% each) as compared to the placebo group (about 7%). Percentages of patients with serious adverse events (SAEs) were slightly higher in the two active treatment groups (1.3% in patients with either active treatment versus 0% in placebo patients), as were the percentages of patients withdrawn due to an AE (0.8% in icatibant-treated, 1.3% in triamcinolone-treated, and 0% in placebo-treated patients). Most preferred terms affected in this study involved only a small number of patients in any treatment group. None of the preferred terms were affected in more than 1.5% of the patients in any treatment group. The preferred terms with the greatest differences in percentage of affected patients were headache and joint effusion, which affected a slightly higher percentage of patients in the icatibant treatment group as compared to the other groups, and erythema, which affected a slightly higher percentage of patients in the triamcinolone group as compared to the other groups. . Two patients died in the primary study period, one due to acute aortic dissection in the on-treatment period and the other due to decompensated Parkinson's disease in the post-treatment period. Both patients were in the triamcinolone treatment group. Neither of these two events was considered to be related to study medication. In addition to the two patients who died, five further patients experienced SAEs; one of these SAEs occurred during the screening period. Of the four non-fatal SAEs that occurred during the on-treatment or post-treatment periods, three were in the icatibant group (in-stent arterial restenosis, pancreatitis, and uterine leiomyoma), and one was in the triamcinolone group (coronary artery insufficiency). None of the fatal or non-fatal SAEs were considered to be related to study medication. In total five patients withdraw from study medication due to an AE: two in the icatibant group, and 3 in the triamcinolone group (including one out of the two fatalities). None of the TEAEs leading to withdrawal were considered to be related to study medication, and study blinding was not broken for any of these cases. Injection site TEAEs (ie, reactions in the affected knee joint) have been experienced in higher percentage by patients in the active treatment groups as compared to the placebo group (1.7% for each of the active treatment groups, 0.8% for the placebo group). The most common injection site-related preferred term was joint effusion, which affected 1.3% (3/236) of patients in the icatibant group but none in the other two groups. For all other preferred terms related to the injection site, there were only minor differences (< 1%) between the treatment groups. The incidence of potentially clinically significant abnormal (PCSA) values for laboratory parameters, ECG parameters, and vital sign parameters showed no relevant differences among the treatment groups.	

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	Extension period (observation period without any further treatment) There were no notable differences between the treatment groups with regard to incidence of AEs in the extension period. Generally, the percentage of patients with AEs in each treatment group (7% to 11%) was lower than that in the primary study period (20% to 23 %). During the extension period, about 2% to 3% of subjects in each treatment group experienced late injection site AEs (ie, reactions in the affected knee joint). There were no notable differences between the treatment groups with respect to incidence or type of injection site AEs. Though patients in the placebo group experienced a higher percentage of AEs than the two active treatment groups, the percentage of SAEs was similar for the three treatment groups; none of the SAEs in the extension period was considered related to study medication. During the extension period, no patients experienced an AE leading to death.	

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Pharmacokinetic results:	A population kinetic approach was to be used for the evaluation of PK properties of icatibant. The results of this evaluation were to be reported separately.	
Conclusions:	[redacted]	
Date of report:	06 June 2008	