SYNOPSIS

Title of the study:	A randomized, double-blind, triple-dummy, dose-ranging study, including an active control of unfractionated heparin and eptifibatide, to evaluate the clinical efficacy and safety of otamixaban, in patients with non-ST elevation acute coronary syndrome and planned early invasive strategy (DRI6624).
Investigator(s):	[redacted]
Study center(s):	195 active centers in 36 countries.
Publications (reference):	Marc S Sabatine, Elliott M Antman, Petr Widimsky, Iftikhar O Ebrahim, Robert G Kiss, André Saaiman, Rostislav Polasek, Charles F Contant, Carolyn H McCabe, Eugene Braunwald. Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial.The Lancet 2009; 374: Issue 9692; 787–795.
Study period:	
Date first patient enrolled:	19/Jun/2006
Date last patient completed:	18/Mar/2009
Phase of development:	Dose ranging

Objectives:

Primary

To demonstrate the clinical efficacy of otamixaban via an evaluation of the dose effect (5 intravenous [IV] regimens) in patients with moderate-to-high-risk non-ST elevation acute coronary syndromes (ACS) and planned early invasive strategy, ie, scheduled to undergo an early (≤ Day 3) diagnostic catheterization followed, when indicated, by a percutaneous coronary intervention (PCI).

Secondary

- To evaluate the net clinical benefit of the various otamixaban regimens, in comparison to UFH plus eptifibatide,
- To evaluate the safety of otamixaban,
- To assess the effects of otamixaban on:
  - post-PCI cardiac markers,
  - coagulation tests (pharmacokinetic [PK]-pharmacodynamic [PD] sites),
  - markers of activation of coagulation (PK-PD sites),
  - markers of inflammation (PK-PD sites),
  - von Willebrand factor (PK-PD sites),
- To assess the otamixaban plasma concentrations (PK-PD sites).

Methodology: Multinational, randomized, double-blind, triple-dummy, dose-ranging study with 6 parallel groups. An independent data monitoring committee dedicated to periodic safety data review, recommended to stop otamixaban dose 1 because of inadequate anticoagulation, as set up by the protocol Amendment No.4. Before protocol Amendment No.4, patients were to be randomized (1:1:1:1:1:1) to 1 of 5 otamixaban dosage regimens (Drug A, dosage group 1-5) or unfractionated heparin (Drug B) plus eptifibatide (Drug C). After protocol Amendment No.4, patients were randomized (2:2:2:2:1) to 1 of 4 otamixaban dosage regimens (Drug A, dosage group 2-5) or unfractionated heparin (Drug B) plus eptifibatide (Drug C), with an adjusted sample size from 2700 to 3240 patients. Blinded study medication A and B was administered from randomization, until the end of the PCI, or if no PCI as clinically indicated, up to Day 4 or until hospital discharge, whichever came first. Blinded study medication C was given from the time of randomization. If the patient underwent PCI, the recommended duration of Drug C was 18-24 hours post-PCI or until hospital discharge, whichever came first. If no PCI, Drug C might be discontinued or could be given as long as clinically indicated (maximum of 72 hours). The dose regimen was a single bolus of 0.180 mg/kg followed by an infusion of 0.002 mg/kg/min. In patients with creatinine clearance (CrCl) <50 mL/min the infusion rate was decreased to 0.001 mg/kg/min. All patients were treated with aspirin and clopidogrel, as recommended in the American College of Cardiology / American Heart Association and European Society of Cardiology guidelines.

Number of patients: Planned: 3240 Evaluated: 3241 (see analysis population flow chart in Section 'Patient dispodsition')

A total of 640 patients in the otamixaban groups and of 115 patients in the UFH/Eptifibatide were counted in the PK population.

Diagnosis and criteria for inclusion:

- Male or non pregnant female ≥ 18 years old (or ≥ country's legal age of majority),
- Ischemic discomfort (ie, ischemic chest pain or equivalent) at rest ≥ 10 min within 24 hours of randomization,
- Patient who met 1 of the 2 following criteria of non-ST elevation ACS:
  - New ST-segment depression ≥ 0.1 mV (≥ 1 mm), or transient (< 30 minutes) ST-segment elevation ≥ 0.1 mV (≥ 1 mm) in at least 2 contiguous leads on the electrocardiogram, OR
  - Elevation of cardiac biomarkers within 24 hours of randomization, defined as elevated troponin T, troponin I, or creatine kinase-myocardial band isoenzyme level above upper limit of normal,
- Planned coronary angiography, followed, when indicated, by PCI on Day 1 (day of randomization) to Day 3.

Investigational product: Otamixaban

Dose: 1 minute IV bolus (bol) of 0.080 mg/kg and continuous infusion (I) of 0.035 mg/kg/h, bolus of 0.080 mg/kg and infusion of 0.070 mg/kg/h, bolus of 0.080 mg/kg and infusion of 0.105 mg/kg/h, bolus of 0.080mg/kg and infusion of 0.140 mg/kg/h, bolus of 0.080 mg/kg and infusion of 0.175 mg/kg/h.

[(bol/I) 0.080 mg/kg / 0.035 mg/kg/h, was closed after Amendment No.4].

Administration: IV solution, bolus followed by continuous infusion

Batch numbers:

Otamixaban Dose 1 (0.035 mg/kg/h)	**Otamixaban Dose 2** (0.070 mg/kg/h)	**Otamixaban Dose 3** (0.105 mg/kg/h)	**Otamixaban Dose 4** (0.140 mg/kg/h)	**Otamixaban Dose 5** (0.175 mg/kg/h)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Duration of treatment: In the otamixaban arm, otamixaban was administered from randomization, until the end of the PCI, or if no PCI as clinically indicated, up to Day 4 or until hospital discharge, whichever came first.

In the UFH/eptifibatide arm, UFH was given from the time of randomization, until the end of the PCI, or if no PCI as clinically indicated, up to Day 4 or until hospital discharge, whichever came first. Eptifibatide was started at randomization and given up to 18-24 hours post PCI, or until hospital discharge, whichever came first. If no PCI, eptifibatide was discontinued or could be given as long as clinically indicated (maximum of 72 hours).

Duration of observation:

• 180 days, or until 90 days after the last patient was randomized, for clinical efficacy, and serious adverse events (SAEs).

• until the Day 30 visit for clinical safety.

Reference therapy: Unfractionated heparin	Eptifibatide	Placebo
Dose: IV bolus of 60 IU/kg (max 4000 IU), continuous infusion of 12 IU/kg/hr (max 1000 IU/kg/hr)	IV bolus of 180 μg/kg, continuous infusion 2 μg/kg/min (decreased to 1 μg/kg/min if CrCl <50 mL/min)	IV bolus, continuous infusion
Administration: IV solution	IV solution	IV solution
Batch numbers: [redacted]	Supplied locally	Ota. placebo: [redacted] UFH placebo: [redacted]

Criteria for evaluation:

Efficacy:

- Primary endpoint: Quadruple efficacy composite of all-cause death, new myocardial infarction (MI), severe recurrent ischemia requiring urgent revascularization and in-hospital bailout use of GPIIb/IIIa inhibitor within 7 days following randomization;

- Secondary endpoints:

  - Main secondary efficacy endpoints:

1- net clinical benefit (composite of all-cause death, new MI, severe recurrent ischemia requiring urgent revascularization, in-hospital bailout use of glycoprotein [GP] IIb/IIIa inhibitor and thrombolysis in myocardial infarction (TIMI) significant bleedings within 7 and 30 days following randomization);

2- quadruple efficacy composite of all-cause death, new MI, severe recurrent ischemia requiring urgent revascularization and in-hospital bailout use of GPIIb/IIIa inhibitor within 30, 90 and 180 days following randomization;

3- triple efficacy composite of all-cause death, new MI, severe recurrent ischemia requiring urgent revascularization within 7, 30, 90 and 180 days following randomization;

4- quadruple efficacy composite of all-cause death, new MI, severe recurrent ischemia requiring urgent revascularization and in-hospital bailout use of GPIIb/IIIa inhibitor (whether or not triggered by an ischemic or thrombotic complication) within 30, 90 and 180 days following randomization.

- Other efficacy endpoints:

1- double efficacy composite of all-cause death and new MI, within 7, 30, 90 and 180 days following randomization,

2- individual components of primary endpoint within 7, 30, 90 and 180 days following randomization,

3- thrombotic procedural complications, during PCI (including abrupt or threatened closure, new intracoronary thrombus, side branch closure, distal embolization, no-reflow, and thrombus in catheter or adherent to guidewire),

4- non-thrombotic procedural complications during PCI (including coronary dissection with decreased flow, difficulty in reaching or crossing lesion, unplanned stent use, suboptimal results, coronary perforation, tamponade),

5- analysis of the effect of otamixaban on the following markers: post PCI cardiac markers, coagulation tests, markers of activation of coagulation, markers of inflammation, Von Willebrand factor.

Safety:

Primary: Incidence of non coronary artery bypass graft (CABG)-related TIMI significant bleedings (composite of TIMI major and minor) within 7 days following randomization.

Secondary: Incidence of non CABG-related TIMI significant bleedings (composite of TIMI major and minor) within 30 days following randomization, incidence of all bleeding (TIMI significant and non significant) within 7 and 30 days following randomization, incidence of adverse events within 7 and 30 days following randomization, incidence of SAEs (including bleeding meeting SAE criteria), incidence of stroke within 7, 30, 90 and 180 days following randomization, and laboratory parameters.

Pharmacokinetics: otamixaban plasma concentrations.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling:

- at baseline (prior to start of the otamixaban bolus injection),

- on treatment (prior to the end of otamixaban infusion, at steady-state) on Day 1 or Day 2 (morning) and, if otamixaban was still administered, on Day 3 (morning),

- after the end of otamixaban infusion (ie, anytime between 0.5 to 8 hours post end of administration), except if PCI was performed. In that case, the last sample could be drawn at time of sheath removal.

Assay: otamixaban plasma concentrations were determined using a validated liquid chromatography - tandem mass spectrometry method with a lower limit of quantification of 1.00 ng/mL.

Pharmacodynamics: prothrombin tests (prothrombin expressed as international normalized ratio [PT/INR]), dilute prothrombin time (dPT) and Russel's Viper Venom Test (RVVT).

Pharmacodynamic sampling times and bioanalytical methods:

Sampling at PK/PD sites only: same as PK measurements.

Assay: PT/INR, dPT and RVVT were determined by clot-based assays using optical diffraction detection.

Statistical methods:

Analysis populations: 'all randomized' patients (efficacy), 'all randomized and treated' patients, ie, who received at least 1 dose of either or all blinded study drug (A, B and/or C) (safety), and PCI populations defined as all randomized population who underwent an index PCI (efficacy) and all randomized and treated population who underwent an index PCI (safety). The medically treated population was the patients who did not undergo index PCI nor CABG through Day 7.

Efficacy analysis: The dose-response relationship between the 5 otamixaban regimens on the primary efficacy endpoint was tested using a two-sided trend test on proportions (using logistic model) at the 0.05 significant level. The same analytical methods were used for the triple efficacy endpoint. All efficacy endpoints were also analyzed up to Day 180 using a time to first event approach. For the net clinical benefit, the various otamixaban regimens were compared to unfractionated heparin and eptifibatide using a two-sided Fisher's exact test.

Safety analysis: The same analytical methods used for the primary efficacy analysis, were used for the TIMI (ie,TIMI major + TIMI minor) significant and all bleeding analyses.

Pharmacokinetics: Plasma concentrations of otamixaban were summarized using descriptive statistics.

Pharmacokinetic/pharmacodynamic relationships: The relationships between primary efficacy endpoints, bleeding occurrence, clotting tests and plasma concentrations were explored using graphical methods.

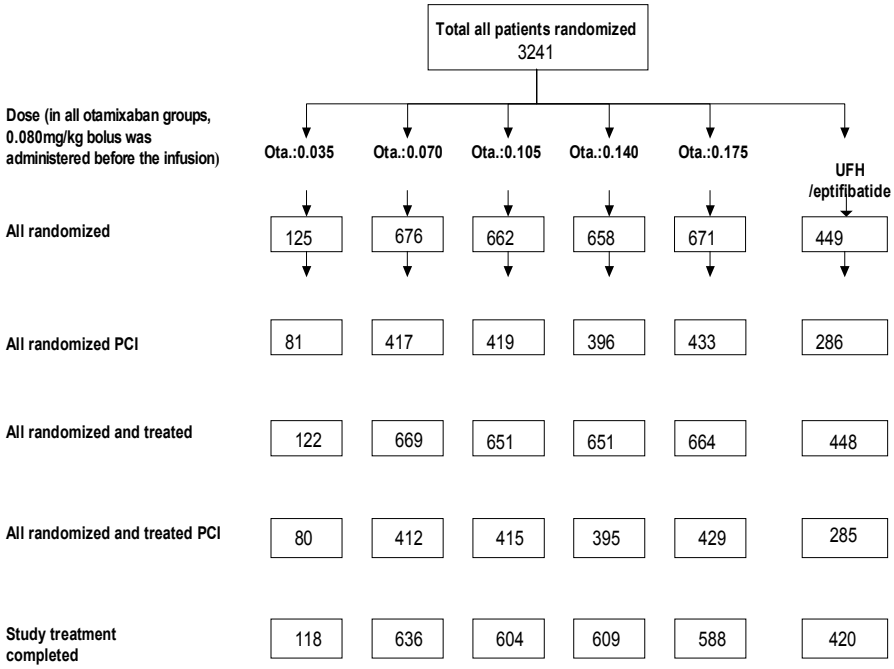
Summary:

Population characteristics:

In this trial, 3241 patients with non ST elevation acute coronary syndromes were evaluated (22.8% with unstable angina and 77.2% with non ST elevation myocardial infarction (NSTEMI). Those patients were adequately treated with oral antiplatelet agents (aspirin and clopidogrel). Demographic and baseline characteristics were similar among the treatment groups.

Patient disposition:

Analysis population flow chart



A total of 62.4% were treated with a PCI, 34.0% were medically treated and 3.6% had a CABG.

Efficacy results:

Primary analysis of primary efficacy endpoint: (all-cause death or new MI or severe recurrent ischemia leading to revascularization or bailout (GP IIb/IIIa receptor inhibitor)), through Day 7- dose response relationship among otamixaban groups - Cochran Armitage test - All randomized population

	Treatment group					
	Ota.: 0.035 (N=125)	**Ota.: 0.070 (N=676)**	**Ota.: 0.105 (N=662)**	**Ota.: 0.140 (N=658)**	**Ota.: 0.175 (N=671)**	**UFH/Eptifibatide (N=449)**
Number of patients with endpoint	9 (7.2%)	31 (4.6%)	25 (3.8%)	24 (3.6%)	29 (4.3%)	28 (6.2%)
95% CI [a]	(3.3% to 13.2%)	(3.1% to 6.4%)	(2.5% to 5.5%)	(2.4% to 5.4%)	(2.9% to 6.1%)	(4.2% to 8.9%)
Cochran Armitage test [b]	0.3364					

Note: Only patients with events occurring from randomization through Day 7 are considered
[a] 95% CIs are computed using exact method
[b] Cochran Armitage test across Otamixaban groups, using infusion rate as covariable

Secondary analysis of primary efficacy endpoint through Day 7: number (%) of patients for each component - all randomized population

	Treatment group					
	Ota.: 0.035 (N=125)	**Ota.: 0.070 (N=676)**	**Ota.: 0.105 (N=662)**	**Ota.: 0.140 (N=658)**	**Ota.: 0.175 (N=671)**	**UFH/Eptifibatide (N=449)**
Individual components:						
All-cause death [b]	1 (0.8%)	6 (0.9%)	6 (0.9%)	4 (0.6%)	5 (0.7%)	8 (1.8%)
95% CI [a]	(0.0% to 4.4%)	(0.3% to 1.9%)	(0.3% to 2.0%)	(0.2% to 1.5%)	(0.2% to 1.7%)	(0.8% to 3.5%)
New MI [b]	5 (4.0%)	11 (1.6%)	9 (1.4%)	13 (2.0%)	12 (1.8%)	14 (3.1%)
95% CI [a]	(1.3% to 9.1%)	(0.8% to 2.9%)	(0.6% to 2.6%)	(1.1% to 3.4%)	(0.9% to 3.1%)	(1.7% to 5.2%)
Severe recurrent ischemia leading to revascularization [b]	1 (0.8%)	2 (0.3%)	4 (0.6%)	2 (0.3%)	4 (0.6%)	3 (0.7%)
95% CI [a]	(0.0% to 4.4%)	(0.0% to 1.1%)	(0.2% to 1.5%)	(0.0% to 1.1%)	(0.2% to 1.5%)	(0.1% to 1.9%)
Protocol-defined bailout [b]	2 (1.6%)	12 (1.8%)	6 (0.9%)	5 (0.8%)	8 (1.2%)	3 (0.7%)
95% CI [a]	(0.2% to 5.7%)	(0.9% to 3.1%)	(0.3% to 2.0%)	(0.2% to 1.8%)	(0.5% to 2.3%)	(0.1% to 1.9%)

Note: Only patients with events occurring from randomization through Day 7 are considered
[a]: two sided 95% CIs are computed using exact method
[b]: only the first event among the 4 components is considered

Analysis of individual efficacy endpoints through Day 7: number (%) of patients - all randomized population

	Treatment group					
	Ota.: 0.035 (N=125)	**Ota.: 0.070 (N=676)**	**Ota.: 0.105 (N=662)**	**Ota.: 0.140 (N=658)**	**Ota.: 0.175 (N=671)**	**UFH/Eptifibatide (N=449)**
All-cause death	1 (0.8%)	9 (1.3%)	8 (1.2%)	8 (1.2%)	8 (1.2%)	8 (1.8%)
New MI	5 (4.0%)	11 (1.6%)	9 (1.4%)	13 (2.0%)	12 (1.8%)	14 (3.1%)
Severe recurrent ischemia leading to revascularization	1 (0.8%)	2 (0.3%)	5 (0.8%)	2 (0.3%)	4 (0.6%)	3 (0.7%)
Any protocol-defined bail out	4 (3.2%)	15 (2.2%)	9(1.4%)	5 (0.8%)	8 (1.2%)	5 (1.1%)

No dose-response was obverved across the otamixaban groups for the rate of the primary efficacy endpoint (composite of all cause-death + MI + severe recurrent ischemia leading to revascularization + protocol defined bailout use of GPIIb/IIIa inhibitor through Day 7). However, in all otamixaban groups except the lowest one (0.035), the point estimate for the primary efficacy endpoint favoured otamixaban over UFH/eptifibatide. Specifically, at intermediate doses (0.105 and 0.140), treatment with otamixaban resulted in approximately 40% reductions in the primary efficacy endpoint (relative risk of 0.61 and 0.58, respectively).

The differences in the rates of the primary endpoint seen by 7 days persisted up to 180 days of follow-up.

These differences in the composite endpoint were driven by ≥45% reductions in death or MI (relative risk of 0.52 and 0.56, respectively, in the otamixaban 0.105 and 0.140 group) as compared with the UFH/eptifibatide group.

In the lowest groups (0.035 and 0.070), the observed incidences of protocol defined bailout use of GPIIb/IIIa inhibitor and thrombotic complications during the index PCI were higher than in the other otamixaban groups or in the UFH/eptifibatide group. In the 2 intermediate groups (0.105 and 0.140), the incidence of protocol defined bailout use of GPIIb/IIIa inhibitor and thrombotic complications during the index PCI was similar to the incidence observed in the UFH/eptifibatide group.

In both the PCI population and in the medically treated population, the efficacy observations were similar as in the all randomized population.

Safety results:

Both Drug A (otamixaban/placebo) and Drug B (UFH/placebo) had to be discontinued as per protocol after the PCI or, if no PCI was performed, could be given if clinically indicated up to Day 4. Drug C (eptifibatide/placebo) had to be continued for 18-24h after the PCI. The observed duration is described in the table below:

Extent of study drug exposure - all randomized and treated population

	Treatment group					
	Ota.: 0.035 (N=122)	**Ota.: 0.070 (N=669)**	**Ota.: 0.105 (N=651)**	**Ota.: 0.140 (N=651)**	**Ota.: 0.175 (N=664)**	**UFH/Eptifibatide (N=448)**
Drug A (Otamixaban or Placebo) treatment duration (hour:minute)						
Number	122	668	650	650	664	448
Mean (SD)	14:18 (15:07)	12:46 (14:56)	12:55 (14:24)	12:40 (14:21)	11:37 (12:35)	12:44 (14:32)
Median	5:25	5:10	5:24	4:55	5:05	4:52
Min : Max	0:43 : 71:50	0:23 : 96:14	0:54 : 93:30	0:02 : 96:43	0:30 : 76:51	0:17 : 95:57
Drug B (UFH or Placebo) treatment duration (hour:minute)						
Number	122	669	651	649	664	447
Mean (SD)	14:14 (15:06)	12:51 (15:00)	12:56 (14:35)	12:33 (14:19)	11:35 (12:45)	12:42 (14:33)
Median	5:23	5:09	5:22	4:53	5:00	4:51
Min : Max	0:41 : 71:49	0:22 : 96:14	0:00 : 93:28	0:20 : 96:44	0:27 : 81:26	0:18 : 95:58
Drug C (Eptifibatide or Placebo) treatment duration (hour:minute)						
Number	122	669	651	650	663	444
Mean (SD)	21:59 (15:09)	21:23 (14:51)	21:27 (15:27)	21:05 (15:05)	19:48 (13:35)	20:35 (14:42)
Median	21:13	21:28	20:58	21:18	20:45	20:29
Min : Max	0:06 : 72:58	0:21 : 96:15	0:51 : 88:43	0:02 : 94:35	0:25 : 89:40	0:03 : 81:00

Note: Number corresponds to the count of patients with non missing data used for the calculation.
Extent of exposure is calculated without taking into account temporary discontinuation.

The primary safety endpoint was the composite of non CABG-related TIMI significant (ie, TIMI major + TIMI minor) bleeding episodes within 7 days following randomization. There was a significant dose response among the 5 otamixaban groups for the incidence of non-CABG related TIMI significant bleedings.

Adjudicated non CABG-related TIMI significant bleedings through Day 7 - Number (%) of patients and dose response relationship in otamixaban groups - Cochran Armitage test - all randomized and treated population

	Treatment group					
	Ota.: 0.035 (N=122)	**Ota.: 0.070 (N=669)**	**Ota.: 0.105 (N=651)**	**Ota.: 0.140 (N=651)**	**Ota.: 0.175 (N=664)**	**UFH/Eptifibatide (N=448)**
Number of patients with endpoint	2 (1.6%)	11 (1.6%)	20 (3.1%)	22 (3.4%)	36 (5.4%)	12 (2.7%)
95% CI [a]	(0.2% to 5.8%)	(0.8% to 2.9%)	(1.9% to 4.7%)	(2.1% to 5.1%)	(3.8% to 7.4%)	(1.4% to 4.6%)
Cochran Armitage test [b]	0.0001					

Note: Only patients with non-CABG significant (minor and/or major) TIMI bleeding occurring from first study medication administration through Day 7 are considered
[a] 95% CIs are computed using exact method
[b] Cochran Armitage test across Otamixaban groups, using infusion rate as covariable

Compared with patients treated with UFH/eptifibatide, patients treated with low doses of otamixaban (0.035 and 0.070) tended to have lower rates of the primary safety endpoint (relative risk of 0.61 and 0.61, respectively), patients treated with intermediate doses (0.105 and 0.140) had similar rates (relative risk of 1.1 and 1.26, respectively), and patients treated with the highest dose (0.175) had a significantly higher rate (relative risk of 2.0).

The majority of bleedings was minimal and observed through Day 7. Similar to the non-CABG related TIMI major + minor, a dose-related increase among the otamixaban groups was observed for the incidence of patients with any bleedings, TIMI minor and TIMI minimal bleedings.

The percentage of patients experiencing treatment-emergent adverse events (TEAEs) and serious TEAEs were similar in the treatment groups. The percentage of patients with TEAE leading to study drug discontinuation increased with the doses of otamixaban and was mainly related to bleedings.

The thrombotic complications are presented in the efficacy results.

The analysis of the other safety parameters, including laboratory parameters, did not reveal any imbalance among the treatment groups.

Pharmacokinetic results:

The doses of otamixaban of 0.035 mg/kg/h, 0.070 mg/kg/h, 0.105 mg/kg/h, 0.140 mg/kg/h and 0.175 mg/kg/h led to mean (SD) plasma concentrations of 76.0 (30.5), 206 (86.8), 548 (1800), 509 (214) and 636 (249) ng/mL, respectively, when taken before the end of infusion.

Pharmacokinetic/pharmacodynamic results:

A linear dose relationship was observed between the PD parameters (PT/INR, dPT, RVVT) and the otamixaban plasma concentrations.

Conclusions:

[redacted]

Date of report: 15-Nov-2010