SYNOPSIS

Title of the study: Randomized, double-blind, triple-dummy trial to compare the efficacy of otamixaban with Unfractionated Heparin + eptifibatide, in patients with Unstable angina/Non ST segment Elevation Myocardial infarction scheduled to undergo an early invasive strategy (EFC6204/TAO)

Investigator(s): Not disclosed

Study centers: 568 active centers in 55 countries

Publications (references):

Steg PG, Mehta SR, Pollack CV, Bode C, Gaudin C, Fanouillere K, et al. Design and rationale of the treatment of acute coronary syndromes with otamixaban trial: a double-blind triple-dummy 2-stage randomized trial comparing otamixaban to unfractionated heparin and eptifibatide in non-ST-segment elevation acute coronary syndromes with a planned early invasive strategy. Am Heart J 2012;164:817-824.e13.

Steg PG, Mehta SR, Pollack CV, Bode C, Cohen M, French WJ, et al. Anticoagulation with otamixaban and ischemic events in non-ST-segment elevation acute coronary syndromes. The TAO randomized clinical trial. JAMA. 2013. Available from: http://dx.doi.org/10.1001/jama.2013.277165.

Study period:

Date first patient enrolled: 01-Apr-2010 (date of first signed informed consent)

Date last patient completed: 06-May-2013 (date of last patient last visit)

Phase of development: 3

Objectives:

***Primary*:** to demonstrate the superior efficacy (composite of all-cause death and myocardial infarction [MI]) of otamixaban as compared to unfractionated heparin (UFH) + eptifibatide.

Secondary:

- To demonstrate the superior efficacy (composite of all-cause death + MI + any stroke) of otamixaban as compared to UFH + eptifibatide
- To document the effect of otamixaban on rehospitalization or prolongation of hospitalization due to a new episode of myocardial ischemia/MI as compared to UFH + eptifibatide
- To document the effect on mortality (all cause mortality) of otamixaban as compared to UFH + eptifibatide
- To document the safety of otamixaban as compared to UFH + eptifibatide
- To document the effect of otamixaban on thrombotic procedural complications during the index percutaneous coronary intervention (PCI) as compared to UFH + eptifibatide
- To characterize otamixaban pharmacokinetics over the entire dosing interval and to evaluate otamixaban exposure-response (safety and efficacy) in the target population

Methodology: Multinational, multicenter, randomized, double-blind, triple-dummy, parallel-group study comparing the efficacy of otamixaban versus the control UFH + eptifibatide in patients with moderate- to-high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) with a planned early invasive strategy. An adaptive 2-stage design was implemented with an interim analysis performed by an independent Data Monitoring Committee (DMC) at the end of the first stage to select 1 of the 2 doses of otamixaban. In the first stage, before the interim analysis, patients were randomized to otamixaban dose 1 (bolus of 0.080 mg/kg followed by infusion of 0.100 mg/kg/h), dose 2 (bolus of 0.080 mg/kg followed by infusion of 0.140 mg/kg/h), or UFH + downstream eptifibatide (started pre-PCI) according to a 1:1:1 ratio. In the second stage, after the interim analysis and the DMC's decision to maintain 1 dose of otamixaban, patients were randomized to the selected dose of otamixaban or UFH + eptifibatide according to a 1:1 ratio. All patients were also to receive aspirin (75-325 mg daily), and clopidogrel or any other oral ADP receptor antagonist, as per local approved label or as recommended by the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines. The study employed an Executive Committee responsible to address scientific issues encountered during the study, a Steering Committee responsible for the good conduct of the study, a DMC responsible for monitoring the patients' safety, performing the interim analysis, and selecting the otamixaban dose to be continued until the end of the study based on the interim analysis results, and a Central Independent Adjudication Committee (CIAC) responsible for adjudicating all prespecified efficacy and safety endpoints.

Number of patients**:** Planned: 13 220 patients Randomized: 13 229

Evaluated:

Population	Otamixaban 0.100 mg/kg/h	Otamixaban 0.140 mg/kg/h	UFH/eptifibatide	Total
Randomized	2657	5106	5466	13229
Randomized and treated	2639	5065	5424	13128
Efficacy and bleeding analyses	2657	5106	5466	13229
Adverse event analyses	2639	5065	5424	13128

Diagnosis and criteria for inclusion:

- Patients with non NSTE-ACS as evidenced by:
  - Ischemic symptoms (chest pain or equivalent) at rest ≥10 minutes within 24 hours of randomization,
  - And electrocardiogram (ECG) changes consisting of 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, and/or elevation of cardiac biomarkers (defined as elevated troponin T, troponin I, or CK-MB level above upper limit of normal) within 24 hours of randomization;
- And planned to have a coronary angiography (followed when indicated by PCI) as early as possible (after at least 2 hours of treatment with study drug) and within 36 hours or on Day 3 at the latest.

Study treatments

Investigational medicinal products (IMPs):

All patients were to be treated with Drug A (otamixaban/matching placebo), Drug B (UFH/matching placebo), and Drug C (eptifibatide/matching placebo). Drugs A and B were to be started immediately after randomization, and Drug C was to be given, only in case a PCI was done, and started immediately before the PCI.

In addition, in all patients, whatever the group, a bailout (Drug D and/or open-label eptifibatide) could be administered after randomization and during initial hospitalization (ie, only because of a significant recurrent ischemia or procedural complication or other clinical instability).

- If the bailout was needed before any administration of Drug C, patients were to receive a first bolus of open-label eptifibatide followed by an infusion of open-label eptifibatide and a second bolus 10 minutes after the first one.

- If the patient was receiving Drug C (eptifibatide/placebo) at the time of the bailout, the boluses were blinded (eptifibatide/matching placebo- Drug D). In the otamixaban arm(s) the Drug D boluses will be boluses of active eptifibatide. In the UFH + eptifibatide arm the Drug D boluses will be a placebo of eptifibatide. In all arms the bolus was to be followed by an infusion of open-label eptifibatide and the Drug C must be stopped. In addition a blinded activated clotting time (ACT) was to be performed and additional bolus(es) of Drug B (UFH/placebo) will be administered as needed. If the patient was not stabilized, the Investigator was advised to measure an unblinded ACT and may switch to open-label anticoagulant.

	Otamixaban (and matching placebo) / Drug A	**UFH (and matching placebo) / Drug B**
Formulation	For boluses: prefilled vials containing 5 mL of solution at 5 mg/mL and matching placebo For infusion: prefilled vials containing 50 mL of solutions at 3.57 mg/mL (dose 1) or 5 mg/mL (dose 2) and matching placebo	For bolus and infusion: prefilled vials containing 5 mL of a 5000 IU/mL solution and matching placebo
Routes of administration	Intravenous: bolus followed by continuous infusion	Intravenous: bolus followed by continuous infusion
Dose regimen	Bolus of 0.080 mg/kg followed by infusion of 0.100 mg/kg/h (dose 1) or 0.140 mg/kg/h (dose 2)	Bolus of 60 IU/kg (maximum 4000 IU) followed by infusion of 12 IU/kg/h (maximum 1000 IU/h) to maintain aPTT at 1.5 to 2.0 times control and at the time of PCI, additional boluses needed if ACT was not in the range of 200-250 s.

Batch numbers

Drug		Treatment	Batch numbers
A	Bolus	Otamixaban 5 mg/mL (5 mL)	Not disclosed
		Placebo (5 mL)	Not disclosed
	Infusion	Otamixaban 5 mg/mL (50 mL)	Not disclosed
		Otamixaban 3.57 mg/mL (50 mL)	Not disclosed
		Placebo (50 mL)	Not disclosed
B		UFH (5 mL)	Not disclosed
		Placebo (5 mL)	Not disclosed

	Eptifibatide (and matching placebo) / Drug C	Eptifibatide bolus for bailout (and matching placebo) / Drug D
Formulation	For bolus and bailout use: prefilled vials containing 10 mL of a 2 mg/mL solution and matching placebo For infusion: prefilled vials containing 100 mL of solution at 0.75 mg/mL per vial and matching placebo	
Routes of administration	Intravenous: bolus followed by continuous infusion	Intravenous: bolus injection only
Dose regimen	First bolus of 180 µg/kg immediately before PCI, followed by continuous infusion of 2.0 µg/kg/min (or 1.0 µg/kg/min in patients with CrCl <50 mL/min), and second bolus of 180 µg/kg 10 min after the first bolus.	After initiation of Drug C, first bolus of 180 µg/kg followed by infusion of open-label eptifibatide and second bolus of 180 µg/kg 10 min after the first one.
Batch numbers	Not disclosed	

Noninvestigational medicinal products (Non-IMPs):

	Aspirin, clopidogrel, or any other oral ADP receptor antagonist	Open-label eptifibatide infusion given for bailout
Formulation	According to local label	According to local label
Routes of administration	Oral	Intravenous
Dose regimen:	As per local approved label or AHA/ACC and ESC guidelines	-If bailout administered before Drug C initiation: first bolus of 180 µg/kg open-label eptifibatide followed by an infusion of 2 µg/kg/min open-label eptifibatide (or 1 µg/kg/min in patients with CrCl <50 mL/min), and a second bolus of 180 µg/kg open-label eptifibatide 10 min after the first one. -If bailout administered after Drug C initiation: the boluses are blinded (see Drug D) and the infusion is an infusion of 2 µg/kg/min open-label eptifibatide (or 1 µg/kg/min in patients with CrCl <50 mL/min).

Duration of treatment: Drugs A and B were to be administered until the end of PCI, or if no PCI was performed, as per Investigator's judgment, up to Day 4 or hospital discharge, whichever came first. Drug C was to be administered up to 18-24 hours post-PCI, or hospital discharge, whichever came first.

Duration of observation: Follow-up visit on Day 30, and telephone contact on Day 90 and Day 180 or end of study.

Criteria for evaluation:

Efficacy:

Primary endpoint: adjudicated composite of all-cause death or new MI from randomization (Day 1) to Day 7.

Secondary endpoints:

- Adjudicated composite of all-cause death or new MI or any stroke from randomization (Day 1) to Day 7
- Adjudicated all-cause death from randomization (Day 1) to Day 30
- Rehospitalization or prolongation of hospitalization due to a new episode of myocardial ischemia/MI from randomization (Day 1) to Day 30.
- Adjudicated thrombotic procedural complications of index angiography/PCI

Safety: The primary safety endpoint was the incidence of TIMI (Thrombolysis In Myocardial Infarction) significant bleeding (composite of TIMI major and minor) adjudicated by a blinded CIAC from randomization (Day 1) to Day 7. Other bleeding related endpoints included coronary artery bypass graft (CABG) and non CABG-related bleedings according to TIMI, GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries), CURRENT, and BARC (Bleeding Academic Research Consortium) classifications, from randomization (Day 1) to Day 7 and Day 30. Adverse events (AEs) were recorded up through Day 30 unless the event was serious and related to IMP, in the investigator's judgment, in which case it was to be reported even after Day 30.

Pharmacokinetics: otamixaban plasma concentrations. Predicted pharmacokinetic (PK) parameters from the population PK analysis are provided in a separate report. In addition, PK parameters for patients with collected PK samples and not included in the population PK analysis were estimated using a Bayesian approach and are provided in a separate report. The exposure parameters (area under the plasma concentration versus time curve [AUC] and concentration at the end of infusion [Ceoi]) issued from the population PK analysis and Bayesian analysis were taken into account in the exposure/response relationship analysis.

Pharmacodynamics: activated partial thromboplastin time (aPTT) and ACT, determined in a blinded manner, were only used at individual patient level for monitoring the patient.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling: In patients enrolled before the interim analysis, 4 to 5 PK samples were collected as follows: 10 minutes after administration of the IV bolus of Drug A, within 15 minutes before the end of the Drug A infusion, within 15 minutes after the end of Drug A infusion, and 1 to 2 hours after the end of Drug A infusion. If the Drug A infusion was maintained on Day 2, a sample was also drawn in the morning of Day 2. In addition, every effort was made to take a sample as soon as possible after the event in patients having a thrombotic complication, MI, stroke, and bleeding perceived as TIMI significant by the Investigator, and still on study Drug A or within 8 hours of study Drug A discontinuation. PK sampling was stopped after the interim analysis.

Assay: Concentrations of otamixaban in plasma samples were determined using a validated liquid chromatography method coupled with tandem mass spectrometry with a lower limit of quantification of 1 ng/mL.

Statistical methods:

Analysis populations:

Efficacy: All efficacy analyses were performed on the intent-to-treat (ITT) population, defined as the randomized population analyzed according to the treatment group allocated by randomization. Thrombotic procedural complications were analyzed on the 'randomized PCI population', defined as the all-randomized population who underwent an index PCI, and analyzed according to the treatment group allocated by randomization.

Safety: Adjudicated bleedings were analyzed on the ITT population. All other safety analyses were performed on the safety population, defined as the randomized population who did actually receive at least 1 dose or partial dose of active IMP analyzed according to the active treatment actually received.

Pharmacokinetics: All the analyses for exposure/response relationships were performed on the subset of patients from the safety population who received otamixaban and with available PK samples.

Efficacy analysis:

The primary analysis compared the number of patients with the primary endpoint (composite of all-cause death or MI centrally adjudicated from randomization [Day 1] to Day 7) between the remaining dose of otamixaban up to the end of the study and UFH + eptifibatide, using a testing procedure ensuring a global alpha level of 0.025.

The testing procedure was based on a combination test, including the following p-values:

- Hochberg-adjusted one-sided p-value from Fisher exact test on stage 1 data
- One-sided p-value from Fisher exact test on stage 2 data

These one-sided p-values were combined using weighted inverse normal combination tests using predefined fixed weights. The two-sided p-value, defined as twice the one-sided p-value, was presented.

Relative risk (RR) and its multiplicity adjusted flexible repeated 95% two-sided confidence interval (CI) were calculated.

A sensitivity analysis compared the composite of all-cause death or MI centrally adjudicated from randomization (Day 1) to Day 30 between the remaining dose of otamixaban and UFH + eptifibatide, using the same methodology as for the primary analysis.

If the primary efficacy endpoint reached statistical significance, 2 secondary endpoints were planned to be tested using a step-down approach:

1. Adjudicated composite of all-cause death or new MI or any stroke from randomization (Day 1) to Day 7.
2. Adjudicated all-cause death from randomization (Day 1) to Day 30.

These 2 secondary efficacy endpoints were to be tested using the same methodology as for the primary efficacy endpoint.

Safety analysis:

The percentages of patients with TIMI significant bleedings from randomization to Day 7 and exact 95% 2-sided CIs were provided for the 3 treatment groups. Relative risks of the otamixaban versus UFH + eptifibatide and their 95% 2-sided CIs were also calculated.

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

Exposure/response relationships: Exploratory descriptive statistics were provided on the proportion of patients for adjudicated MI, adjudicated thrombotic complications, adjudicated stroke, TIMI significant bleedings, non–CABG TIMI significant bleedings, TIMI major bleedings, non–CABG TIMI major bleedings, CABG TIMI major bleedings, and TIMI minor bleedings, death, and the primary efficacy endpoint in the subgroups of patients defined by ranges of AUC. A similar analysis was performed by ranges of Ceoi. Logistic regression models were also used for occurrence of each endpoint according to individual exposure parameters (Ceoi and AUC, taken separately) and covariates (eg, age, race, sex, body weight, and renal status as defined by creatinine clearance at baseline). The nullity of individual exposure parameters was tested (Wald Test) to assess the predictability of Ceoi and AUC, taken separately, on the occurrence of the primary efficacy and main bleeding endpoints.

Summary:

During the course of the study, potential or confirmed GCP non-compliance at 5 sites were addressed and are disclosed in the clinical study report. No sensitivity analysis was necessary given that the deviations were either corrected or not related to the primary efficacy and safety endpoints.

The dose of 0.140 mg/kg/h otamixaban was selected by the DMC as the one to be continued until the end of the study based on the interim analysis performed in 7088 patients. The dose of 0.100 mg/kg/h was discontinued for futility.

Population characteristics:

A total of 13 229 patients with moderate- to high-risk NSTE-ACS planned for an early invasive strategy were randomized and evaluated. Demographic and baseline characteristics were similar across treatment groups.

Efficacy results:

The actual global study power based on the observed event rate in the control group was 90.3%, ie, slightly above the initially planned 88% power.

Otamixaban 0.140 mg/kg/h did not show superiority over UFH/eptifibatide for the primary endpoint of all-cause death or MI from randomization through Day 7 (5.5% versus 5.7% patients): the RR (95% CI) was 0.993 (0.848 to 1.163) (p=0.9321). Results were consistent regardless of patients' demographic characteristics, medical history, prior medications, or disease characteristics.

The incidences of the secondary endpoints, ie, all-cause death, MI, or stroke from randomization through Day 7, all-cause death from randomization to Day 30, rehospitalization or prolongation of hospitalization due to a new episode of myocardial ischemia/MI from randomization to Day 30, or thrombotic procedural complications during the index PCI were similar in the otamixaban 0.140 mg/kg/h and UFH/eptifibatide groups.

Similar results were observed over time and for all other efficacy endpoints. All efficacy results were overall highly consistent.

Safety results:

In the ITT population, the risk of TIMI significant (major or minor, CABG or not CABG-related) bleeding from randomization to Day 7 (primary safety endpoint) was higher in the otamixaban 0.140 mg/kg/h group compared to the UFH/eptifibatide group; the RR was 2.128 (95% CI 1.631 to 2.776). Results were consistent across all subgroups analyzed.

The rate of TIMI major bleeding (CABG or not CABG-related) was low in all treatment groups (1.2% patients in the otamixaban 0.100 mg/kg/h group, 1.7% patients in the otamixaban 0.140 mg/kg/h group, and 0.8% patients in the UFH/eptifibatide group).

The risk of any type of bleeding from randomization to Day 7 was also approximately twice in the otamixaban 0.140 mg/kg/h group compared to the UFH/eptifibatide group.

Overall, the percentages of patients who experienced AEs, SAEs, or AEs leading to permanent discontinuation of IMP, excluding bleedings, were similar across treatment groups. There were no clinically meaningful differences between treatment groups for any adverse events with prespecified monitoring defined in the protocol, and additional AEs for which potential concerns were raised during the study, and including hepatic disorders, acute kidney injury, thrombocytopenia, convulsion, or allergic reaction.

Pharmacokinetic results:

The occurrence of primary efficacy endpoint (all-cause death or adjudicated MI from randomization to Day 7) was related to an increase in AUC (p=0.0325) while no relation was observed with Ceoi (p=0.3915).

The occurrence of primary safety endpoint (TIMI significant bleeding from randomization to Day 7) was related to an increase in both Ceoi (p=0.0141) and AUC (p<0.0001).

Conclusions:

Not disclosed

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