Synopsis (C0116T40)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: ReoPro		
Name of Active Ingredient: abciximab		

Protocol: C0116T40 (CR005410)	**EudraCT No.** 2004-000548-26

Title of the study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Reteplase and Abciximab Combination Therapy with Abciximab Alone Administered Early or Just Prior to Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

Principal/Coordinating Investigator(s): Stephen Ellis, MD; Cleveland Clinic Foundation

Study Center(s): 208

Publication (reference): Ellis SG, Tendera M, de Belder MA et al., for the FINESSE Investigators. Facilitated PCI in patients with ST-Elevation myocardial infarction. *N Engl J Med*. 2008;358(21):2205-2217.

Studied Period: 22 Aug 2002/16 Jan 2008	**Phase of Development:** 3

Objectives:

The primary objective of the study was to demonstrate that administration of aspirin, abciximab, reteplase, and heparin followed by early diagnostic angiography and intervention, when not contraindicated (reteplase/abciximab facilitated percutaneous coronary intervention [PCI] group), had superior efficacy compared with the administration of aspirin and heparin followed by early diagnostic angiography and primary intervention with abciximab, when not contraindicated (primary PCI group).

Superior efficacy was measured in subjects who presented with ST-segment elevation and were randomized within 6 hours of symptom onset, by the reduction of the composite of the following endpoints, which occurred within 90 days of randomization:

- All-cause mortality ***or***
- Complications of myocardial infarction (MI), defined as: rehospitalization *or* emergency department treatment for congestive heart failure (CHF); *or* resuscitated ventricular fibrillation occurring > 48 hours after randomization; *or* cardiogenic shock.

The major secondary efficacy objectives of this study were to:

1. Evaluate if reteplase/abciximab facilitated PCI reduces the incidence of all-cause mortality or complications of MI as defined in the primary objective compared with abciximab facilitated PCI within 90 days of randomization
2. Evaluate if reteplase/abciximab facilitated PCI reduces the incidence of all-cause mortality compared with primary PCI or abciximab facilitated PCI within 90 days of randomization
3. Evaluate if abciximab facilitated PCI reduces the incidence of all-cause mortality or complications of MI as defined in the primary objective compared with primary PCI within 90 days of randomization
4. Evaluate if the strategy of reteplase/abciximab facilitated PCI compared with the strategies of primary PCI or abciximab facilitated PCI, increases the prevalence of ST-segment resolution > 70% from pretreatment baseline when assessed at 60 to 90 minutes after randomization.

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The major safety objectives of this study were to:

1. Evaluate the safety profiles of reteplase/abciximab facilitated PCI, abciximab facilitated PCI, and primary PCI with regard to the incidence of nonintracranial bleeding.
2. Evaluate the safety profiles of reteplase/abciximab facilitated PCI, abciximab facilitated PCI, and primary PCI with regard to the incidence of intracranial bleeding.

Low Molecular Weight Heparin (LMWH) Substudy Objective:
The objective of the substudy was to obtain clinical data on the safety of enoxaparin when used in combination with abciximab in subjects undergoing primary PCI, as well as to assess the safety in subjects undergoing facilitated PCI with both abciximab and reteplase and with abciximab alone.

Methodology: This was a multicenter, randomized, double blind, placebo-controlled study. The study population consisted of subjects with ST-segment elevation MI who were randomized within 6 hours of symptom onset. Subjects who could be transferred directly to the catheterization laboratory within 60 minutes of qualifying electrocardiogram (ECG) were excluded from the study. Subjects were randomized and began treatment in the Emergency Department (or hospital room if inpatient, or according to local practice). Subjects were randomized in equal proportions to 1 of the following 3 treatment groups: 1) reteplase/abciximab facilitated PCI, 2) abciximab facilitated PCI, or 3) primary PCI.

Subjects in all groups were transferred to the cardiac catheterization laboratory for further treatment unless they met criteria for early reperfusion. After initial Emergency Department treatment, or during the wait for coronary angiography, some subjects may have met the criteria for early ST-segment resolution **and** low risk clinical characteristics. Subjects who met these criteria may have had catheterization delayed or deferred at the discretion of the investigator. All subjects were to have received aspirin 81-325 mg orally (or 250-500 mg intravenously, based on approval per country) as soon as possible after randomization and daily for at least 90 days postrandomization. The use of coronary stenting, as well as administration of clopidogrel or ticlopidine, was at the discretion of the investigator. Subjects in all groups were to have received an initial unfractionated heparin (UFH) bolus of 40 U/kg (maximum bolus 3000 U) in the Emergency Department (or hospital room if inpatient). Adjustment of subsequent doses was made to maintain an activated clotting time (ACT) 200-250 seconds in subjects undergoing immediate PCI or to maintain an activated partial thromboplastin time (aPTT) between 50 and 70 seconds for subjects undergoing delayed intervention.

Abciximab was given as a 0.25 mg/kg IV bolus. Subjects in the reteplase/abciximab and abciximab facilitated PCI groups received their blinded abciximab bolus at the initial point of care and blinded placebo bolus in the cardiac catheterization laboratory. Subjects in the primary PCI group received blinded abciximab placebo bolus and blinded reteplase placebo boluses at the initial point of care and the blinded active abciximab bolus in the cardiac catheterization laboratory. All subjects were to receive an IV infusion of abciximab (0.125 μg/kg/min to a maximum of 10 μg/min) continuing for 12 hours from initiation of the IV infusion. Reteplase or placebo for reteplase was given to subjects as two 5U IV boluses ideally separated in time by 30 minutes. Subjects 75 years of age or older were only to receive one 5U bolus. Reteplase and abciximab were administered as soon as possible, preferably within 30 minutes after randomization. The first reteplase bolus was given as soon as possible after the abciximab or placebo for abciximab bolus (anticipated ≤ 15 minutes). Transfer of subjects for catheterization and intervention procedures were made according to local custom and accepted medical practice. If subjects met the criteria for early ST-segment resolution **and** low-risk clinical characteristics, transfer to the catheterization laboratory may have been delayed or deferred at

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the investigator's discretion. Subjects who did not undergo immediate intervention were to have remained on UFH, at the investigator's discretion. Adjustment of subsequent UFH doses was made to maintain the aPTT between 50 and 70 seconds. Use of LMWH was prohibited during the first 24 hours after randomization with the exception of those subjects participating in the LMWH substudy. Subjects who participated in the LMWH substudy did not receive UFH but rather were treated according to the instructions in the LMWH substudy protocol.
All subjects were evaluated 90 days (maximum 100 days) after randomization for the occurrence of death or complications of MI (ie, hospitalization or emergency department visit for CHF, resuscitated ventricular fibrillation occurring > 48 hours after randomization, or cardiogenic shock). Subjects were contacted for longer-term follow-up at 1 year and possibly longer after randomization. The end of study was defined as the last 1-year after randomization follow-up visit for the last subject being assessed.

Number of Subjects (Planned and Analyzed): Overall, 3000 including 1000 in LMWH substudy planned; 2452 analyzed

Diagnosis and Main Criteria for Inclusion:
Eligible subjects were men and women who were at least 21 years old. Subjects were to have had prolonged, continuous (lasting at least 20 minutes) signs and symptoms of ischemia not eliminated with nitrates and had an onset within 6 hours of randomization, in addition to 1 of the following:

- ST-segment elevation ≥ 2 mm in 2 (minimum of 4 mm total in all leads) or more contiguous precordial ECG leads (anterior infarction)
- ST-segment depression ≥ 2 mm in V1, V2 or V2, V3 with reciprocal 1 mm ST-elevation in II, augmented unipolar foot (left leg) lead (AVF), and V6 (true posterior infarction)
- ST-segment elevation ≥ 1 mm in 2 or more contiguous limb ECG leads (other infarction)
- New or presumably new left bundle branch block (LBBB)

All subjects were required to provide written informed consent before randomization and agree to comply with all protocol-specified procedures, including protocol-mandated follow-up(s). Key exclusion criteria included:

- Local inferior infarction in subjects < 60 years of age
- Angiography expected < 60 minutes or > 4 hours after qualifying ECG
- Prohibited medications (eg, bivalirudin, GPIIb/IIIa, fibrinolytics, oral anticoagulants, or LMWH)
- Contraindications for abciximab (eg, active bleeding, recent major surgery, history of stroke or transient ischemic attack [TIA] within the previous 2 years or any stroke with a residual neurological deficit)
- UFH within 6 hours prior to randomization unless aPTT ≤ 70 seconds

Test Product, Dose and Mode of Administration, Batch Number:

Abciximab study agent was available in 5-mL vials (abciximab 2 mg/mL, or placebo). Abciximab study agent was prefiltered through a 0.22-micron low protein-binding filter before bolus injection. All continuous infusions were filtered when mixed using a sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron syringe filter or upon administration using an in-line, sterile, non-pyrogenic, low protein binding 0.2 or 0.22 micron filter. There were 8 abciximab lots used in this study: 00G06, 01A08, 03A10, 03A13, 03G08, 03H06, 05C01, and 05D09. There were 6 abciximab readministration lots used in this study: 00G06, 03A10, 03F01AA, 05C01, 109664, and A3A10.

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Reteplase study agent was available in vials containing 10 U of sterile, lyophilized reteplase powder or placebo. Each reteplase study agent vial was reconstituted with 10 mL Sterile Water for Injection, USP, to produce 10 mL of reteplase as a 1 U/mL solution or matching placebo for IV administration. There were 8 reteplase lots used in this study: 03M054A, 764486-01, 765297-01, 765567-01, 767223-01, 767223-02, 767532-02, and 768985-01.

Duration of Treatment: Abciximab: 12-hour continuous infusion initiated up to 3 hours following the bolus; reteplase: 30 minutes between bolus administrations in subjects < 75 years of age; 1-year follow-up.

Reference Therapy, Dose and Mode of Administration, Batch Number: N/A

Criteria for Evaluation:

Pharmacokinetics/Pharmacodynamics: Not applicable

Efficacy: Efficacy analyses included all randomized subjects. The primary endpoints were all-cause mortality or complications of MI, defined as: rehospitalization *or* emergency department treatment for CHF; *or* resuscitated ventricular fibrillation occurring > 48 hours after randomization; *or* cardiogenic shock.

Safety: Safety analyses were performed in randomized subjects who received at least 1 dose of study agent and included evaluating the safety profiles of reteplase/abciximab facilitated PCI, abciximab facilitated PCI, and primary PCI with regard to the incidence of nonintracranial (TIMI major or minor bleeding) and intracranial bleeding.

Statistical Methods: Simple descriptive statistics, graphs, and subject listings were used to summarize most data. For endpoints assessed at 90 days or more after randomization, the Kaplan-Meier method was employed to assess the proportion of subjects with events of interest with censored data, hazard ratios were calculated for treatment comparison of the proportion of subjects with events, and the log-rank test was used for treatment comparison (Lee, 1992). Chi-square tests without continuity correction were used for treatment group comparisons in the analysis of dichotomous endpoints that were assessed at less than 90 days after randomization, such as revascularization, and odds ratios (Fleiss, 1981; Hosmer and Lemeshow, 2000) were calculated for estimating the proportion of subjects with events. Frequencies and percentages were used for descriptive purposes. Fisher's exact test was used for treatment group comparisons, as appropriate, where events were expected to be infrequent. For continuous variables, descriptive statistics (such as mean, median, standard deviation, interquartile range, minimum, and maximum) were used.

SUMMARY – CONCLUSIONS

Study Population Results:
A total of 2452 subjects were randomized in this study: 828, 818, and 806 subjects in the reteplase/abciximab facilitated PCI, abciximab facilitated PCI, and primary PCI groups, respectively. Of all randomized subjects, 759 were randomized into the LMWH substudy: 258, 255, and 246 subjects in the reteplase/abciximab facilitated PCI, abciximab facilitated PCI, and primary PCI groups, respectively. The FINESSE study began enrollment in August 2002. It was planned that approximately 3,000 subjects would be enrolled. Because of enrollment difficulty, subject enrollment was stopped on 30 Dec 2006.

Pharmacokinetic/Pharmacodynamic Results: Not applicable

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Efficacy Results:

- No significant improvement in the primary endpoint or components was observed with either reteplase/abciximab facilitated PCI or abciximab facilitated PCI compared to primary PCI with in-lab administration of abciximab.
- Reteplase/abciximab administered early was associated with an increase in pre-PCI TIMI 3 flow, pre-PCI patency (ie TIMI 2 or 3 flow) and > 70% ST-segment resolution at 60-90 minutes.
- Post-PCI TIMI 3 flow and ST-segment resolution at 180-240 minutes was similar in all 3 strategies.
- In general, there was a consistent lack of benefit for either facilitated strategy in the primary endpoint across the pre-specified subgroups.
- Neither facilitated PCI strategy provided clinical benefit compared with primary PCI with in-lab abciximab.

Safety Results:

- Significant increases were observed in nonintracranial TIMI major or minor bleeding in the reteplase/abciximab group compared to both the abciximab and primary PCI groups. In addition, the abciximab facilitated PCI group had more bleeding than the Primary PCI group.
- Although the occurrence of stroke was similar across all treatment groups, there were more subjects with ICH in the reteplase/abciximab group compared with either of the other treatment groups.
- Although not a randomized comparison, nonintracranial TIMI major bleeding events tended to be slightly less common, while the overall number of nonintracranial TIMI major or minor bleeding events tended to be slightly more common in subjects treated with LMWH compared with UFH.
- Within the LMWH substudy, there was in general a similar pattern of increased bleeding in the facilitated groups with a significant increase in the reteplase/abciximab group compared with the primary PCI group and with the abciximab facilitated group.

Conclusions:

- The final 90-day results of the FINESSE study demonstrated that the combination of half dose reteplase and abciximab did not significantly improve the primary composite endpoint.
- Overall outcomes in FINESSE were better than expected in subjects with longer delays, resulting in lower power than originally planned, despite a high-risk population.
- Reteplase/abciximab facilitation, and to a lesser extent abciximab facilitation, increased bleeding compared to the in-lab administration of abciximab.
- Despite stopping prematurely due to difficulty in enrollment (82% of planned size), it is unlikely that the overall results of the study would have differed if full enrollment had been achieved.
- Primary PCI with in-lab abciximab provides a better benefit/risk profile than the 2 facilitated strategies in subjects with ST-segment elevation myocardial infarction (STEMI) who can undergo PCI within 4 hours of first medical contact.

Date of Revised Report: 02 Sep 2008

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