Synopsis

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

Protocol: C0116T41 (CR004768)	**EudraCT No.:** 2004-000547-20
Title of the study: Abciximab (ReoPro®) in Acute Ischemic Stroke: A Phase 3, Multinational, Multicenter, Randomized, Double-blind, Placebo-controlled Trial	
Principal/Coordinating Investigators: Dr. Harold P. Adams, Jr. – University of Iowa and Prof. Dr. Werner Hacke – University of Heidelberg	
Study Center(s): 112 study centers in 18 countries	
Publication (reference): None	
Studied Period: 26 Dec 2003 to 19 Dec 2005	**Phase of Development:** 3

Objectives:

Primary Objectives

The primary efficacy objective was to compare abciximab and placebo with regard to functional outcome, as measured by the proportion of modified Rankin scale (mRS) responders at 3 months in the primary population, which comprises subjects with planned treatment initiation within 5 hours of stroke symptom onset (ie, randomized within 4 hours and 30 minutes).

An mRS responder was defined as a subject with:

- mRS at 3 months = 0 and baseline National Institutes of Health Stroke Scale (NIHSS) score was 4 – 7, or
- mRS at 3 months ≤ 1 and baseline NIHSS score was 8 – 14, or
- mRS at 3 months ≤ 2 and baseline NIHSS score was 15 – 22.

The primary safety objective was to compare abciximab and placebo with regard to the incidence of fatal intracranial hemorrhage (ICH), nonfatal symptomatic parenchymal hemorrhage, or other symptomatic ICH through discharge or Day 5, whichever was earlier (discharge/Day 5), in the primary population.

Secondary Objectives

Major secondary efficacy objectives in the primary population were to compare abciximab and placebo with regard to the proportion of subjects with the following:

- Neurological recovery (NIHSS 0 - 1) at 3 months,
- All-cause mortality through 3 months.

Secondary safety objectives in the primary population were to compare abciximab and placebo with regard to the proportion of subjects with the following:

- Fatal ICH, nonfatal symptomatic parenchymal hemorrhage, or other symptomatic ICH through 3 months;
- Asymptomatic parenchymal hemorrhage or other asymptomatic ICH through discharge/Day 5 and 3 months;
- Non-intracranial bleeding through discharge/Day 5.

Other objectives

All efficacy and safety objectives described for the primary population were to be evaluated for a companion population, which was to comprise subjects with planned treatment initiation between 5 and 6 hours after stroke symptom onset (ie, randomized after 4 hours and 30 minutes through 5 hours and 30 minutes) and those who awakened with stroke and could be treated within 3 hours of awakening. In addition, the efficacy and

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safety of abciximab treatment compared with placebo was to be evaluated in all randomized subjects (ie, both the primary population and the companion population).

Methodology:
This was a multinational, multicenter, randomized, double-blind, placebo-controlled study. Subjects were to be included into 3 populations based on the time from stroke symptom onset to planned treatment initiation. The primary population was to comprise randomized subjects in whom the planned treatment initiation was to be within 5 hours of stroke symptom onset. The companion population comprised the following: randomized subjects in whom the planned treatment initiation was to be between 5 and 6 hours since stroke symptom onset (companion [5-6 hours] population) and randomized subjects who awakened with stroke symptoms and in whom the planned treatment initiation was to be within 3 hours of awakening (companion [wake-up] population). Subjects received abciximab 0.25 μg/kg bolus (to a maximum of 30 mg) followed by a 0.125 μg/kg/min infusion (to a maximum of 10 mg/min) for 12 hours, or placebo bolus followed by infusion for 12 hours, and were to be followed through 3 months from randomization.

Eligible subjects were to be randomized via an IVRS in a 1:1 ratio to receive either abciximab or an identically appearing placebo. To maintain balance in treatment assignments with respect to investigational center, stroke severity, and time since symptom onset to treatment initiation, subjects were to be assigned to treatment groups using a biased coin minimization stratified by center, baseline NIHSS score, and time from symptom onset.

Number of Subjects (Planned and Analyzed): 1800 planned; 801 randomized; 794 treated

Diagnosis and Main Criteria for Inclusion:
Eligible subjects were adult men or women who were at least 18 years old. Subjects were to have had a diagnosis of acute ischemic stroke with onset within 5 hours and 30 minutes before randomization and planned treatment initiation within 6 hours of onset – or subjects who awakened with stroke symptoms and unknown time of stroke onset, and in whom the planned treatment initiation was to be within 3 hours of awakening. Acute ischemic stroke was defined as a measurable neurological deficit of sudden onset, presumed secondary to focal cerebral ischemia, and not otherwise attributable to ICH or another disease process. Stroke onset was defined as the time of first symptoms or signs of neurological deficit. Subjects whose deficits had worsened in the last 6 hours were not eligible if their first symptoms started > 6 hours since symptom onset. If the stroke started during sleep, stroke onset was to be recorded as the time the subject was last known to be intact.

Test Product, Dose and Mode of Administration, Batch Number:
Abciximab was supplied as a sterile, nonpyrogenic solution containing 2 mg of abciximab per mL of 0.15 M sodium chloride, 0.01 M sodium phosphate, and 0.001% polysorbate 80 at a pH of 7.2. Each 5 mL abciximab vial contained 10 mg. Subjects were to receive the study agent bolus at a dose of 0.125 mL/kg [0.25 mg/kg] body weight (to a maximum of 15 mL [30 mg]). The study agent bolus was to be administered over a 1 – 2-minute period as soon as possible after randomization. The continuous IV infusion was to begin after the bolus was completed. Two lots of abciximab (03A10 and 03H06) were used in this study.

Duration of Treatment: 12 hours; 3 month follow-up

Reference Therapy, Dose and Mode of Administration, Batch Number:
The placebo solution was 0.15 M sodium chloride, 0.01 M sodium phosphate, and 0.001% polysorbate 80 at a pH of 7.2. Two lots of placebo (03A13 and 03G08) were used in this study.

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Criteria for Evaluation:

Pharmacokinetics/Pharmacodynamics: Not Applicable

Efficacy: Efficacy analyses included all the randomized subjects and were performed by randomized treatment. The primary endpoint was the proportion of mRS responders at 3 months in the primary population. Major secondary efficacy endpoints included: (1) the proportion of subjects with neurological recovery (NIHSS 0 - 1) at 3 months in the primary population, and (2) all cause mortality through 3 months in the primary population.

Safety: Safety analyses (through 3 months) were to be performed in the safety population, which was defined as all treated subjects, with subjects classified according to the actual treatment received. Subjects receiving study agent were to be included, even if the full dose of study agent was not received. Among treated subjects, separate analyses were to be performed for the primary population and the companion population. The primary safety endpoint was fatal ICH, nonfatal symptomatic parenchymal hemorrhage, or other symptomatic ICH through discharge/Day 5.

Statistical Methods:
Simple descriptive statistics, such as means, medians, standard deviations, percentiles, minimum and maximum values for continuous data, and counts and percentages for categorical variables, were used to summarize most data. For key efficacy endpoints, odds ratios and the upper and lower 95% confidence limits of those estimates were calculated. Wald chi-square test statistic from a logistic regression model with randomized treatment as a factor and baseline NIHSS stratum as a covariate was used to compare the proportion of mRS responders in the abciximab group with that in the placebo group. Chi-square tests were used for treatment group comparisons in the analysis of dichotomous efficacy endpoints. For rare events, like recurrent strokes, Fisher's Exact test was performed to assess the treatment effects. For continuous variables other than time to event variables, a rank test based on normal scores was used to test for treatment differences. The logrank test was used to test treatment differences for mortality through 3 months. Graphs, including bar and pie charts for categorical endpoints and Kaplan-Meier curves for mortality, supplemented tables of descriptive statistics.

SUMMARY – CONCLUSIONS

Study Population Results:
A total of 801 subjects: 439, and 319, and 43 subjects were randomized to the primary, companion (5-6 hours), and companion (wake-up) populations, respectively. Although 1800 subjects were planned, on 20 May 2005, the study prematurely discontinued enrollment into the companion (wake-up) stroke arm of the study, where the time last known to be neurologically intact (free of symptoms) was more than 6 hours prior to planned treatment, after 47 subjects were enrolled (45 randomized). This was due to an excess of symptomatic or fatal ICH among these subjects. Enrollment in the primary population and in a companion population comprised only of those subjects in whom treatment was planned between 5 and 6 hours after the stroke onset was to remain unmodified. On 12 Sep 2005, the AbESTT-II SEMC recommended that enrollment in the study be temporarily suspended due to concerns over safety and a less than acceptable benefit-risk profile based on efficacy data from approximately two-thirds of the patients who had been enrolled. The Safety and Efficacy Monitoring Committee (SEMC) met on 13 Oct 2005 to review efficacy data through 3 months on over 80% of subjects and through 6 weeks on over 90% of subjects. These data continued to show an unfavorable benefit-risk profile. Therefore, the SEMC recommended that subject enrollment be permanently discontinued. This recommendation was accepted and implemented.

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Efficacy Results:

- The proportion of mRS responders at 3 months was similar among the abciximab group versus the placebo group in the primary and companion (5-6 hours) populations; 32.1% versus 33.0% ($p = 0.944$), and 25.6% versus 23.3% ($p = 0.624$), respectively. In the companion (wake-up) population, a greater proportion of subjects in the placebo group versus the abciximab group was mRS responders at 3 months; 14.3% versus 4.5% ($p = 0.290$).
- Among all randomized subjects, the proportion of subjects who had neurological recovery at 3 months was similar among the abciximab group versus the placebo group in the primary and companion (5-6 hours) populations; 43.4% versus 42.2% ($p = 0.794$) and 40.6% versus 40.3% ($p = 0.946$), respectively. In the companion (wake-up) population, there was a greater proportion of subjects in the placebo group versus the abciximab group who had neurological recovery; 28.6% versus 13.6% ($p = 0.234$).
- Mortality was not significantly different among any of the populations. However, there was a trend toward increased mortality among the abciximab groups in the primary and companion (wake-up) populations.
- Subgroup analyses indicated that there is a lack of efficacy in all of the subgroups and populations.

Safety Results:

- The primary safety endpoint was fatal ICH, nonfatal symptomatic parenchymal hemorrhage, or other symptomatic ICH through discharge/Day 5. Through discharge/Day 5, across all populations, fatal or symptomatic ICH occurred in 4.5% of abciximab-treated and 0.8% of placebo-treated subjects ($p < 0.001$). Across all populations, fatal ICH occurred in 3.0% of abciximab-treated and 0.5% of placebo-treated subjects ($p = 0.007$).
- Through 3 months, across all populations, fatal or symptomatic ICH occurred in 5.5% of abciximab-treated and 1.3% of placebo-treated subjects ($p < 0.001$). Across all populations, fatal ICH occurred in 3.8% of abciximab-treated and 1.0% of placebo-treated subjects ($p = 0.011$).
- The incidence of symptomatic or fatal ICH was similar across all populations among subjects who received aspirin versus those who did not receive aspirin within 7 days or 24 hours prior to randomization.
- Hypodensity had no apparent association with a higher risk of symptomatic or fatal ICH, and too few subjects received warfarin to determine an association between it and risk of symptomatic or fatal ICH.
- Both at 5 days and through 3 months, the occurrence of asymptomatic ICH was similar between the abciximab and placebo groups across all populations.
- Through 3 months, investigator-reported bleeding events occurred in a higher proportion of abciximab-treated subjects than in placebo-treated subjects (29.2% versus 18.4%). The most frequently reported bleeding event was intracranial bleeding.
- From baseline through discharge/Day 5, thrombocytopenia occurred in 11 abciximab-treated subjects and no placebo-treated subjects. Five abciximab-treated and 2 abciximab-treated subjects had a platelet count $< 50{,}000/\mu L$ and $< 20{,}000/\mu L$ (profound thrombocytopenia), respectively.
- Through discharge/Day 5 in the primary, companion (5-6 hours), and companion (wake-up) populations, the median change in hemoglobin, adjusted for transfusions, was -0.3, -0.1, and -0.4 (abciximab group), and -0.2, -0.5, and -0.6 (placebo group), respectively. Nine subjects (8 abciximab, 1 placebo) received blood transfusions.
- Through 3 months, the overall rate of AEs among placebo-treated subjects was higher than abciximab-treated subjects (81.6% versus 76.6%).

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Conclusions:

- In this Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study, there was a consistent lack of efficacy for subjects treated with abciximab, regardless of endpoint and subgroup.
- There was an increase in fatal and symptomatic ICH rate in both the primary and companion (wake-up) populations.
- This study did not confirm previous findings that early administration of abciximab would be effective with an acceptable safety profile in the treatment of acute ischemic stroke.

Date of Revised Report: 18 Jun 2007

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