Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

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Title of trial:	Comparison of the safety and efficacy of a strategy of early fibrinolytic treatment with tenecteplase and additional antiplatelet and antithrombin therapy followed by catheterisation within 6-24 hours or rescue coronary intervention versus a strategy of standard primary PCI in patients with acute myocardial infarction within 3 hours of onset of symptoms **STREAM (Strategic Reperfusion Early After Myocardial Infarction)**
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre Study, cf. Appendix 16.1.4
Publication (reference):	N Engl J Med 2013;368:1379-1387 (P13-06468)
Clinical phase:	IIIb/IV
Objectives:	In patients with acute ST-elevation myocardial infarction randomised within 3 hours of onset of symptoms the efficacy and safety of a strategy of early fibrinolytic treatment with tenecteplase and additional antiplatelet and antithrombin therapy followed by catheterisation within 6-24 hours or rescue coronary intervention as required will be compared to a strategy of primary PCI according to established local standards.
Methodology:	Open-label, prospective, randomised, parallel, comparative international multi-centre trial
No. of subjects:	
planned:	entered: 2,000
actual:	enrolled: 1,915 entered: 1,899 analysed (in Full Analysis Set): 1,897 Treatment Group A (tenecteplase with concomitant antiplatelet and

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anticoagulant treatment and timely coronary intervention):
entered: 950 treated: 930 analysed (for primary endpoint): 949
Treatment Group B (primary PCI):
entered: 949 treated: 932 analysed (for primary endpoint): 948

Diagnosis and main criteria for inclusion:

Patients with acute ST-segment elevation myocardial infarction randomised within 3 hours of symptom onset in a pre-hospital setting or in the emergency room of hospitals without PCI facility that cannot reliably undergo primary PCI within 60 min of ECG diagnosis

Test product:

Tenecteplase with concomitant antiplatelet and anticoagulant treatment followed by timely coronary intervention (pharmacoinvasive treatment) (Group A)

dose:

Pre-hospital treatment / or treatment in the emergency room:
Tenecteplase
50 mg of drug reconstituted in 10 ml sterile water for injection given as single weight-adjusted i.v. bolus over 5 - 10 seconds according to the following scheme:

< 75 years:

Weight (kg)	Dose (mg)	Dose (ml)
≥55 to <60	30.0 mg	6.0 ml
≥60 to <70	35.0 mg	7.0 ml
≥70 to <80	40.0 mg	8.0 ml
≥80 to <90	45.0 mg	9.0 ml
≥90	50.0 mg	10.0 ml

≥75 years: as per clinical trial protocol amendment 2 (24 August 2009)

Weight (kg)	Dose (mg)	Dose (ml)
≥55 to <60	15.0 mg	3.0 ml
≥60 to <70	17.5 mg	3.5 ml
≥70 to <80	20.0 mg	4.0 ml
≥80 to <90	22.5 mg	4.5 ml
≥90	25.0 mg	5.0 ml

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Enoxaparin

< 75 years:
- 30 mg i.v. bolus
- S.c. injections of 1.0 mg/kg every 12 hours until hospital discharge (4 days); the first injection should be given within 15 min of the bolus
- For the first two subcutaneous injections, a maximum of 100 mg should not be exceeded

≥ 75 years:
- No bolus; s.c. injections of 0.75 mg/kg every 12 hours until hospital discharge (4 days); the first injection should be given immediately
- For the first two subcutaneous injections, a maximum of 75 mg should not be exceeded

For patients of any age with a creatinine clearance < 30 ml/min, s.c. injections of 1.0 mg/kg will be given in intervals of 24 hours.

Clopidogrel

< 75 years:
- 300 mg p.o. loading dose
- Maintenance dose of 75 mg p.o. once daily

≥ 75 years:
- No loading dose; 75 mg p.o. immediately after randomisation
- Maintenance dose of 75 mg p.o. once daily

Following usage of study drug (until day 4 or discharge, whichever occurs first), the maintenance dose of clopidogrel (75 mg p.o. per day) is recommended to be continued until day 30 for patients who did not receive a stent, or, if stenting is performed, for a longer period according to accepted guidelines.

Additional treatment with **acetylsalicylic acid** as per local guidelines.

In-hospital treatment:
- Assessment of reperfusion (by ECG and evaluation of clinical symptoms) 90 min after injection of tenecteplase or earlier, if clinically indicated

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	- Catheterisation: - If ST-segment resolution is ≥ 50 % in the qualifying lead (i.e. with maximum initial ST-segment elevation in the baseline ECG), diagnostic coronary angiography (followed by elective PCI +/- stenting, if indicated) should be performed no sooner than 6 hours but within 24 hours after administration of tenecteplase (considered as planned catheterisation according to protocol) - If ST-segment resolution is < 50 % in the qualifying lead, irrespective of the presence or absence of clinical symptoms, rescue coronary intervention should be performed promptly - In case of haemodynamic or electrical instability or worsening ischaemia requiring coronary intervention, urgent coronary intervention is indicated at any time (irrespective of previous ST-segment resolution)
mode of admin.:	As described under dose
batch no.:	Cf. Appendix 16.1.6
Reference therapy:	**Standard primary Percutaneous Coronary Intervention (primary PCI) (Group B)**
dose:	Not applicable
mode of admin.:	Patients randomly assigned to treatment group B will receive primary PCI according to local standards: **<u>Pre-hospital treatment / or treatment in the emergency room:</u>** In agreement with international guidelines, upfront antiplatelet and antithrombin treatment according to local standards (e.g., acetylsalicylic acid; clopidogrel 300 or 600 mg; unfractionated heparin/ enoxaparin/ bivalirudin) **<u>In-hospital treatment:</u>** Standard primary PCI following angiography (additional GP IIb/IIIa antagonists at the investigator's discretion)
batch no.:	Not applicable
Duration of treatment:	Not applicable

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Criteria for evaluation:

Efficacy:

Primary endpoint
- All-cause mortality, cardiogenic shock, congestive heart failure and recurrent myocardial infarction within 30 days

Single efficacy endpoints within 30 days:
- All-cause mortality
- Cardiac mortality
- Cardiogenic shock
- Congestive heart failure
- Recurrent myocardial infarction
- Rehospitalisation for cardiac reasons
- Rehospitalisation for non-cardiac reasons
- Serious repeat target vessel revascularisation

Composite efficacy endpoints within 30 days:
- Death and shock
- Death and shock and congestive heart failure
- Death and shock and reinfarction

Safety:

Single safety endpoints within 30 days:
- total stroke (including: fatal, disabling, non-disabling)
- ischaemic stroke
- intracranial haemorrhage
- non-intracranial bleeds (including: total, major (including blood transfusions), minor)
- Serious resuscitated ventricular fibrillation
- Serious resuscitated ventricular fibrillation in association during with invasive procedures (during catheterisation and urgent/elective PCI)

Composite efficacy and safety endpoints within 30 days:
- All cause death and non-fatal stroke
- All cause death and shock and CHF and reinfarction and disabling stroke

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Statistical methods: The trial was a hypothesis-generating study to examine a new medical question. No confirmatory statistical hypothesis was pre-specified. All statistical tests were of exploratory nature based on descriptive p-values for formal statistical hypotheses generation. An intent-to-treat analysis of all patients randomised was carried out.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Demographic and other baseline characteristics

There were no significant differences between both treatment groups in demographic data. Mean age was 60 years (range: 20 to 96 years), 87% of patients were below 75 years of age, and 79% of patients were male. No differences were observed in medical history with the exception of congestive heart failure and prior percutaneous coronary intervention (PCI), which were more frequent in the primary PCI arm, however overall prevalence was low.

Timelines and procedures

The median time from the onset of symptoms of myocardial infarction to ambulance arrival was 61 min in both groups. The median time interval from symptom onset to first reperfusion treatment was 100 min in the pharmaco-invasive arm and 178 min in the primary PCI arm, with median time intervals of 9 min or 76 min between randomisation and treatment start (i.e., tenecteplase bolus or sheath insertion), respectively.

98% of patients in the pharmacoinvasive arm did receive tenecteplase. ST segment resolution ≥ 50% was observed in 69% of patients, ST resolution <50% in 31%. The number of patients receiving rescue PCI was corresponding: 36% (as per investigator's assessment), mostly based on low ST segment resolution (69%) or pre-defined medical symptoms requiring prompt intervention (31%). Accordingly, rescue intervention (based on sheath insertion) was performed after a median time of only 2.2 hrs following tenecteplase administration as compared to 17.4 hrs for scheduled coronary intervention.

97% of patients in the pharmacoinvasive arm underwent catheterisation as required by the trial protocol. Of these, 81% of patients actually had a percutaneous coronary intervention (PCI), whereas 5% received a bypass.

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Corresponding rates in the primary PCI arm were 98.5%, 89% and 2%, respectively. A stent was placed in 77% of cases in the pharmacoinvasive arm vs. 86% in the primary PCI arm, with bare metal stents deployed in about two thirds of cases and drug-eluting stents in one third.

Endpoints

There was no statistically significant difference in the frequency of the primary endpoint – all-cause death or shock or congestive heart failure or reinfarction within 30 days of randomisation – between the pharmacoinvasive strategy and standard primary PCI (12.3% vs. 14.3%; P= 0.195).

There was no statistical difference in any of the pre-defined single or combined secondary efficacy endpoints.

Nevertheless, the rate of all-cause mortality of 4.6% in the pharmacoinvasive arm (primary PCI: 4.4%; P=0.904) was lower than the mortality rate of 6 to 7% observed in several large previous trials with tenecteplase.

Analysis of pre-specified subgroups did not reveal any statistically significant differences between both treatment groups for the most of the subgroups. Results of additional analyses, an adjusted analysis for the Full Analysis Set as well as the analysis of the randomised Full Analysis Set and the modified Full Analysis Set (particularly accounting for the change in protocol design following protocol amendment 2) for the primary and key secondary endpoints were consistent with the results of the Full Analysis Set.

Safety results:

No statistical difference was observed between pharmacoinvasive treatment and primary PCI in the rate of non-intracranial total bleeds (28.3% vs. 25.0%, P = 0.107), major bleeds (6.5% vs. 4.8%, P = 0.111) or serious clinical events (20.2% vs. 21.8%).

The rate of total strokes was significantly higher in the pharmacoinvasive arm than in the primary PCI arm (1.59% vs. 0.53%, P=0.032), mainly triggered by the rate of intracranial haemorrhages (0.95% vs. 0.21%, P=0.054), but was similar to previous studies with tenecteplase and the known safety profile of tenecteplase (cf. Investigator Brochure, U07-1971, and Company Core Data Sheet, CCDS 0245-05).

To address the difference in stroke rate and to account for the generally higher bleeding risk in elderly patients, the dose of tenecteplase was reduced to 50% in

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patients ≥ 75 years of age as per protocol amendment 2. As a result, the rates of total stroke and intracranial haemorrhage were reduced in patients randomised to pharmacoinvasive treatment after amendment 2 (from 3.1% to 1.2% and 2.6% to 0.5%, respectively) and did no longer show any statistical difference to primary PCI. In elderly patients ≥ 75 years treated with half-dose tenecteplase no cases of stroke of any type – ischaemic and haemorrhagic – were observed following protocol amendment 2.

The rate of serious resuscitated ventricular fibrillation was similar in both groups with 3.4% (pharmacoinvasive arm) vs. 4.0% (primary PCI) (P=0.471), while it was statistically significant lower in the pharmacoinvasive arm when associated with invasive trial procedures, with rates of 1.1% vs. 3.1% (P=0.003), respectively.

No statistical difference was seen between both treatment groups in any of the observed routine laboratory parameters of haematology and clinical chemistry obtained locally upon hospital arrival. Measurement of cardiac enzymes and baseline ECG confirmed the initial diagnosis in 97% of cases. There was no relevant difference between the treatment groups in cardiac enzymes obtained at different times. Values were characteristic of acute myocardial infarction.

Overall, cardiac events were the most frequent causes of death, with a frequency of 72% in the pharmacoinvasive arm and 76% in the primary PCI arm, with cardiogenic shock as the most frequent single cause, reported in 37.2% and 45.2% of cases per arm, respectively. Mortality rates were generally higher in the elderly than in younger patients. However there was no statistical difference between both treatment groups in all-cause mortality or cardiac mortality for patients <75 and ≥ 75 years of age, respectively, or for any other age subgroups analysed.

Conclusions:

The analysis of the primary endpoint – all-cause death or shock or congestive heart failure or reinfarction within 30 days of randomisation – in the Full Analysis Set showed statistically equal results, with rates of 12.3% in group A and 14.3% in group B (Table 11.4.1.1: 1). Although the frequency of the primary endpoint was numerically lower in group A than in group B, statistical significance was not reached (P= 0.195).

This may have been influenced by the fact that the trial was designed for

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approximately 2,000 patients. However, due to a persistently low pace of recruitment over a period of more than four years finally 1,915 patients were enrolled by the time study medication expired and 1,897 patients were finally included in the analysis (Full Analysis Set).

In terms of individual efficacy endpoints, again, no statistical difference was shown between both treatment groups. Nevertheless, rates were numerically lower in group A for cardiogenic shock, congestive heart failure, and rehospitalisations for non-cardiac reasons (Table 11.4.1.2: 1). The lower rates of cardiogenic shock and congestive heart failure can be attributed to the effect of earlier reperfusion in the pharmacoinvasive arm, where the median time interval from symptom onset to reperfusion treatment was 78 min shorter than for primary PCI (100 min vs. 178 min).

The efficacy of the pharmacoinvasive approach was also confirmed by the rate of all-cause mortality of 4.6% in group A, which was almost identical to the rate of 4.4% in group B, and was lower than the rate of 6-7% seen in large previous trials with tenecteplase (P06-02212, P01-06210, P07-06940, P03-05516).

The enrolment settings in STREAM – the majority of patients (80%) were enrolled in the pre-hospital setting, whereas 20% of patients were enrolled at community hospitals without 24/7 PCI facility – did not reveal any impact on the primary endpoint, cf. Figure 15.2.3: 1, or any individual secondary endpoints. The STREAM strategy can thus be considered effective in both settings. Results of combined efficacy and safety endpoints i) all-cause death or non-fatal stroke and ii) all-cause death or shock or congestive heart failure or reinfarction or disabling stroke confirmed overall similar outcomes of both treatment strategies.

With regard to key safety endpoints, the overall rate of total strokes (consisting of ischaemic stroke and intracranial haemorrhage) was significantly higher in group A than in group B (1.59% vs. 0.53%, P=0.032). Since there was no statistical difference in the frequencies of ischaemic stroke, the intracranial haemorrhage rate in group A mainly influenced the overall difference in total stroke rate though it did not reach statistical significance (0.95% vs. 0.21%, P=0.054). However, taking into account that there was an obvious imbalance in the intracranial haemorrhage rate prior to protocol amendment 2

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to the disadvantage of group A (2.59% vs. none, N=382), the strategy to reduce the dose of tenecteplase by 50% in patients ≥ 75 years of age (as per protocol amendment 2) was an adequate measure: rates of both intracranial haemorrhage and overall stroke decreased in group A so that a statistical difference to the rates in group B was no longer observed. In addition, the reduction to half-dose tenecteplase also sustained clinical outcomes with regard to the intracranial haemorrhage rate and stroke-related mortality in patients ≥ 75 years of age: no cases of intracranial haemorrhage or fatal stroke were seen in 92 patients on half-dose regimen as compared to rates of 7.3% and 4.9%, respectively, in those who had received full dose tenecteplase. However, overall numbers were too small to draw any conclusion or issue any recommendation on the tenecteplase dose in patients ≥ 75 years of age.

Furthermore, the overall intracranial haemorrhage rate of 0.95% was consistent with the rate seen in previous studies with tenecteplase and the known safety profile of the substance (U07-1971, CCDS 0245-05). Similar and generally low rates of fatal strokes and disabling strokes in both groups confirmed the safety profile of the pharmacoinvasive treatment strategy.

Other safety results were also similar in both treatment groups, i.e. there was no statistical difference in the overall rate of non-intracranial bleeds (28.3% vs. 25.0%, P = 0.107), major non-intracranial bleeds (6.5% vs. 4.8%, P = 0.111) or serious clinical events (20.2% vs. 21.8%), cf. Table 12.2.1: 1, and confirmed the safety of the pharmacoinvasive approach.

In summary the objective of the STREAM trial was achieved: pharmacoinvasive treatment in group A was shown to be a feasible and effective treatment option with acceptable safety in early STEMI patients presenting in the pre-hospital or community hospital setting who cannot undergo primary PCI within an hour of first medical contact. Pharmacoinvasive treatment with fibrinolysis therefore offers a strategic treatment option to a substantial cohort of STEMI patients worldwide.