Clinical Study Synopsis

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2. **Synopsis**

<table>
<thead>
<tr>
<th>Date of report:</th>
<th>14 May 2015</th>
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<tbody>
<tr>
<td>Study title:</td>
<td>A prospective, randomized, verum controlled, open label, parallel group multi-center phase III clinical trial to demonstrate the superiority of 500 or 250 mg Aspirin® i.v. (BAY 81-8781) treatment versus 300 mg Aspirin® N tablets p.o. (BAY e4465A) in patients with Acute Coronary Syndrome, measured by time dependent thromboxane inhibition</td>
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| Study objectives: | **Primary objective:** To demonstrate superiority of 500 mg and 250 mg Aspirin® IV (D,L lysine acetylsalicylate glycine, BAY 81-8781) treatment over oral treatment with 300 mg Aspirin® N tablet to inhibit thromboxane A₂-release (measured as the stable metabolite in serum thromboxane B₂ [TXB₂]) at 5 minutes after a single dose of study drug administration.  
**Secondary objectives:**  
- Assessments of TXB₂ levels at 20 minutes, serum prostacyclin levels (measured by the metabolite 6-keto prostaglandin F₁α [PGF₁α]) and platelet aggregation inhibition at 5 minutes and 20 minutes after single dose study drug administration,  
- Incidence of a composite clinical endpoint of cardiovascular death, stroke and myocardial infarction (MI) up to Day 30 as well as the incidence of death from all causes and cardiovascular deaths, ischemic strokes and MI (re-infarction) within 24 hours, 7 days and 30 days after single dose study drug administration,  
- Safety evaluation including adverse events (AEs), vital signs, electrocardiogram (ECG), and safety laboratory measurements. |
### Test drug:
Lysine acetylsalicylate (Aspirin, BAY 81-8781)

### Name of active ingredient(s):
D,L-lysine acetylsalicylate (LAA)*glycine
(a hydrolytic class III bottle filled in with 1 g of LAA corresponding to 500 mg acetylsalicylic acid)

### Dose:
A single administration of freshly prepared solution for injection (1 g of LAA dissolved in 5 mL water) in the following doses:
- 500 mg Aspirin IV (the total amount of the injection solution was administered)
- 250 mg Aspirin IV (half of the injection solution volume was administered)

### Route of administration:
Bolus infusion injection through the vein for approximately 30 seconds.

### Duration of treatment:
A single administration

### Reference drug:
Acetylsalicylic acid (Aspirin N, BAY e4465)

### Name of active ingredient(s):
Acetylsalicylic acid

### Dose:
A single administration of 300 mg Aspirin N tablet

### Route of administration:
Oral

### Duration of treatment:
A single administration

### Indication:
Acute coronary syndrome (ACS)

### Diagnosis and main criteria for inclusion:
Male and female Caucasian subjects (age ≥18 years) with ACS, angina pectoris lasting for more than 20 minutes within 24 hours before study treatment (or equivalent acute symptoms such as increasing dyspnea, diaphoresis, nausea, abdominal/epigastric pain, syncope, etc.) and at least one of the following:
- ECG changes suggestive for ischemia (ST elevation or T-wave change or ST depression, new or presumed left bundle-branch block),
- Elevated troponin T levels (>0.01 ng/mL) or any other elevated troponin levels according to local laboratory reference values,
- Risk factors for ACS such as known coronary artery disease, diabetes mellitus, impaired renal function, peripheral artery or cerebrovascular disease, current smoking.

### Study design:
Multicenter, randomized, open-label, verum-controlled, parallel-group, prospective study
### Methodology:

Eligible subjects were randomized in 1:1:1 ratio to one of the following treatment groups:

- 300 mg Aspirin N tablet p.o.
- 250 mg Aspirin IV,
- 500 mg Aspirin IV.

A stratified randomization procedure was applied to achieve the intended allocation of subjects to 2 subgroups: STEMI and NSTEMI/unstable angina pectoris (UAP). All randomized subjects received a single dose of study drug.

The study comprised the following periods:

- Screening followed by randomization and single dose study treatment on Day 1,
- End of treatment on Day 2,
- 7-day follow-up after study drug administration (Day 7),
- 30-day follow-up after study drug administration (Day 30).

For evaluations of TXB2 concentrations, serum prostacyclin levels, and platelet aggregation inhibition, blood samples were taken prior to study drug administration (baseline sample) and 5 and 20 minutes after study drug administration on Day 1.

Physical examination (including height and weight), vital signs, electrocardiogram (ECG), and safety laboratory assessments were performed at screening and end of treatment (Day 2).

Treatment-emergent AEs (TEAEs) were defined as events which started or worsened up to 24 hours after study drug administration. Non-serious TEAEs were documented from signing informed consent to 24 hours after study drug treatment, except for AEs of special interest (bleeding and vascular events) which were reported until Day 7. Serious AEs (SAEs) including death, stroke, and myocardial infarction (re-infarction) were documented until Day 30; all other SAEs were documented until Day 7.

A Central Endpoint Adjudication Committee (CEAC) consisting of medical experts (2 cardiologists, 2 neurologist, and 2 angiologists) was involved in the study to assess and confirm all cardiovascular, stroke, and hemorrhagic outcome events reported during the study.

### Study center(s):

Germany, 12 centers

### Publication(s) based on

None at the time of report creation.
### Study (references):

#### Study period:
- **First subject, first visit:** 18 MAR 2011
- **Last subject, last visit:** 01 JUL 2014
- **End of study:** 01 JUL 2014

#### Early termination
- **No**

#### Number of subjects:
- **Planned:** 264 subjects (88 subjects for each treatment group)
- **Analyzed:** 270 subjects were randomized and all were valid for the safety analysis (SAF) set. 263 subjects were valid for the pharmacodynamics (PD) set and 211 subjects were valid for the per protocol (PP) set.

#### Criteria for evaluation

**Efficacy / clinical pharmacology:**

The primary efficacy variable was serum TXB$_2$ concentration at 5 minutes after study drug administration.

Secondary efficacy variables included:

- Serum TXB$_2$ concentration at 20 minutes after study drug administration,
- Platelet aggregation inhibition at 5 and 20 minutes after study drug administration,
- Serum prostacyclin levels (measured by its metabolite 6-keto PGF1α) at 5 and 20 minutes after study drug administration,
- Incidence of the composite clinical endpoint of cardiovascular death, stroke, and MI (re-infarction) up to Day 30,
- Incidence of post-randomization deaths from all causes, cardiovascular deaths, MI (re-infarction) and ischemic strokes up to 24 hours, 7 days and 30 days after single dose of study drug administration.
Safety:

- Adverse events (AEs), serious adverse events (SAEs) and AEs of special interests (bleeding AEs and vascular events),
- Safety laboratory parameters,
- Electrocardiogram (ECG),
- Vital signs (blood pressure and heart rate),
- Incidence of all post-randomization strokes of unknown etiology and bleedings by TIMI classification including intracerebral bleeding until 24 hours (treatment-emergent), and within 7 days after study drug administration,
- Incidence of the composite of post-randomization thrombolysis in myocardial infarction (TIMI) major bleeding, TIMI minor bleeding, and bleeding requiring medical attention up to 24 hours after study drug administration,
- Hospital mortality during hospitalization for ACS.

Other:

Not applicable.

Statistical methods:

**Primary efficacy variable:**

The primary efficacy analysis was done in the PD population. The PP analysis was supportive. Aspirin IV doses were compared to explore whether a dose-response relationship exists. A step-down multiple testing procedure was applied for control of the family-wise error rate ($\alpha$) to test the null hypotheses of no difference between geometric means. The step-down testing procedure was performed at one-sided 2.5% confidence level by calculating individual nominal two-sided 95% confidence intervals (CI) for the differences in mean TXB$_2$ levels and one-sided nominal p-values.

Post-dose geometric means were compared pair-wise between the treatment groups by analysis of covariance (ANCOVA) with baseline TXB$_2$ as a covariate and use of concomitant treatment affecting the measurement up to the 5 minutes and baseline strata as factors.

TXB$_2$ concentrations were presented by number of non-missing values and missing values, number of values $\geq$ lower limit of quantification (LLOQ), arithmetic mean, arithmetic standard deviation (SD), arithmetic coefficient of variation CV-A%, geometric mean, geometric SD, arithmetic coefficient of variation
Secondary efficacy variables:

The analysis of secondary efficacy variables was performed for the PD and PP populations. Clinical outcomes were summarized for the SAF population. Continuous secondary efficacy variables were summarized by descriptive statistics (number of observations, arithmetic mean, arithmetic SD, minimum, quartiles, median, and maximum). Incidences of composite outcomes were presented as counts and percentages. TXB₂, platelet aggregation and prostacyclin values below LLOQ were substituted by 1/2 LLOQ. Invalid values were set to “missing” for statistical analysis.

TXB₂ values at 20 minutes after study drug administration as well as platelet aggregation measurements at 5 and 20 minutes were compared between treatment groups using the same method as for the primary efficacy analysis.

Differences in incidences of the composite clinical efficacy endpoints between treatment groups and their 2-sided 95% CIs and p-values were calculated by stratified Mantel-Haenszel method (strata: STEMI and NSTEMI/UAP). The Mantel-Haenszel Q-statistic was used to test for heterogeneity across strata.

Mixed models were fitted for TXB₂ and platelet aggregation inhibition measurements with time of blood sample and usage of concomitant treatment affecting the TXB₂ values as covariates, and treatment group and strata as factors.

Descriptive statistics for secondary efficacy variables were performed by study center and by gender.

Safety variables:

Safety analysis was performed in the SAF set. The incidence of TEAEs was summarized using the Medical Dictionary for Regulatory Activities (MedDRA), version 17.1.

The incidences of binary safety endpoints were calculated as the number of subjects experiencing the event divided by the number of subjects valid for safety analysis in each treatment group.
Substantial protocol changes:
The original protocol (version 1.0, dated 08 DEC 2008) was amended five times.

Main changes in Amendment 1, dated 30 APR 2009, included:
- Addition of 2 inclusion criteria.
- Inclusion of 2 additional secondary efficacy variables.
- Involvement of a CEAC to confirm cardiovascular, stroke, and hemorrhagic endpoints.

Main changes in Amendment 2, dated 03 AUG 2010, included:
- Number of randomized subjects was reduced and sample size calculations were modified accordingly. One study definition and definitions of populations for analysis were slightly modified.
- Pregnancy test was excluded since pregnancy testing has not been routinely performed on sites.
- Elaboration of an inclusion criterion by adding a statement on subject’s capacity to consent prior enrollment.

Main changes in Amendment 3, dated 18 OCT 2011, included:
- Selected inclusion/exclusion criteria were modified in accordance with clinical practice and relevant guidelines.
- A definition of the PD population for analysis was implemented and “hematology (full blood count)” was excluded from the safety laboratory assessments.

Amendment 4, dated 16 JAN 2012, and Amendment 5, dated 15 NOV 2012, introduced changes in the responsible Study Medical Expert and did not affect the content of the study protocol.

Study subjects
All 270 subjects randomized in the study received study drug and were valid for the SAF set: 88 subjects received 500 mg Aspirin IV, 85 subjects received 250 mg Aspirin IV, and 97 subjects received 300 mg Aspirin N tablet. Most subjects (98.9%) were white and 3 (1.1%) subjects were Asian. 64.4% of the subjects were men. Mean age was 60.2 years. The majority of subjects (144 [53.3%] subjects) were 40 to <65 years of age.

In total, 64.8% of subjects in the SAF had smoked in the past or were present smokers, with a mean number of 19.1 cigarettes smoked per day. Light alcohol consumption was reported by 54.4% of subjects and about one third of the subjects (27.1% to 29.9%) were abstinent. Overall, 176 (65.2%) subjects in the SAF had medical history of vascular hypertensive
disorders, 54 (20.0%) subjects had diabetes mellitus, and 46 (17%) subjects had hyperlipidaemias.

**Efficacy / clinical pharmacology evaluation**

Treatment with Aspirin IV caused a rapid decrease in the mean TXB2 concentrations in both 500 mg and 250 mg Aspirin IV groups (geometric means: 573.94 and 581.66 ng/mL at baseline and 3.10 and 3.86 ng/mL at 5 minutes post-baseline, respectively). This rapid decrease in serum TXB2 concentrations was considerably higher in the two Aspirin IV groups than in the Aspirin N tablet p.o. group (geometric means: 652.03 ng/mL at baseline and 223.74 ng/mL at 5 minutes post-baseline), and the differences were statistically significant (one-sided p-values <0.0001). The robustness of the results was supported by analyzing the superiority of both Aspirin IV doses over 300 mg Aspirin N tablet in the PP set (one-sided p-values <0.0001). At 20 minutes post-baseline, serum TXB2 concentrations remained low in both Aspirin IV groups and were significantly lower than the levels achieved with 300 mg Aspirin N oral treatment (one-sided p-values <0.0001).

No dose-dependent effect on the TXB2 concentrations was shown by the comparison between 500 mg and 250 mg Aspirin IV groups in both PD and PP analysis (one-sided p-values: 0.21 and 0.12, respectively).

A rapid and large treatment effect on platelet aggregation inhibition was observed in both Aspirin IV groups within 5 minutes after study drug administration, with 77% median inhibition of platelet aggregation with either Aspirin IV dose. The rapid inhibition of platelet aggregation was not observed in the 300 mg Aspirin N tablet p.o. group at 5 minutes post-dose (median inhibition: 8.2%) but was seen at 20 minutes post-dose when the median percentage inhibition of 61.1% was similar to that achieved in the Aspirin IV groups.

Changes from baseline in mean 6-keto PGF1α values at 5 and 20 minutes after study drug administration showed similar pattern as observed for the TXB2 concentrations: A rapid decrease in 6-keto PGF1α concentration was achieved at 5 minutes post-dose in both 500 mg and 250 mg Aspirin IV groups (mean change from baseline: -693 pg/mL and -774 pg/mL, respectively) and remained stable up to 20 minutes post-dose. In the 300 mg Aspirin N tablet p.o. group, 6-keto-PGF1α concentrations also decreased after study drug administration but not so rapidly (mean change: -232 pg/mL at 5 minutes and -534.7 pg/mL at 20 minutes) as in both Aspirin IV groups.

There were no significant differences in the incidence of composite clinical outcomes for any of the pair-wise comparisons between the treatment groups.

The incidence of each clinical outcome (death from all causes, cardiovascular death, MI [re-infarction], and ischemic stroke) was very low for all time-periods assessed (1.0 % to 2.3%). No subject in the 250 mg Aspirin IV group experienced any of the post-randomization clinical outcomes for any time period. There were no significant differences between the treatment groups in the incidence of any post-randomization clinical endpoint for all time-periods assessed (p-values >0.05).

Analyses of the secondary efficacy variables by gender showed no relevant differences between the treatment groups.
Any differences between the STEMI and NSTEMI/UAP subgroups in the secondary efficacy variables were to be interpreted with caution due to the small sample size of the STEMI subgroup compared to the NSTEMI/UAP subgroup.

**Safety evaluation**

52 subjects in the SAF reported at least one TEAE (i.e. events that started within 24 hours after study drug administration). The frequency of TEAEs was lower in the 250 mg Aspirin IV group (11 [12.9%] subjects) than in the 500 mg Aspirin IV group (18 [20.5%] subjects) and the 300 mg Aspirin N tablet p.o. group (23 [23.7%] subjects). The most commonly reported TEAEs by system organ class were vascular disorders, ranging from 4 (4.7%) subjects in the 250 mg Aspirin IV group to 9 (9.3%) in the 300 mg Aspirin N tablet p.o. group. Haematoma was the most common TEAE in all treatment groups, reported for 3 (3.4%) subjects in the 500 mg Aspirin IV group, 3 (3.5%) subjects in the 250 mg Aspirin IV group, and 4 (4.1%) subjects in the 300 mg Aspirin N tablet p.o. group. Most TEAEs were of mild intensity. A higher frequency of moderate TEAEs was observed in the 300 mg Aspirin N tablet p.o. group than in the 500 mg and 250 mg Aspirin IV groups (8.2% vs. 4.5% and 1.2%, respectively). Overall, 2 severe TEAEs occurred: sudden cardiac death (1 subject in the 500 mg Aspirin IV group) and dyspnoea (1 subject in the 250 mg Aspirin IV group).

The frequency of drug-related TEAEs was low across the treatment groups; however, it was somewhat higher in the 500 mg Aspirin IV group than in the 250 mg Aspirin IV and 300 mg Aspirin N tablet p.o. groups (6 [6.8%] vs. 3 [3.5%] and 3 [3.1%] subjects, respectively). Drug-related TEAEs reported in the study were: injection site haematoma, vessel puncture site haematoma, epistaxis, rash, arteriovenous fistula, and haematoma. None of them was severe in intensity.

22 subjects experienced at least one SAE during the study. The frequency of SAEs was somewhat lower in the 250 mg Aspirin IV group (5 [5.9%] subjects) compared to the other 2 groups (8 [9.1%] and 9 [9.3%] subjects in the 500 mg Aspirin IV and 300 mg Aspirin N tablet p.o. groups, respectively). None of the SAEs was assessed as drug-related.

Three subjects died during the study. The AEs leading to death were: cardiac arrest (reported for 1 subject in the 300 mg Aspirin N tablet p.o. group), sudden cardiac death and staphylococcal sepsis (each reported for 1 subjects in the 500 mg Aspirin IV group).

34 subjects experienced at least one bleeding AE. The frequency of bleeding AEs was similar across the treatment groups: 13 (14.8%) subjects in the 500 mg Aspirin IV group, 10 (11.8%) in the 250 mg Aspirin IV group, and 11 (11.3%) in the 300 mg Aspirin N tablet p.o. group. Drug-related bleeding AEs were reported in 8 (9.1%) subjects treated with 500 mg Aspirin IV, 7 (8.2%) subjects treated with 250 mg Aspirin IV, and 4 (4.1%) subjects treated with 300 mg Aspirin N tablet. The number of subjects who experienced at least one bleeding TEAE was low across the treatment groups (up to 6 subjects per group): the lowest frequency was observed in the 250 mg Aspirin IV group, with 3 (3.5%) subjects experiencing at least one bleeding TEAE. Haematoma was the only bleeding TEAE occurring in all treatment groups. Drug-related bleeding TEAEs were more frequently reported in the Aspirin IV groups (5 [5.7%] and 3 [3.5%] subjects in the 500 mg and 250 mg Aspirin IV groups, respectively) than in the 300 mg Aspirin N tablet p.o. group (1 [1.0%] subject).
Vascular AEs were reported in 3 subjects overall; all events were serious and not drug-related. No pregnancies were reported during the study.

Post-randomization stroke of unknown etiology occurred in 1 subject only in this study, in the 300 mg Aspirin N tablet p.o. group.

The incidence of composite of post-randomization bleedings (TIMI major, TIMI minor, and bleeding requiring medical attention) up to 24 hours after treatment was low in the 250 mg Aspirin IV group (3 [3.5%] subjects) and somewhat higher in the other 2 groups (6 [6.8%] and 6 [6.2%] subjects in the 500 mg Aspirin IV and 300 mg Aspirin N tablet p.o. groups). The same frequency was observed for post-randomization bleedings by TIMI classification including intracerebral bleeding up to 24 hours. The incidence of post-randomization bleedings including intracerebral bleeding up to 7 days after treatment was comparable across the treatment groups.

The incidence of instrumented bleedings was similar to that of spontaneous bleedings reported within 24 hours or up to 7 days after study treatment. Most of the bleedings at different sites occurred in single subjects and their incidence was similar across the treatment groups.

Three subjects died during hospitalization for ACS: 2 subjects with NSTEMI/UAP in the 500 mg Aspirin IV group and 1 subject with STEMI in the 300 mg Aspirin N tablet p.o. group. None of the deaths was assessed as drug-related.

Clinical laboratory parameters, vital signs variables, and results of ECG parameters including QT and QTc showed no clinically relevant differences across the treatment groups.

**Overall conclusions**

Treatment with Aspirin IV caused a rapid decrease in the mean TXB\(_2\) concentrations in both 500 mg and 250 mg Aspirin IV groups (geometric means: 573.94 and 581.66 ng/mL at baseline and 3.10 and 3.86 ng/mL at 5 minutes post-baseline, respectively). This rapid decrease in serum TXB\(_2\) concentrations was considerably higher in the Aspirin IV groups than in the Aspirin N tablet p.o. group, and the differences were statistically significant (one-sided p-values <0.0001). More than 95% inhibition of thromboxane generation and more than 75% inhibition of platelet aggregation could be achieved within 5 minutes after administration of either 250 mg of 500 mg Aspirin IV. The inhibition of platelets was also achieved with the oral dose of 300 mg Aspirin, but only at 20 minutes post-baseline; thus, the time latency needed for absorption after the oral intake of Aspirin may be a potential disadvantage in the setting of an ACS, in particular for STEMI patients.

Overall, the safety profile of the test drug was consistent with the ACS population represented in this study, the nature of the underlying disease, and the known safety profile of Aspirin. Both doses of Aspirin IV were well tolerated. A slight difference in favor of the lower IV dose of 250 mg versus 500 mg Aspirin was observed with regard to frequency of TEAEs, drug-related and bleeding events; however, this finding should be considered with caution due to the small number of drug-related events reported in both Aspirin IV groups overall.
# Investigational Site List

## Marketing Authorization Holder in Germany

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<th>Bayer Vital GmbH</th>
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<td>Postal Address</td>
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## Sponsor in Germany (if applicable)

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## List of Investigational Sites

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<td>1</td>
<td>Hr. Prof. Dr. U Zeymer</td>
<td>Klinikum d. Stadt Ludwigshafen</td>
<td>Bremserstr. 79</td>
<td>67063</td>
<td>Ludwigshafen</td>
<td>Germany</td>
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<td>Hr. Prof. Dr. R Erbel</td>
<td>Universitätsklinikum Essen</td>
<td>Hufelandstr. 55</td>
<td>45147</td>
<td>Essen</td>
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<td>Hr. Prof. Dr. R Braun-Dullaeus</td>
<td>Otto-von-Guericke-Universität</td>
<td>Leipziger Strasse 44</td>
<td>39112</td>
<td>Magdeburg</td>
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<td>Hr. PD Dr. M A Weber</td>
<td>Klinikum Dachau</td>
<td>Sigmund-Freud-Straße 25</td>
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<td>St. Antonius Krankenhaus gGmbH</td>
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<td>50968</td>
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<td>Hr. Prof. Dr. D Trenk</td>
<td>Universitätskerzcentrum</td>
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<td>Bad Krozingen</td>
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<td>8</td>
<td>Hr. Dr. G Claus</td>
<td>Asklepios Klinikum Melsungen</td>
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<td>Hr. PD Dr. E Giannitsis</td>
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<td>Stadtkrankenhaus Worms gGmbH</td>
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<td>Langenbeckstr. 1</td>
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