Report Synopsis of Study: **TROPICAL-ACS**

EudraCT-Nr.: **2013-001636-22**

Vorlage-Nr.: **4039149**

1) **Name of Sponsor/Company:** Klinikum der Universität München	4) **Individual Study Table Referring to Part of the Dossier:** not applicable[1]	*(For National Authority Use only)*
2) **Name of Finished Product:** Plavix		
3) **Name of Active Substance:** Clopidogrel	Volume: not applicable Page: not applicable	

5) **Title of Study[2]:**

Testing Responsiveness to platelet inhibition on chronic antiplatelet treatment for acute coronary syndromes (TROPICAL-ACS) trial - an investigator initiated prospective, randomized, parallel-group, open-label, non-inferiority, multicenter trial of a 12 month vs. a short-term platelet function testing guided prasugrel therapy in acute coronary syndrome patients undergoing coronary stenting

Latest protocol version: Version 6.0 - March 30, 2015 (Amendment 4 included)

Protocol Amendments:

Protocol Amendment 25.07.2013, Protocol Version 2.0

Protocol Amendment 13.09.2013, Protocol Version 3.0

Protocol Amendment 03.12.2013, Protocol Version 4.0

Protocol Amendment 02.04.2014, Protocol Version 5.0

Protocol Amendment 03.06.2014, Protocol Version 5.1

Protocol Amendment 30.03.2015, Protocol Version 6.0

6) **Principal Investigator(s):**

Poland:

Zenon Huczek (National Lead Investigator)

Radoslaw Parma (3rd Department of Cardiology, Medical University of Silesia, Katowice)

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

Anna Lesiak (1st Department of Cardiology, Poznan University of Medical Science, Poznan)

Zenon Huczek (1st Department of Cardiology, Medical University of Warsaw, Warsaw)

Mariusz Klopotowski (Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw)

Hungary:

Daniel Aradi (National Lead Investigator)

Daniel Aradi (Heart Center Balatonfüred and Heart and Vascular Center, Semmelweis University Budapest)

Béla Merkely (Heart and Vascular Center, University of Semmelweis, Budapest)

Róbert Gábor Kiss (Department of Cardiology, Military Hospital, Budapest)

Csaba András Dézsi (Department of Cardiology, Petz Aladár County Teaching Hospital, Győr)

Zoltán Ruzsa (Bács-Kiskun County Hospital, Kecskemét)

András Komócsi (Department of Interventional Cardiology, Heart Institute, University of Pécs, Pécs)

Imre Ungi (Department of Cardiology, University of Szeged, Szeged)

Austria:

Kurt Huber (National Lead Investigator)

Gabor Toth (Medizin-Universität Graz, Univ. Klinik für Innere Medizin, Abteilung für Kardiologie, Graz)

Kurt Huber (3rd Medical Department, Cardiology and Intensive Care Medicine, and Sigmund Freud Private University. Medical School, Wien)

Germany:

Dirk Sibbing (National Lead Investigator)

Wolfgang von Scheidt (Klinikum Augsburg, Department of Cardiology, Augsburg)

Dietmar Trenk (University Heart Center Freiburg, Bad Krozingen, Department of Cardiology and Angiology II, Bad Krozingen)

Hans Ulrich Kreider-Stempfle (Asklepios Stadtklinik Bad Tölz, Internal Medicine, Bad Tölz)

Andreas Mügge (St. Josef Hospital, Katholisches Klinikum Bochum, Department of Cardiology, Bochum)

Stephan Fichtlscherer (Universitätsklinikum Frankfurt, Department of Cardiology,

Frankfurt/Main)

Martin Hinterseer (Kliniken Ostallgaeu-Kaufbeuren, Klinik Füssen, Füssen)

Claudius Jacobshagen (Department of Cardiology und Pneumology, Heart Center / Georg-August-University Göttingen, Göttingen)

Astrid Hummel (Department of Internal Medicine B, University Medicine Greifswald, Germany und DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald)

Mahir Karakas (Universitäres Herzzentrum Hamburg, UKE, Hamburg)

Tanja Rudolph (Herzzentrum der Universität zu Koeln, Koeln)

Tommaso Gori (Zentrum für Kardiologie, Kardiologie I, Universitätsmedizin Mainz und DZHK (German Center for Cardiovascular Research), partner site Rhein-Main, Mainz)

Andreas May (Klinikum Memmingen, Innere Medizin I, Memmingen)

Johannes Rieber (Heart Center Munich-Bogenhausen, Department of Cardiology and Intensive Care Medicine, Munich)

Dirk Sibbing (Ludwig-Maximilians-Universität München (LMU Munich), Department of Cardiology, Munich)

Harald Mudra (Department of Cardiology, Pulmonology and Internal Intensive Care Medicine, Klinikum Neuperlach, Städtisches Klinikum München GmbH, Munich)

Torsten Schütz (Klinikum Oldenburg gGmbH, Herz-Kreislauf-Zentrum, Klinik für Kardiologie, Oldenburg)

Hüseyin Ince (Universitätsmedizin Rostock, Zentrum für Innere Medizin, Rostock)

Peter Boekstegers (Helios-Klinikum Siegburg, Abteilung für Kardiologie und Angiologie, Siegburg)

Tobias Geisler (University Hospital Tübingen, Department of Cardiology and Cardiovascular Disease, Tübingen)

Robert Schwinger (Medizinische Klinik II, Klinikum Weiden, Kliniken Nordoberpfalz AG, Weiden)

7) **Study centre(s):**

Poland:

3rd Department of Cardiology, Medical University of Silesia, Katowice

1st Department of Cardiology, Poznan University of Medical Science, Poznan

1st Department of Cardiology, Medical University of Warsaw, Warsaw

Department of Interventional Cardiology and Angiology, Institute of Cardiology, Warsaw

Report Synopsis of Study: **TROPICAL-ACS**

EudraCT-Nr.: **2013-001636-22**

Vorlage-Nr.: **4039149**

Austria:

Medizin-Universität Graz, Univ. Klinik für Innere Medizin, Abteilung für Kardiologie, Graz

3rd Medical Department, Cardiology and Intensive Care Medicine, and Sigmund Freud Private University. Medical School, Wien

Germany:

Klinikum Augsburg, Department of Cardiology, Augsburg

University Heart Center Freiburg, Bad Krozingen, Department of Cardiology and Angiology II, Bad Krozingen

Asklepios Stadtklinik Bad Tölz, Internal Medicine, Bad Tölz

St. Josef Hospital, Katholisches Klinikum Bochum, Department of Cardiology, Bochum

Universitätsklinikum Frankfurt, Department of Cardiology, Frankfurt/Main

Kliniken Ostallgaeu-Kaufbeuren, Klinik Füssen, Füssen

Department of Cardiology und Pneumology, Heart Center / Georg-August-University Göttingen, Göttingen

Department of Internal Medicine B, University Medicine Greifswald, Germany und DZHK (German Center for Cardiovascular Research), partner site Greifswald, Greifswald

Universitäres Herzzentrum Hamburg, UKE, Hamburg

Herzzentrum der Universität zu Koeln, Koeln

Zentrum für Kardiologie, Kardiologie I, Universitätsmedizin Mainz und DZHK (German Center for Cardiovascular Research), partner site Rhein-Main, Mainz

Klinikum Memmingen, Innere Medizin I, Memmingen

Heart Center Munich-Bogenhausen, Department of Cardiology and Intensive Care Medicine, Munich

Ludwig-Maximilians-Universität München (LMU Munich), Department of Cardiology, Munich

Department of Cardiology, Pulmonology and Internal Intensive Care Medicine, Klinikum Neuperlach, Städtisches Klinikum München GmbH, Munich

Klinikum Oldenburg gGmbH, Herz-Kreislauf-Zentrum, Klinik für Kardiologie, Oldenburg

Universitätsmedizin Rostock, Zentrum für Innere Medizin, Rostock

Helios-Klinikum Siegburg, Abteilung für Kardiologie und Angiologie, Siegburg

University Hospital Tübingen, Department of Cardiology and Cardiovascular Disease, Tübingen

Medizinische Klinik II, Klinikum Weiden, Kliniken Nordoberpfalz AG, Weiden

Report Synopsis of Study: **TROPICAL-ACS**

EudraCT-Nr.: **2013-001636-22**

Vorlage-Nr.: **4039149**

8) **Publication (reference):**

Sibbing D, Aradi D, Jacobshagen C, Gross L, Trenk D, Geisler T, Orban M, Hadamitzky M, Merkely B, Kiss RG, Komócsi A, Dézsi CA, Holdt L, Felix SB, Parma R, Klopotowski M, Schwinger RHG, Rieber J, Huber K, Neumann FJ, Koltowski L, Mehilli J, Huczek Z, Massberg S; TROPICAL-ACS Investigators.

Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomised, open-label, multicentre trial.

Lancet. 2017 Aug 25. pii: S0140-6736(17)32155-4. doi: 10.1016/S0140-6736(17)32155-4. [Epub ahead of print]

9) **Studied period (years)**[3]**:**	10) **Phase of development:** IV
First enrolment: Dec 2013 Last completed: May 2017	

11) **Objectives:**

The trial was designed to investigate the safety and efficacy of early de-escalation of antiplatelet treatment from prasugrel to clopidogrel guided by platelet function testing (PFT) in ACS patients undergoing successful PCI.

Primary Objectives:

The primary objective was to evaluate the incidence of the primary endpoint, defined as a combined ischaemic and bleeding end point (net clinical benefit), which was the composite of death from cardiovascular causes (all deaths were assumed cardiovascular in nature unless a non-cardiovascular cause can be clearly provided), myocardial infarction (defined according to the 3rd universal definition of MI), stroke and bleeding grade ≥2 defined according to Bleeding Academic Research Consortium (BARC) criteria at 12 months after randomization.

Secondary Objectives:

The key secondary endpoint was defined as BARC class ≥2 bleeding events at 12 months. Further secondary endpoints included the ischaemic components (combined and singular)

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

of the primary endpoint (cardiovascular death, MI, stroke), stent thrombosis defined according to Academic Research Consortium (ARC) criteria, the incidence of death from any cause and urgent ischaemia-driven revascularization at 12 months.

12) **Methodology:**

TROPICAL-ACS is an investigator-initiated, international, randomized, parallel-group, assessor-blinded, open-label, multicenter trial.

13) **Number of patients (planned and analyzed):**

Sample size calculations (nQuery Advisory, Statistical Solutions Ltd., 7B Airport East Business Park, Farmer's Cross, Cork, Ireland) were performed based on a 1-sided type I error of 5% and a power of 80%. For the primary endpoint assumptions, 1172 patients in each group were needed. Assuming an incidence of BARC ≥2 bleeding in the control group of 4.9% and an expected reduction of BARC ≥2 bleeding by 45% in the de-escalation group, 1179 patients per group would be required to demonstrate superiority (based on 2-sided type I error of 5% and a power of 80% for the key secondary endpoint (BARC ≥2 bleeding). In order to compensate for losses to follow-up and in order to be powered for the primary and secondary endpoint assessment the enrolment of a total of 2600 patients (1300 patients per group) was planned. A total of 2610 patients were enrolled and analyzed in the trial.

14) **Diagnosis and main criteria for inclusion:**

Inclusion criteria:

1. Patients with biomarker positive ACS
2. Successful PCI (defined as a post PCI diameter stenosis <20% and TIMI flow ≥2)
3. A planned treatment of prasugrel for 12 months after the procedure
4. Written informed consent

15) **Test product, dose and mode of administration:**

Clopidogrel (Plavix), 75 mg daily, oral administration

16) **Duration of treatment:**

11 ¾ months

17) **Reference therapy, dose and mode of administration:**

Prasugrel (Effient), 10/5 mg daily, oral administration

18) **Criteria for evaluation:**

The primary endpoint of this study was a net clinical benefit endpoint that captured both, efficacy and safety. It was a combined ischaemic and bleeding end point, which was the

composite of death from cardiovascular causes, myocardial infarction, stroke and bleeding grade ≥2 defined according to Bleeding Academic Research Consortium (BARC) criteria at 12 months after randomization.

Efficacy:

Secondary efficacy endpoints are cardiovascular death, MI, stroke, stent thrombosis defined according to Academic Research Consortium (ARC) criteria, the incidence of death from any cause and urgent ischaemia-driven revascularization at 12 months.

Safety:

The key secondary endpoint was defined as BARC class ≥2 bleeding events at 12 months. With respect to bleeding events, all reported bleedings were assessed and reported according to BARC classification (BARC type 1 to 5).

19) **Statistical methods:**

The study was designed to demonstrate non-inferiority for the guided de-escalation vs. control group regarding the primary composite endpoint. Considering the results of a landmark analysis from the TRITON-TIMI 38 trial, based on the incidence of early vs. late major bleeding events and based on the incidence of BARC ≥2 bleeding complications in a PCI cohort, the incidence of the primary endpoint of this study was assumed to be 10.5% in the control group. A non-inferiority margin of 30% was estimated, which is in accordance with non-inferiority margins used in contemporary trials of antithrombotic treatment in cardiovascular diseases. All analyses were performed on intention-to-treat basis. In addition, per-protocol analyses were conducted. Differences in endpoints were analysed in Cox-regression models for survival analysis. In all cases of the use of the Cox proportional hazards model, the proportional hazards assumption was met. Kaplan-Meier plots were generated to visualize the risk of outcome events in both groups. Binary and other categorical variables were compared using fisher's exact test and chi-square test respectively, for continuous data 2-sided unpaired Wilcoxon test or t-test were used as appropriate. Analysis was done with the statistical software R version 3.3.0.

20) **Summary – Conclusions:**

Overall, at 1-year, the combined primary endpoint (net clinical benefit) occurred in 95 patients in the guided de-escalation group and in 118 patients in the control group (7.3% vs 9.0%, p for non-inferiority=0.0004; HR 0.81, 95% CI: 0.62–1.06, p for superiority=0.1202). Per-protocol analyses yielded similar results to the intention-to-treat analyses for the primary study endpoint (HR 0.84, 95% CI 0.64–1.19, p for non-inferiority=0.0013, for guided de-

escalation vs. control group) of the study.

Efficacy results:

The ischaemic components of the primary endpoint (cardiovascular death, MI, stroke) occurred in 32 patients in the guided de-escalation group and in 42 patients in the control group (2.5% vs 3.2%, HR 0.77, 95% CI 0.48–1.21, p=0.2526), indicating that early de-escalation did not result in an increased risk of cardiovascular death, myocardial infarction or stroke (p for non-inferiority=0.0115). No significant differences were observed for any of the ischaemic components of the primary endpoint (p≥0.22) as well as for the rate of urgent revascularization (p=0.1342). All-cause mortality at 1-year was 0.9% (12 events) in the control group vs. 0.8% (11 events) in the guided de-escalation group (P=0.8507). For study group comparisons, STEMI patients (HR: 0.54, 95% CI: 0.35–0.83, p=0.004; p for interaction=0.0116) and younger (age≤70) patients (HR: 0.70, 95% CI: 0.51–0.96, p=0.0270; p (categorical model) for interaction=0.1052, p (continuous model) for interaction=0.0229) showed significant differences favouring guided de-escalation.

Safety results:

The incidence of the key secondary endpoint of BARC≥2 bleedings was 4.9% (64 events) in the guided de-escalation group vs. 6.1% (79 events) in the control group (HR: 0.82, 95% CI: 0.59–1.13, p=0.2257). The cumulative incidence of all bleeding events (BARC class 1 to 5) was 8.7% (114 events) in the guided de-escalation group vs. 10.5% (137 events) in the control group (HR: 0.83, 95% CI: 0.65–1.06, p=0.1409). Per-protocol analyses yielded similar results to the intention-to-treat analyses for the key secondary endpoint of BARC≥2 bleedings (HR 0.81, 95% CI 0.58–1.17, p=0.2404 for guided de-escalation vs. control group) of the study. There were 116 dropouts and 1269 protocol deviations for the TROPICAL-ACS trial. The overall SAE count was 578.

Conclusion:

Guided de-escalation of antiplatelet treatment was non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit. The TROPICAL-ACS trial shows that early de-escalation of antiplatelet treatment can be considered as an alternative approach in ACS patients managed with PCI.

21) **Date of the report:** May 8, 2018

Prof. Dr. Dirk Sibbing
Klinikum der Universität München
Medizinische Klinik und Poliklinik I
Marchioninistr. 15, 81377 München
Tel.: 089 4400-73028
Fax: 089 4400-76028
Email: dirk.sibbing@med.uni-muenchen.de