Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Klinik für Herz- und Kreislauferkrankungen Deutsches Herzzentrum München Klinik an der Technischen Universität München Lazarettstr. 36 80636 München Germany	Brilique	Ticagrelor (CAS number 274693-27-5)

Synopsis of Final Study Report

(according to ICH Topic E3 Structure and Content of Clinical Study reports – Annex I)

Title of Study:

A Randomized, Parallel Group, Double-Blind, Study of Ticagrelor Compared with Aspirin for Prevention of Vascular Events in Patients Undergoing Coronary Artery Bypass Graft Operation

TiCAB– Ticagrelor in CABG

Investigators and Study Centers:

Deutsches Herzzentrum München
Klinik an der Technischen Universität München
Klinik für Herz- und Kreislauferkrankungen
Lazarettstr. 36
80636 München
Investigator: Prof. Dr. Heribert Schunkert

Universitätsklinikum Aachen
Klinik für Thorax-, Herz- und Gefäßchirurgie
Pauwelsstr. 30
52074 Aachen

Deutsches Herzzentrum Berlin
Klink für Herz-, Thorax- und Gefäßchirurgie
Augustenburger Platz 1
13353 Berlin

Charité-Universitätsmedizin Berlin
Klinik für Kardiovaskuläre Chirurgie
Charitéplatz 1
10117 Berlin

Gesundheit Nord gGmbH
Klinikum Links der Weser gGmbH
Klinik für Kardiologie u. Angiologie
Senator-Weßling-Str. 1
28277 Bremen

Herzzentrum Brandenburg in Bernau
Herzchirurgie
Ladeburger Str. 17
16321 Bernau

Sana-Herzzentrum Cottbus GmbH
Kardiologie
Leipziger Str. 50
03048 Cottbus

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Klinik für Herz- und Kreislauferkrankungen Deutsches Herzzentrum München Klinik an der Technischen Universität München Lazarettstr. 36 80636 München Germany	Brilique	Ticagrelor (CAS number 274693-27-5)

Universitätsklinikum Düsseldorf
Klinik für Kardiologie, Pneumologie, Angiologie
Moorenstr. 5
40225 Düsseldorf

Kliniken Maria Hilf GmbH
Viersener Str. 450
41063 Mönchengladbach

St. Antonius Hospital Eschweiler
Dechant-Deckers-Str. 8
52249 Eschweiler

Klinikum Nürnberg Süd
Klinik für Herzchirurgie
Breslauer Straße 201
90471 Nürnberg

Universitätsklinikum Erlangen
Medizinische Klinik 2
Ulmenweg 18
91054 Erlangen

Kerckhoff-Klinik Forschungsgesellschaft mBH
Küchlerstr. 10
61231 Bad Nauheim

Herz- und Kreislaufzentrum Rotenburg / Fulda
Klinik für Herz- und Gefäßchirurgie GmbH
Heinz-Meise-Str. 100
36199 Rotenburg a. d. Fulda

Universitäts-Herzzentrum Freiburg – Bad Krozingen
Klinik für Herz- und Gefäßchirurgie
Hugstetter Str. 55
79106 Freiburg

Justus-Liebig Universität Gießen
Klinik für Herz-, Kinderherz- und Gefäßchirurgie
Rudolph-Buchheim-Str. 7
35392 Gießen

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
Klinik für Herz- und Kreislauferkrankungen Deutsches Herzzentrum München Klinik an der Technischen Universität München Lazarettstr. 36 80636 München Germany	Brilique	Ticagrelor (CAS number 274693-27-5)

Universitätsmedizin Göttingen
Klinik für Thorax-, Herz- und Gefäßchirurgie
Robert-Koch-Str. 40
37075 Göttingen

Universitäres Herzzentrum Hamburg GmbH
Klinik für Herz- und Gefäßchirurgie
Martinistr. 52
20246 Hamburg

Asklepios Klinik St. Georg
Herzchirurgische Abteilung
Lohmühlenstr. 5
20099 Hamburg

Herz- und Gefäßzentrum Bad Bevensen
Klinik für Herz-Thorax-Chirurgie
Römstedter Str. 25
29549 Bad Bevensen

Universitätsklinikum Jena
Klinik für Herz- und Thoraxchirurgie
Erlanger Allee 101
07747 Jena

Universitätsklinikum Schleswig-Holstein, Campus Kiel
Klinik für Herz- und Gefäßchirurgie
Arnold-Heller-Str. 3, Haus 18
24105 Kiel

Herzzentrum Leipzig GmbH – Universitätsklinik
Klinik für Herzchirurgie
Strümpellstr. 39
04289 Leipzig

Universitätsklinikum Schleswig-Holstein
Campus Lübeck
Medizinische Klinik 2
Ratzeburger Allee 160
23538 Lübeck

Krankenhaus der Barmherzigen Brüder Trier
Abteilung für Herz- und Thoraxchirurgie
Nordallee 1
54292 Trier

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Klinik für Herz- und Kreislauferkrankungen Deutsches Herzzentrum München Klinik an der Technischen Universität München Lazarettstr. 36 80636 München Germany	Brilique	Ticagrelor (CAS number 274693-27-5)

Klinikum der Stadt Ludwigshafen am Rhein gGmbH
Medizinische Klinik B
Herzzentrum Ludwigshafen
Bremserstr. 79
67063 Ludwigshafen

Medizinische Universität Wien
AKH
Währinger Gürtel 18-20
1090 Wien
Österreich

Medizinische Universität Innsbruck
Universitätsklinik für Herzchirurgie
Anichstr. 35
6020 Innsbruck

Klinikum Wels-Grieskirchen
Abteilung für Herz-, Gefäß- und Thoraxchirurgie
Grieskirchnerstr. 42
4600 Wels
Österreich

Universitätsklinik für Herz- und Gefäßchirurgie
Inselspital
Freiburgstr. 18
3010 Bern
Schweiz

Publication (reference):
A randomized, parallel group, double-blind study of ticagrelor compared with aspirin for prevention of vascular events in patients undergoing coronary artery bypass graft operation: Rationale and design of the Ticagrelor in CABG (TiCAB) trial: An Investigator-Initiated trial.

Am Heart J. 2016 Sep;179:69-76. doi: 10.1016/j.ahj.2016.05.017. Epub 2016 Jun 18.

de Waha A, Sandner S, von Scheidt M, Boening A, Koch-Buettner K, Hammel D, Hambrecht R, Danner BC, Schöndube FA, Goerlach G, Fischlein T, Schmoeckel M, Oberhoffer M, Schulz R, Walther T, Ziegelhöffer T, Knosalla C, Schönrath F, Beyersdorf F, Siepe M, Attmann T, Misfeld M, Mohr FW, Sievers HH, Joost A, Putman LM, Laufer G, Hamm C, Zeymer U, Kastrati A, Radke PW, Lange R, Cremer J, Schunkert H.

Studied period (years)	**Phase of development:** III
first patient in: April 24, 2013 **last patient out:** May 19, 2018	

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient:**
Klinik für Herz- und Kreislauferkrankungen Deutsches Herzzentrum München Klinik an der Technischen Universität München Lazarettstr. 36 80636 München Germany	Brilique	Ticagrelor (CAS number 274693-27-5)

Objectives:

The primary objective of this study was to test the hypothesis that Ticagrelor is superior to Aspirin (ASA) for the prevention of major cardiovascular and cerebrovascular events (MACCE; cardiovascular death, myocardial infarction, recurrent revascularization or stroke) in patients undergoing coronary artery bypass graft operation (CABG).

The primary efficacy MACCE-endpoint is the composite of cardiovascular death, myocardial infarction, recurrent revascularization, and stroke at twelve month after coronary artery bypass operation.

Methodology:

This was a randomized, phase III, double-blind, parallel group, multicenter study comparing the efficacy and safety of Ticagrelor 90mg administered twice daily with Acetylsalicylic acid (ASA) 100mg administered once daily for the prevention of major cardiovascular events after CABG operation.

Number of patients (planned and analysed):

The following assumptions have been made in order to perform sample size calculation:

1. The event rate after CABG surgery in the patient cohort addressed is 12.4 % (Serruys P, SYNTAX study NEJM 2009).
2. For the purpose of this trial, an event rate of 13 % was assumed.
3. Based on an absolute 13 % event rate, the relative event rates by component were estimated to be: cardiac death 17 %, stroke 18 %, myocardial infarction 27 %, repeat revascularization 38 %.
4. A post-hoc analysis of the PLATO trial data suggests that Ticagrelor in addition to an Aspirin dose of 81 mg/day results in a relative risk reduction of 25 % in the primary endpoint as compared to Clopidogrel + Aspirin.
5. For the purpose of this trial, a 22.5 % relative risk reduction was assumed for the primary endpoint (odds ratio 0.775 in active group).

Based on an event rate of 13 % of the primary endpoint within the first twelve month after CABG operation in the control group, a two-sided α level of 0.0492 (to preserve the overall significance level of 0.05 after planned interims analysis), a power of 0.80, two-sided testing and an expected relative risk of 0.775 in the active group, a total of 3760 patients were required. With a drop- out rate of 2.0 % a total of 3850 patients were required to be randomized.

A planned interim analysis by the DSMB was carried out after about half of the intended number of patients was included. Shortly before this analysis the producer of ticagrelor had terminated the contract with the German Heart Centre resulting in a premature stop of external financial funding. There was no safety issue arising from the data analysis by the DSMB. However, based on the analysis of the data from the first 1800 patients the DSMB suggested stopping the recruitment early because of futility. The change in the financial support had further motivated this proposition. While the blinding of all investigators and the SC was maintained the SC followed the advice of the DSMB. The follow up all patients was continued until completion of study participation. Therefore, a total of 1893 patients was enrolled and all patients completed the study participation according to the protocol. The study was then stopped completely.

Diagnosis and main criteria for inclusion:

Male and female patients aged 18 years and over with coronary artery disease, undergoing coronary artery bypass operation.

Test product, dose and mode of administration, batch number:

Ticagrelor 90mg or placebo: tablet taken twice daily, oral administration
Batch numbers: FAAH, FAAM
Batch numbers placebo to Ticagrelor: 172-01, 173-01

Duration of treatment:

The duration of treatment for an individual patient was 12 months.

Reference therapy, dose and mode of administration, batch number:

Acetylsalicylic acid (ASA) 100mg or placebo: tablet taken once daily, oral administration
Batch numbers: CZ8132, DX2822
Batch numbers placebo to ASA: 08827G005

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient:
Klinik für Herz- und Kreislauferkrankungen Deutsches Herzzentrum München Klinik an der Technischen Universität München Lazarettstr. 36 80636 München Germany	Brilique	Ticagrelor (CAS number 274693-27-5)

Criteria for evaluation:

Primary Endpoints:

Composite of cardiovascular death, myocardial infarction, recurrent revascularization, and stroke at 12 months after coronary artery bypass operation

Secondary Endpoints:

1. Safety endpoint: The incidence of major bleeding at 12 months after coronary artery bypass operation (Class 4 or 5 periprocedurally respectively Class 3-5 after discharge as defined by the Bleeding Academic Research Consortium, see Appendix 1.).
2. Incidence of the individual components of the primary endpoint at 12 months after coronary artery bypass operation (cardiovascular death, myocardial infarction, recurrent revascularization, and stroke)

Statistical methods:

Categorical variables such as demographics and medical history data were summarized using frequencies and proportions and were compared using the Chi-square test or Fischer's exact test, as appropriate. Continuous data were summarized using mean ± standard deviation or median (25th, 75th percentile) and were compared using either Student's t test or the nonparametric Wilcoxon rank sum test. Outcomes were compared between treatment and control groups by the use of Cox proportional hazards model effect after checking for fulfilment of the proportional hazard assumption. All analyses were performed according to a modified intention-to-treat principle with inclusion of all patients who were randomly assigned to one of the two study groups with the exception of those patients who withdrew their consent before undergoing CABG or did not undergo the planned surgery, and consequently, did not receive any study drug. The primary endpoint of the study was also analysed in various subgroups of interest (age, gender, diabetes, history of a percutaneous coronary intervention, number of arterial and venous bypass grafts) including those pre-specified as defined by stratification for acute coronary syndrome, after testing for interaction for the treatment effect. All statistical analyses were performed with the use of R v3.5.1 software.

Summery – Conclusions:

In this prematurely terminated trial, the use of ticagrelor as compared to aspirin in patients undergoing CABG did not significantly impact on the risk of major cardiovascular events nor major bleeding events.

Efficacy Results:

Twelve months after CABG, the primary endpoint occurred in 73 out of 928 patients (8.2%) in the aspirin group and in 86 out of 931 patients (9.7%) in the ticagrelor group (hazard ratio, 1.19; 95% confidence interval (CI) 0.87-1.62; P=0.28). All cause mortality (aspirin 2.6% vs ticagrelor 2.5%, hazard ratio 0.96, CI 0.53-1.72, P=0.89) and cardiovascular mortality (aspirin 1.4% vs ticagrelor 1.2%, hazard ratio 0.85, CI 0.38-1.89, P=0.68) were similar in both groups. No significant differences were observed regarding other individual components of the primary outcome.

Safety Results:

The incidence of major bleeding was not significantly different (aspirin 3.2% vs ticagrelor 3.7%, hazard ratio 1.17, CI 0.71-1.92, P=0.53).

Conclusion:

In conclusion, our trial involving patients undergoing coronary bypass surgery, ticagrelor-monotherapy was not found to be superior to aspirin-monotherapy in reducing the composite endpoint of cardiovascular death, myocardial infarction, repeat revascularisation, or stroke. Moreover, no difference was observed with respect to bleeding events.

Date, Signature:

22.11.2018

Prof. Dr. Heribert Schunkert
(Sponsor Representative)