Report Synopsis of Study : Resolution of Left Atrial-Appendage Thrombus – Effects of Dabigatran in patients with AF (RE-LATED AF) – A Prospective, multicenter, randomized, open-label, controlled, explorative, blinded-endpoint (PROBE) trial to compare the efficacy of Dabigatran (150 mg bid) with Phenprocoumon for the resolution of left atrial appendage thrombus formation in patients with atrial fibrillation

EudraCT-Nr.: 2013-005364-26

Vorlage-Nr.: 4039811

1) **Name of Sponsor/Company:**

University Medical Center of the Johannes Gutenberg-University Mainz represented by the executive board of the University
represented by the scientific member of the executive board
Univ.-Prof. Dr. U. Förstermann
Delegated to the Center of Cardiology – Cardiology II
Represented by the director
Univ.-Prof. Dr. Thomas Rostock, MD

2) **Name of Finished Product:**

Investigational product: Pradaxa®

Comparator: Marcumar®

3) **Name of Active Substance:**

Investigational product:
Dabigatran etexilate

Comparator:
Phenprocoumon

4) **Individual Study Table Referring to Part of the Dossier:** na[1]

Volume: na

Page: na

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5) **Title of Study[2]:** Resolution of Left Atrial-Appendage Thrombus – Effects of Dabigatran in patients with AF (RE-LATED AF) –

A Prospective, multicenter, randomized, open-label, controlled, explorative, blinded-endpoint (PROBE) trial to compare the efficacy of Dabigatran (150 mg bid) with Phenprocoumon for the resolution of left atrial appendage thrombus formation in patients with atrial fibrillation

First submission: Protocol Version 1.0 dated 19.03.2014

Version	Date	Page	Amendments / Changes from previous version
1.1	15.05.2014	Pg 1	Change of Coordinating Investigator *Reason:* Due to formal reasons
		Pg 2	Addition of Deputy of the Coordinating Investigator *Reason:* Due to formal reasons
		Pg 57	Change of Coordinating Investigator and addition of Deputy of the Coordinating Investigator *Reason:* Due to formal reasons
1.2	23.06.2014	Pg 6	Inclusion Criterion 2: Change of the wording from "newly diagnosed and confirmed LAA thrombus" to "newly diagnosed or confirmed LAA thrombus" *Reason:* To clarify the status of the diagnosis of the LAA thrombus
		Pg 9	Footnote 2: Clarification of TEE diagnostics in clinical routine and within the study *Reason:* To assure that informed consent is obtained before any study specific method is applied
		Pg 23	Inclusion Criterion 2: Change of the wording from "newly diagnosed and confirmed LAA thrombus" to "newly diagnosed or confirmed LAA thrombus" *Reason:* To clarify the status of the diagnosis of the LAA thrombus
		Pg 23	Inclusion Criterion 8: Addition of prolonged contraception after the last intake of study medication *Reason:* To align content with the *Fachinformation* of Marcumar®
		Pg 23	Inclusion Criterion 8: Addition of a remark that contraception method has to be discussed with the investigator *Reason:* To assure that a save and adequate contraception is applied

[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.

Report Synopsis of Study : Resolution of Left Atrial-Appendage Thrombus – Effects of Dabigatran in patients with AF (RE-LATED AF) – A Prospective, multicenter, randomized, open-label, controlled, explorative, blinded-endpoint (PROBE) trial to compare the efficacy of Dabigatran (150 mg bid) with Phenprocoumon for the resolution of left atrial appendage thrombus formation in patients with atrial fibrillation

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Amendment 1: Protocol Version 1.3 dated 18.09.2014

Version	Date	Page	Amendments / Changes from previous version
1.3	18.09.2014	Pg 37	"7.1.4 Procedure concerning core laboratory" and "7.2 Core Laboratory": Description of the pseudonymisation procedure *Reason:* Due to technical reasons

Amendment 2: Protocol Version 1.4 dated 07.10.2015

Version	Date	Page	Amendments / Changes from previous version
1.4	07.10.2015	Pg 02	Changes in personnel data *Reason:* Due to actualisation
		Pg 06	Secondary objectives: Change of the wording from "LAA thrombus volume" to "LAA thrombus size" *Reason:* Due to technical reasons
		Pg 06	Inclusion Criterion 2: Change of the time of detection from "≤ 7 days" to "≤ 28 days" *Reason:* To increase chance for patient recruitment
		Pg 06	Exclusion Criterion 4: Addition of an exception in the case of continued INR out of the target range *Reason:* To increase chance for patient recruitment
		Pg 07	Secondary endpoints: Change of the wording from "LAA thrombus volume" to "LAA thrombus size" *Reason:* Due to technical reasons
		Pg 07	Statistical analysis: Change of the wording from "LAA thrombus volume" to "LAA thrombus size" *Reason:* Due to technical reasons
		Pg 15	Changes in personnel data *Reason:* Due to actualisation
		Pg 16	Changes in personnel data *Reason:* Due to actualisation
		Pg 18	Changes in personnel data *Reason:* Due to actualisation
		Pg 23	Secondary objectives: Change of the wording from "LAA thrombus volume" to "LAA thrombus size" *Reason:* Due to technical reasons
		Pg 24	Secondary endpoints Change of the wording from "LAA thrombus volume" to "LAA thrombus size" *Reason:* Due to technical reasons
		Pg 25	Inclusion Criterion 2: Change of the time of detection from "≤ 7 days" to "≤ 28 days" *Reason:* To increase chance for patient recruitment
		Pg 26	Exclusion Criterion 4: Addition of an exception in the case of continued INR out of the target range *Reason:* To increase chance for patient recruitment
		Pg 38	Procedure of TEE: Modification of the LAA analysis by TEE examination *Reason:* Due to technical reasons
		Pg 44	Immediate reporting of SAEs by investigator: Changes in contact data *Reason:* Due to actualisation
		Pg 45	Immediate Reporting of pregnancy by investigator: Changes in contact data *Reason:* Due to actualisation
		Pg 49	Analysis of secondary endpoints: *Change of the wording from "LAA thrombus volume" to "LAA thrombus size"* *Reason:* Due to technical reasons
		Pg 59	Signatures: Changes in personnel *Reason:* Due to actualisation

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Amendment 3: Protocol Version 1.5 dated 04.07.2016

Version	Date	Page	Amendments / Changes from previous version
1.5	04.07.2016	Pg 1	Change of Coordinating Investigator *Reason*: Due to formal reasons
		Pg 2	Change of deputy of the Coordinating Investigator *Reason*: Due to formal reasons
		Pg 6	Inclusion Criterion 5: Change of the creatinine clearance (CrCL) to a minimum level of ≥ 30 mL/min (Cockcroft-Gault) *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 6	Exclusion Criterion 20: Change of the Renal insufficiency to a maximum value below 30 mL/min CrCL (Cockcroft-Gault) *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 21	Editorial change of the wording *Reason*: Due to formal change
		Pg 23	Change of the creatinine clearance (CrCL) to a minimum level of ≥ 30 mL/min (Cockcroft-Gault) *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 27	Inclusion Criterion 5: Change of the creatinine clearance (CrCL) to a minimum level of ≥ 30 mL/min (Cockcroft-Gault) *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 28	Exclusion Criterion 20: Change of the Renal insufficiency to a maximum value below 30 mL/min CrCL (Cockcroft-Gault) *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 33	Overdose instructions: Addition of the specific antidote (Praxbind®, idarucizumab) to Dabigatran *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 42	Assessment of renal function: Change of the Renal insufficiency to a maximum value below 30 mL/min CrCL (Cockcroft-Gault) *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 42	Assessment of renal function: Change of the wording from "moderate renal impairment" to "severe renal impairment" *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 49	Major Bleedings: Addition of the specific antidote (Praxbind®, idarucizumab) to Dabigatran *Reason*: To align content with the *Fachinformation* of Pradaxa®
		Pg 62	Signatures: Changes in personnel *Reason*: Due to formal reasons

Amendment 4: Protocol Version 1.6 dated 20.10.2016

Version	Date	Page	Amendments / Changes from previous version
1.6	20.10.2016	Pg 6	Study Phase: Change of the phase of the study. *Reason*: Due to formal correction
		Pg 26	Trial design: Change of the phase of the study. *Reason*: Due to formal correction
		Pg 60	Financing of the trial: Change of the phase of the study. *Reason*: Due to formal correction

Amendment 5: Protocol Version 1.7 dated 19.06.2017 (Last Version)

Version	Date	Page	Amendments / Changes from previous version
1.7	19.06.2017	Pg 2	Changes in personnel data Reason: Due to actualisation
		Pg 30	Ingredients of Dabigatran capsule: Change of the ingredient list of Dabigatran capsule. *Reason*: To align content with the Fachinformation of Pradaxa®

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EudraCT-Nr.: 2013-005364-26

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

1	Universitätsmedizin Mainz	Univ.-Prof. Dr. med. Thomas Rostock
2	Universitäres Herzzentrum Hamburg GmbH	Univ.-Prof. Dr. med. Stephan Willems
3	Medizinische Hochschule Hannover	Prof. Dr. med. Christian Veltmann
4	Herzzentrum Uniklinik Köln	Univ.-Prof. Dr. med. Daniel Steven
5	Universitätsherzzentrum Freiburg / Bad Krozingen	Prof. Dr. med. Thomas Arentz
6	Vivantes Klinikum Berlin Am Urban	Prof. Dr. med. Hüseyin Ince
8	St. Vincenz-Krankenhaus GmbH Paderborn	Univ.-Prof. Dr. med. Andreas Götte
9	Universitätsmedizin Dresden	PD Dr. med. Christopher Piorkowski
10	Universitätsmedizin Rostock	Univ.-Prof. Dr. med. Dietmar Bänsch
12	Klinikum Coburg GmbH	Prof. Dr. med. Johannes Brachmann
13	Charité Universitätsmedizin Berlin	Prof. Dr. med. Fabian Knebel
15	Universitätsmedizin Leipzig	Dr. med. Martin Neef

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

1: Universitätsmedizin Mainz, Zentrum für Kardiologie, Kardiologie II, Langenbeckstraße 1, 55131 Mainz

2: Universitäres Herzzentrum Hamburg GmbH, Klinik für Kardiologie mit Schwerpunkt Elektrophysiologie, Martinistraße 52, 20246 Hamburg

3. Medizinische Hochschule Hannover, Klinik für Kardiologie und Angiologie, Carl-Neuberg-Straße 1, 30625 Hannover

4: Herzzentrum Uniklinik Köln, Klinik für Kardiologie, Kerpener Straße 62, 50937 Köln

5: Universitätsherzzentrum Freiburg / Bad Krozingen, Klinik für Kardiologie und Angiologie II, Südring 15, 79189 Bad Krozingen

6: Vivantes Klinikum Berlin Am Urban, Allgemeine Innere Medizin und konservative Intensivmedizin, Klinik für Kardiologie, Dieffenbachstraße 1, 10967 Berlin

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10: Universitätsmedizin Rostock, Klinik und Poliklinik für Innere Medizin I, Schillingallee 35, 18055 Rostock

12: Klinikum Coburg GmbH, II. Medizinische Klinik, Ketschendorfer Straße 33, 96450 Coburg

13: Charité Universitätsmedizin Berlin, Medizinische Klinik m.S. Kardiologie und Angiologie, CC11, Campus Charité Mitte, Charité Platz 1, 10117 Berlin

14: (Center did not sign a contract and did not participate in the study.)

15: Universitätsmedizin Leipzig, Abteilung für Kardiologie und Angiologie, Liebigstraße 20, 04103 Leipzig

8) **Publication (reference):**

Rationale and design of the RE-LATED AF--AFNET 7 trial: REsolution of Left atrial-Appendage Thrombus--Effects of Dabigatran in patients with Atrial Fibrillation; Ferner M. et al.; Clin Res Cardiol. 2016 Jan; 105(1):29-36.

9) **Studied period (years)[3]:**

Date of first enrolment: 10.09.2014

Date of last completed: 24.04.2018

On 17.05.2018 the sponsor notified the temporary halt of the trial.

On 04.06.2018 the sponsor notified the prematurely termination of the trial due to

10) **Phase of development:** Phase II

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

recruiting problems.	

11) **Objectives:**

Primary objective:
To assess whether Dabigatran leads to a faster complete LAA thrombus resolution as compared to Phenprocoumon.

Secondary objectives:
To assess the impact of Dabigatran on
- complete LAA thrombus resolution rate until week 6
- change in LAA thrombus size under treatment
To assess and compare safety and tolerability of Dabigatran and Phenprocoumon

12) **Methodology:**

Prospective, multicenter, randomized, open-label, controlled, explorative, blinded-endpoint (PROBE) trial.

Randomization in a 1:1 ratio (Dabigatran etexilate : Phenprocoumon)

After inclusion of the patients with LAA thrombus, they are treated according to the randomization either with Pradaxa® (150 mg bid) or Marcumar® (INR 2-3) for at least three weeks.
Thrombus resolution will be determined by transesophageal echocardiography (TEE) 3 weeks after start of treatment and subsequently at week 4 and 6 if necessary, i.e. LAA thrombus has not yet resolved.
The study is terminated for each patient with the resolution of the LAA thrombus. For those patients whose thrombus still exists after 6 weeks treatment, the study is also terminated. Further treatments will be decided at the discretion of the treating physician.
All patients, including withdrawals, will be invited to a telephone follow-up 1 week after their last treatment.

The images of the TEE examinations are sent to one out of the two randomly assigned core laboratories, which asses' whether a LAA thrombus is visible on the TEE images or not. It was ensured that the core laboratories are kept blinded concerning study treatment (rater-blinding study), thus a blinded assessment of the primary outcome was warranted.

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

It was planned to randomize 110 patients.
64 patients were randomized (plus. 1 void randomization).
64 patients were analyzed
39 patients were analyzed mITT
62 patients were analyzed for safety

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

Diagnosis: Left atrial-appendage thrombus in atrial fibrillation

Main criteria for inclusion:
- Patients with documented non-valvular AF or atrial flutter (12-lead ECG)
- Newly diagnosed or confirmed LAA thrombus in TEE (time of detection ≤ 28 days)
- Patients > 18 years old
- CHA_2DS_2-VASc Score ≥ 1
- CrCL > 30 mL/min (Cockcroft-Gault)
- Women with childbearing potential have to practice a medically accepted contraception
- Ability of patient to understand the character and the individual consequences of the clinical trial
- Signed and dated informed consent before start of any specific trial procedures

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

Dabigatran etexilate (Investigational drug)

Drug code:	*TC: B01AE07*	
International nonproprietary name (INN):	*Dabigatran etexilate mesylate*	
Registered trade name	*Pradaxa®*	
Formulation:	*Capsule*	
Manufacturer:	*Boehringer Ingelheim Pharma GmbH & Co. KG*	
Dosage authorized:	*150 mg (bid)*	
Mode of administration in the trial:	*oral, 150 mg bid according to label*	
Batch number:	***Charge***	***Protocol-No.***
	402738	*S2014/131*
	402738	*S2014/148*
	402738	*S2014/168*

402738	*S2014/169*
402738	*S2014/262*
402738	*S2015/065*
404510	*S2015/096*
404510	*S2016/089*
404510	*S2016/312*
606012	*S2016/326*
606012	*S2017/067*
606012	*S2017/098*

16) **Duration of treatment:**

Minimal duration of treatment: 3 weeks (depending on persistence of LAA-thrombus)
Maximal duration of treatment: 6 weeks (depending on persistence of LAA-thrombus)

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

Phenprocoumon (Comparator)

Drug code:	*ATC: B01AA04*
International nonproprietary name (INN):	*Phenprocoumon*
Registered trade name	*Marcumar®*
Formulation:	*Tablet*
Manufacturer:	*MEDA Pharma GmbH & Co. KG*
Dosage authorized:	*depending on indication (INR = 2 – 3.5), one tablet contains 3 mg*
Mode of administration in the trial:	*oral, (INR 2-3) according to label*

Batch number:

Charge	***Protocol-No.***
G0H099A	*S2014/097*
G0H099A	*S2014/111*
G0H099A	*S2014/170*
G0H099A	*S2014/263*
GPE069A	*S2015/065*
GPLA017A	*S2015/511*
GPE069A	*S2015/064*
GQI0528	*S2016/090*
GRI054B	*S2017/110*
GSA085C	*S2017/124*

18) **Criteria for evaluation[4]:**

Efficacy:
- Time to complete LAA thrombus resolution. LAA thrombus existence and resolution have to be confirmed by the core laboratory.
- Complete LAA thrombus resolution until week 6 (yes/no)
- Change in LAA thrombus size under treatment

Safety:
- Adverse Events
  - Occurrence of any adverse event
  - Occurrence of major bleedings
  - Occurrence of strokes (all-type, haemorrhagic, ischemic) ascertained by CCT or cMRT
  - Occurrence of TIAs
  - Occurrence of cardiovascular events requiring hospitalization (e.g. myocardial infarction, acute coronary syndrome, severe tachyarrhythmia)
  - Occurrence of other thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism)
- Vital Signs
- Laboratory values

19) **Statistical methods:**

Primary analysis:

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

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The time to complete LAA thrombus resolution is compared using the two-sided log-rank test at a significance level of 5%. The analysis is based on the modified intention-to-treat population which includes all randomized patients except for those for whom LAA thrombus existence is not confirmed by the core laboratory. In addition, Kaplan-Meier curves are presented for both groups.

Secondary analyses:
Complete LAA thrombus resolution rates until week 6 are calculated and compared between treatment groups by an explorative two-sided Chi square test. The analysis of the change in LAA thrombus size under treatment is skipped due to invalid calculation model for the LAA thrombus volume.

Frequencies of patients experiencing at least one adverse event (AE) are displayed by body system and preferred term according to MedDRA terminology. All other secondary endpoints are analyzed by absolute and relative frequencies for each treatment arm.

20) **Summary – Conclusions[5]:**

From the 64 patients 31 patients were randomized to the Pradaxa® treatment group and 33 were randomized to the Marcumar® treatment group.

Demographics:
In the demographics there were no treatment group differences apparent. The mean age was 64.43 (±10.19) years in the Pradaxa® treatment group and 64.28 (±7.99) years in the Marcumar® treatment group. There were 8 females (26.7%) with Pradaxa® treatment and 10 females (34.4%) with Marcumar® treatment.

CHA_2DS_2-VASc Score:
The CHA_2DS_2-VASc is a score assessing the risk for atrial fibrillation stroke. The score ranges from 0 to 9. Higher scores indicating a higher risk. According to the inclusion criteria patients had to have CHA_2DS_2-VASc Score of greater than or equal to 1 representing an at least low to moderate risk where antiplatelet or anticoagulation should be considered. The average maximum CHA_2DS_2-VASc Score amounted to 2.80 (±1.45) in the Pradaxa® treatment group and 2.63 (±1.21) years in the Marcumar® treatment group.

NYHA:
The NYHA classification classifies the extent of heart failure. It classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain. In the Pradaxa® treatment group 6 patients (20.0%) had no limitation (NYHA Class I), 12 patients (40.0%) had slight limitations at normal physical activity (NYHA Class II) and 12 patients (40.0%) had a walking distance of more than 200 m, but no dyspnea at rest (NYHA Class III). In the Marcumar® treatment group 4 patients (12.5%) had no limitation (NYHA Class I), 16 patients (50.0%) had slight limitations at normal physical activity (NYHA Class II) and 12 patients (37.5%) had a walking distance of more than 200 m, but no dyspnea at rest (NYHA Class III).

Concomitant medication:
The following table 1 displays the subjects taking any concomitant medication at an ATC level 2. ATC levels of medications taken only by 1 patient were omitted in the table for easier overview. The most frequent drug classes belonged to the cardiac system (diuretics, beta blocking agents, agents acting on the renin angiotensin system, antithrombotic agents, cardiac therapy, lipid modifying agents) followed by drugs used in diabetes and drugs for acid related disorders.

Table 1: Concomitant medications by ATC level 2

	Number (%) of Subjects / Events					
	Pradaxa®		Marcumar®		Total	
ATC level 2	(N=30)	(nCM=177)	(N=32)	(nCM=217)	(N=62)	(nCM=394)
Subjects with any concomitant medication	30 (100%)	177 (100%)	32 (100%)	217 (100%)	62 (100%)	394 (100%)
Diuretics	21 (70.00%)	35 (19.77%)	22 (68.75%)	42 (19.35%)	43 (69.35%)	77 (19.54%)
Beta Blocking Agents	28 (93.33%)	28 (15.82%)	30 (93.75%)	35 (16.13%)	58 (93.55%)	63 (15.99%)
Agents Acting On The Renin-Angiotensin System	25 (83.33%)	25 (14.12%)	26 (81.25%)	28 (12.90%)	51 (82.26%)	53 (13.45%)

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

Antithrombotic Agents	4 (13.33%)	7 (3.95%)	19 (59.38%)	30 (13.82%)	23 (37.10%)	37 (9.39%)
Cardiac Therapy	9 (30.00%)	13 (7.34%)	11 (34.38%)	14 (6.45%)	20 (32.26%)	27 (6.85%)
Lipid Modifying Agents	10 (33.33%)	10 (5.65%)	14 (43.75%)	14 (6.45%)	24 (38.71%)	24 (6.09%)
Drugs Used In Diabetes	6 (20.00%)	10 (5.65%)	4 (12.50%)	8 (3.69%)	10 (16.13%)	18 (4.57%)
Drugs For Acid Related Disorders	7 (23.33%)	7 (3.95%)	8 (25.00%)	8 (3.69%)	15 (24.19%)	15 (3.81%)
Calcium Channel Blockers	7 (23.33%)	7 (3.95%)	7 (21.88%)	7 (3.23%)	14 (22.58%)	14 (3.55%)
Drugs For Obstructive Airway Diseases	4 (13.33%)	6 (3.39%)	1 (3.13%)	2 (0.92%)	5 (8.06%)	8 (2.03%)
Thyroid Therapy	5 (16.67%)	5 (2.82%)	3 (9.38%)	3 (1.38%)	8 (12.90%)	8 (2.03%)
Antigout Preparations	4 (13.33%)	4 (2.26%)	3 (9.38%)	3 (1.38%)	7 (11.29%)	7 (1.78%)
Psychoanaleptics	4 (13.33%)	5 (2.82%)	2 (6.25%)	2 (0.92%)	6 (9.68%)	7 (1.78%)
Mineral Supplements	3 (10.00%)	3 (1.69%)	3 (9.38%)	3 (1.38%)	6 (9.68%)	6 (1.52%)
Antibacterials For Systemic Use	3 (10.00%)	3 (1.69%)	1 (3.13%)	2 (0.92%)	4 (6.45%)	5 (1.27%)
Antihemorrhagics	0 (0.00%)	0 (0.00%)	2 (6.25%)	3 (1.38%)	2 (3.23%)	3 (0.76%)
Endocrine Therapy	2 (6.67%)	2 (1.13%)	1 (3.13%)	1 (0.46%)	3 (4.84%)	3 (0.76%)
Analgesics	1 (3.33%)	1 (0.56%)	1 (3.13%)	1 (0.46%)	2 (3.23%)	2 (0.51%)
Anti-Parkinson Drugs	1 (3.33%)	1 (0.56%)	1 (3.13%)	1 (0.46%)	2 (3.23%)	2 (0.51%)
Corticosteroids For Systemic Use	1 (3.33%)	1 (0.56%)	1 (3.13%)	1 (0.46%)	2 (3.23%)	2 (0.51%)
Psycholeptics	1 (3.33%)	1 (0.56%)	1 (3.13%)	1 (0.46%)	2 (3.23%)	2 (0.51%)
Urologicals	1 (3.33%)	1 (0.56%)	1 (3.13%)	1 (0.46%)	2 (3.23%)	2 (0.51%)

Concomitant diseases

The following table 2 displays the concomitant diseases by system organ class. The most frequently affected system organ class was cardiac disorder followed by vascular disorders and metabolism and nutrition disorders.

Table 2: Concomitant diseases by system organ class

	Number (%) of Subjects / Events					
	Pradaxa®		Marcumar®		Total	
System Organ Class	**(N=30)**	**(nMH=34)**	**(N=32)**	**(nMH=52)**	**(N=62)**	**(nMH=86)**
Subjects with any previous diseases	12 (40.00%)	34 (100%)	17 (53.13%)	52 (100%)	29 (46.77%)	86 (100%)
Cardiac disorders	3 (10.00%)	6 (17.65%)	8 (25.00%)	14 (26.92%)	11 (17.74%)	20 (23.26%)
Vascular disorders	6 (20.00%)	6 (17.65%)	7 (21.88%)	7 (13.46%)	13 (20.97%)	13 (15.12%)
Metabolism and nutrition disorders	2 (6.67%)	3 (8.82%)	7 (21.88%)	8 (15.38%)	9 (14.52%)	11 (12.79%)
Nervous system disorders	2 (6.67%)	2 (5.88%)	4 (12.50%)	6 (11.54%)	6 (9.68%)	8 (9.30%)
Respiratory, thoracic and mediastinal disorders	2 (6.67%)	4 (11.76%)	2 (6.25%)	3 (5.77%)	4 (6.45%)	7 (8.14%)
Surgical and medical procedures	3 (10.00%)	3 (8.82%)	3 (9.38%)	4 (7.69%)	6 (9.68%)	7 (8.14%)
Gastrointestinal disorders	4 (13.33%)	4 (11.76%)	2 (6.25%)	2 (3.85%)	6 (9.68%)	6 (6.98%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (10.00%)	3 (8.82%)	2 (6.25%)	2 (3.85%)	5 (8.06%)	5 (5.81%)

Endocrine disorders	1 (3.33%)	1 (2.94%)	1 (3.13%)	1 (1.92%)	2 (3.23%)	2 (2.33%)
Infections and infestations	1 (3.33%)	1 (2.94%)	1 (3.13%)	1 (1.92%)	2 (3.23%)	2 (2.33%)
Renal and urinary disorders	0 (0.00%)	0 (0.00%)	2 (6.25%)	2 (3.85%)	2 (3.23%)	2 (2.33%)
General disorders and administration site conditions	0 (0.00%)	0 (0.00%)	1 (3.13%)	1 (1.92%)	1 (1.61%)	1 (1.16%)
Immune system disorders	1 (3.33%)	1 (2.94%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (1.16%)
Psychiatric disorders	0 (0.00%)	0 (0.00%)	1 (3.13%)	1 (1.92%)	1 (1.61%)	1 (1.16%)

Extent of Exposure:

The mean number of days in the study was 31.33 (±10.60) days in the Pradaxa® treatment group and 28.63 (±11.68) days in the Marcumar® treatment group. The average sum of capsules taken during the study were 58.96 (±23.49) in the Pradaxa® treatment group and 27.47 (±13.39) tablets in the Marcumar® treatment group. The average number of capsules taken per day during the study were 1.77 (±0.39) in the Pradaxa® treatment group and 0.94 (±0.37) tablets per day in the Marcumar® treatment group.

Efficacy results:

Primary Endpoint:
The Time to LAA Thrombus resolution (days) was analyzed by Kaplan-Meier estimates and a log-rank test for comparing treatment groups. Additionally there was a Cox-regression analysis performed to adjust for the possible confounding factors gender and age and to yield hazard ratios. 39 complete TEE profiles were available 18 from the Pradaxa® treatment group and 21 TEE profiles from the Marcumar® treatment group. The median time to thrombus resolution was 42 days [95% CI 23-65] in the Pradaxa® treatment group and 24 days [95% CI 23-n.a.] in the Marcumar® treatment group. There was no statistically significant difference between treatment groups (p=0.4034). The Cox regression model mirrored the result for the treatment difference (p=0.5724). The effects for gender (p=0.5724), age (p=0.5670) and BMI (p=0.0990) were also not statistically significant.

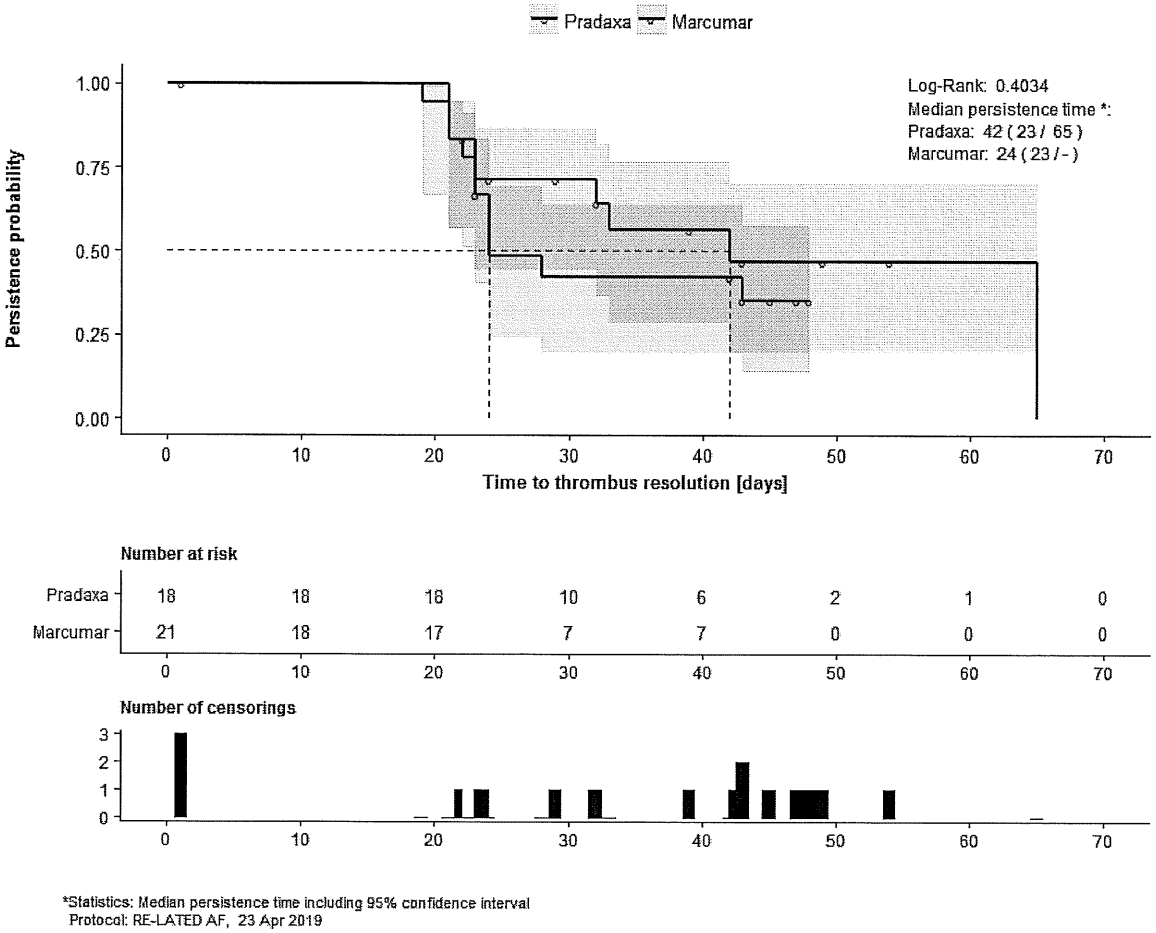
Report Synopsis of Study : Resolution of Left Atrial-Appendage Thrombus – Effects of Dabigatran in patients with AF (RE-LATED AF) – A Prospective, multicenter, randomized, open-label, controlled, explorative, blinded-endpoint (PROBE) trial to compare the efficacy of Dabigatran (150 mg bid) with Phenprocoumon for the resolution of left atrial appendage thrombus formation in patients with atrial fibrillation

EudraCT-Nr.: 2013-005364-26

Vorlage-Nr.: 4039811

Graph 1: Primary Analysis: Time to LAA Thrombus Resolution [Days]

Analysis Set = mITT Population (N=39)



*Statistics: Median persistence time including 95% confidence interval
Protocol: RE-LATED AF, 23 Apr 2019

Secondary efficacy endpoints:

Complete LAA thrombus resolution until week 6:
The secondary efficacy endpoint was the thrombus resolution at visit 4 (after 6 week treatment). In the Pradaxa® treatment group 18 patients had a confirmed (by Core Laboratory) presence of an LAA thrombus at visit 1, for 9 of them a complete LAA thrombus resolution was confirmed at week 6. In the Marcumar® treatment group 21 patients had a confirmed (by Core Laboratory) presence of an LAA thrombus at visit 1, for 11 of them a complete LAA thrombus resolution was confirmed at week 6. However, the difference between treatment groups was not statistically significant (p=0.8821).

In the Pradaxa® treatment group 18 patients had a confirmed (by Core Laboratory) presence of an LAA thrombus at visit 1. Thrombus resolutions in 5 patients at visit 2, in three patients at visit 3 and an additional 1 patient at visit 4 with a thrombus resolution (9 resolutions overall). In the Marcumar® treatment group 21 patients had a confirmed presence of an LAA thrombus. Thrombus resolutions in 9 patients at visit 2, in one patient at visit 3 and an additional patient at visit 4 with a thrombus resolution (11 resolutions overall). There were no statistically treatment group differences at any visit.

Change in LAA thrombus size under treatment: The analysis of the change in LAA thrombus size under treatment was skipped due to invalid calculation model for the LAA thrombus volume. This means in case of LAA thrombus movements the cutting planes could not be adhered to. A change in cutting planes would have led to incomparable measurement results.

Safety results:

Secondary safety endpoints

Occurrence of any adverse event:

All AEs were documented on the appropriate pages of the eCRF and coded with the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. The relatedness between each event and the intake of study medication was judged by the investigators according to modified WHO criteria. AEs assessed with "certain", "probable" or "possible" causal relationship to study medication were graded as adverse reactions, AEs assessed as "unlikely" or "not related" were considered as not related to study medication. Seriousness was defined according to the Seriousness Criteria of Good Clinical Practice Guideline (GCP).

35.48% of all patients reported at least one AE while under study medication. A total of 39 AEs were reported (0.63 per pat.). Thereof, 12 AEs (30.77%, 0.40 per pat.) occurred in the Pradaxa® treatment group and 27 AEs (69.23%, 0.84 per pat.) occurred in the Marcumar® treatment group. The following table shows an overview of the reported AEs.

Table 3: Overview of reported AEs

	Pradaxa®		Marcumar®		Total	
Patients with	**Patients (N=30)**	**AEs (nAE=12)**	**Patients (N=32)**	**AEs (nAE=27)**	**Patients (N=62)**	**AEs (nAE=39)**
at least one AE	9 (30.00%)	12 (100%)	13 (40.63%)	27 (100%)	22 (35.48%)	39 (100%)
at least one related AE	3 (10.00%)	4 (33.33%)	4 (12.50%)	7 (25.93%)	7 (11.29%)	11 (28.21%)
at least one serious AE	4 (13.33%)	4 (33.33%)	6 (18.75%)	6 (22.22%)	10 (16.13%)	10 (25.64%)
at least one related serious AE	1 (3.33%)	1 (8.33%)	1 (3.13%)	1 (3.70%)	2 (3.23%)	2 (5.13%)

Occurrence of major bleedings:
One major bleeding was reported. Patient 05011 in the Pradaxa® treatment group: A The event "Bleeding after removal of pericardial drainage" (6 days after removal) was regarded as major bleeding, because it met the protocol definition of a bleeding leading to transfusion of two or more units of whole blood or red cells. Treatment with Pradaxa® was discontinued and the patient received 2 units of blood transfusions (erythrocyte concentrates). The outcome of this bleeding event was "recovered".

Occurrence of strokes (all-type, haemorrhagic, ischemic) ascertained by CCT or cMRT:
No event belonging to this category was reported .

Occurrence of TIAs:
No TIA was reported.

Occurrence of cardiovascular events requiring hospitalization (e.g. myocardial infarction, acute coronary syndrome, severe tachyarrhythmia):
Seven cardiovascular events requiring hospitalization were reported:

Pradaxa® treatment group:
Patient 01011 was hospitalized due to ventricular tachycardia (PT: ventricular tachycardia).
Patient 13002 was hospitalized due to brady-tachy-syndrome (PT: sinus node dysfunction).

Marcumar® treatment group:
Patient 03007 was hospitalized due to arterial hypotension (PT: hypotension).
Patient 01003 was hospitalized due to hypertensive crisis (PT: hypertensive crisis).
Patient 10001 was hospitalized due to LAD stenosis (PT: coronary artery stenosis).
Patient 01006 was hospitalized due to acute decompensation of heart failure (PT: cardiac failure acute).
Patient 03019 was hospitalized due to cardiac insufficiency (PT: cardiac failure) before first intake of study medication.

Occurrence of other thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism):
No thromboembolic events were reported.

Further information on Safety Results:

The following table shows the number of AEs allocated to MedDRA system organ classes (SOCs) and treatment group.

Table 4: AEs allocated to MedDRA system organ classes (SOCs)

	Pradaxa®		Marcumar®		Total	
System Organ Class	**Patients (N=30)**	**AEs (nAE=12)**	**Patients (N=32)**	**AEs (nAE=27)**	**Patients (N=62)**	**AEs (nAE=39)**
Investigations	0 (0.00%)	0 (0.00%)	4 (12.50%)	9 (33.33%)	4 (6.45%)	9 (23.08%)
Gastrointestinal disorders	3 (10.00%)	4 (33.33%)	2 (6.25%)	3 (11.11%)	5 (8.06%)	7 (17.95%)
Cardiac disorders	2 (6.67%)	2 (16.67%)	3 (9.38%)	3 (11.11%)	5 (8.06%)	5 (12.82%)
Infections and infestations	2 (6.67%)	2 (16.67%)	2 (6.25%)	2 (7.41%)	4 (6.45%)	4 (10.26%)
Renal and urinary disorders	1 (3.33%)	1 (8.33%)	2 (6.25%)	2 (7.41%)	3 (4.84%)	3 (7.69%)
Vascular disorders	0 (0.00%)	0 (0.00%)	2 (6.25%)	3 (11.11%)	2 (3.23%)	3 (7.69%)
Respiratory, thoracic and mediastinal disorders	0 (0.00%)	0 (0.00%)	2 (6.25%)	2 (7.41%)	2 (3.23%)	2 (5.13%)
General disorders and administration site conditions	1 (3.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (2.56%)
Hepatobiliary disorders	0 (0.00%)	0 (0.00%)	1 (3.13%)	1 (3.70%)	1 (1.61%)	1 (2.56%)
Injury, poisoning and procedural complications	1 (3.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (2.56%)
Metabolism and nutrition disorders	0 (0.00%)	0 (0.00%)	1 (3.13%)	1 (3.70%)	1 (1.61%)	1 (2.56%)
Reproductive system and breast disorders	1 (3.33%)	1 (8.33%)	0 (0.00%)	0 (0.00%)	1 (1.61%)	1 (2.56%)
Skin and subcutaneous tissue disorders	0 (0.00%)	0 (0.00%)	1 (3.13%)	1 (3.70%)	1 (1.61%)	1 (2.56%)

Adverse Events considered as related to study medication (ADRs):

In 11 (28.21%, 0.18 per pat.) of all AEs at least a possible causal relationship was assessed between the occurrence of the AE and the intake of study medication. 4 (36.36%, 0.13 per pat.) of these adverse drug reactions (ADRs) occurred in the Pradaxa® treatment group and 7 (63.64%, 0.22 per pat.) in the Marcumar® treatment group.

The MedDRA system organ classes (SOCs) in which the ADRs in the Pradaxa® treatment group occurred were "gastrointestinal disorders" (3 ADRs in 2 (6.67%) patients) and "injury, poisoning and procedural complications" (1 ADR in 1 (3.33%) patient). The following ADRs occurred (MedDRA preferred terms (PTs)): "epigastric discomfort" (1 ADR in 1 patient), "mouth haemorrhage" (1 ADR in 1 patient), "nausea" (1 ADR in 1 patient) and "post procedural haemorrhage" (1 ADR in 1 patient).

The MedDRA system organ classes (SOCs) in which the ADRs in the Marcumar® treatment group occurred were "investigations" (5 ADRs in 3 (9.38%) patients) and "gastrointestinal disorders" (2 ADRs in 1 (3.13%) patient). The following ADRs occurred (MedDRA preferred terms (PTs)): "international normalised ratio abnormal" (4 ADRs in 2 patients), "international normalised ratio increased" (1 ADR in 1 patient), "haemorrhoids" (1 ADR in 1 patient) and "rectal haemorrhage" (1 ADR in 1 patient).

Severity of Adverse Events:

18 (46.15%) of all AEs were judged as mild, 19 (48.72%) as moderate and 2 (5.13%) as severe. 1 (50.00%, 0.03 per pat.) of the 2 severe AEs occurred in the Pradaxa® treatment group and 1 (50.00%, 0.03 per pat.) in the Marcumar® treatment group. None of the severe AEs was assessed as related to study medication.

Seriousness of Adverse Events:

In summary, 10 (25.64%, 0.16 per pat.) AEs were judged as serious according to the definition in the study protocol and 2 (5.13%, 0.03 per pat.) AEs were judged as serious and related (SAR) to the study medication. None of these 2 SARs was assessed as unexpected by the sponsor and therefore no suspected unexpected serious adverse reaction (SUSAR) had to be reported to the competent authority, ethics committee and all investigators. 4 (40.00%, 0.13 per pat.) of the 10 total SAEs occurred in the Pradaxa® treatment group and 6 (60.00%, 0.19 per pat.) in the Marcumar® treatment group. In addition, one SAE with MedDRA preferred term (PT) "cardiac failure" occurred before the first intake of study medication in the Marcumar® treatment group.

The MedDRA system organ class (SOC) with most SAEs was cardiac disorders (4 SAEs). All SAEs (MedDRA preferred terms (PTs)) were reported only once: "cardiac failure acute", "coronary artery stenosis", "sinus node dysfunction", "ventricular tachycardia", "urosepsis", "post procedural haemorrhage" (SAR in the Pradaxa® treatment group), "international normalised ratio increased" (SAR in the Marcumar® treatment group), "renal failure", "hypertensive crisis" and "hypotension". The following table shows the number of SAEs allocated to MedDRA system organ classes (SOCs) and treatment group.

Table 5: SAEs allocated to MedDRA system organ classes (SOCs)

	Pradaxa®		**Marcumar®**		**Total**	
System Organ Class	**SAEs (N=4)**	**Related SAEs (N=1)**	**SAEs (N=6)**	**Related SAEs (N=1)**	**SAEs (N=10)**	**Related SAEs (N=2)**
Cardiac disorders	2 (50.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	4 (40.00%)	0 (0.00%)
Infections and infestations	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	1 (10.00%)	0 (0.00%)
Injury, poisoning and procedural complications	1 (25.00%)	1 (100%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	1 (50.00%)
Investigations	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (100%)	1 (10.00%)	1 (50.00%)
Renal and urinary disorders	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (10.00%)	0 (0.00%)
Vascular disorders	0 (0.00%)	0 (0.00%)	2 (33.33%)	0 (0.00%)	2 (20.00%)	0 (0.00%)

Deaths:

In this clinical trial no SAE with fatal outcome was reported.

Summary concerning safety:

In summary, in this clinical trial only 0.63 (0.03 severe) adverse events (AEs) per patient, 0.16 serious adverse events (SAEs) per patient and 0.03 serious adverse drug reactions (SARs) per patient were reported to the sponsor.

There were more adverse events in the Marcumar® treatment group (0.84 per pat.) than in the Pradaxa® treatment group (0.40 per pat.), especially in the system organ class "investigations" (9 AEs in the Marcumar® treatment group, no AE in the Pradaxa® treatment group). In all other system organ classes there seemed to be no obvious treatment group differences.

In addition, frequency of SAEs in the Marcumar® treatment group (0.19 per pat.) was higher than in the Pradaxa® treatment group (0.13 per pat.). There was no difference in the frequency of SARs in the Marcumar® and Pradaxa® treatment group.

Vital signs:

Vital signs were collected at screening and at the visits 2, 3, and 4. Only body temperature at visit 3 differed between treatment groups. However, this seems to be a random finding.

Table 6: Vital Signs

Variable/ Visit		Pradaxa® (N=30)	Marcumar® (N=32)	Total (N=62)	P (t-Test)
Systolic blood pressure [mmHg]					
Visit 1 (Screening)	Mean (SD)	127.87 (15.76)	134.28 (18.21)	131.18 (17.23)	0.1426
Visit 2	Mean (SD)	133.33 (27.08)	127.43 (20.93)	130.33 (24.11)	0.3713
Visit 3	Mean (SD)	132.50 (16.49)	134.80 (26.61)	133.55 (21.15)	0.8153
Visit 4	Mean (SD)	128.70 (22.25)	137.75 (22.12)	133.64 (22.13)	0.3527
Diastolic blood pressure [mmHg]					
Visit 1 (Screening)	Mean (SD)	79.70 (10.65)	81.91 (10.19)	80.84 (10.39)	0.4085
Visit 2	Mean (SD)	84.22 (13.89)	84.89 (13.29)	84.56 (13.46)	0.8556
Visit 3	Mean (SD)	89.25 (17.34)	81.90 (14.14)	85.91 (16.04)	0.2864
Visit 4	Mean (SD)	83.60 (13.25)	87.92 (17.18)	85.95 (15.32)	0.5137
Pulse [bpm]					
Visit 1 (Screening)	Mean (SD)	93.90 (27.71)	93.50 (28.95)	93.69 (28.12)	0.9559
Visit 2	Mean (SD)	85.15 (21.69)	86.07 (22.08)	85.62 (21.69)	0.8763
Visit 3	Mean (SD)	82.33 (21.94)	89.90 (15.54)	85.77 (19.25)	0.3567
Visit 4	Mean (SD)	76.30 (15.87)	83.50 (13.38)	80.23 (14.67)	0.2708
Body temperature [°C]					
Visit 1 (Screening)	Mean (SD)	36.29 (0.38)	36.49 (0.42)	36.39 (0.41)	0.0794
Visit 2	Mean (SD)	36.13 (0.38)	36.41 (0.39)	36.26 (0.41)	0.0218
Visit 3	Mean (SD)	36.16 (0.36)	36.34 (0.28)	36.24 (0.33)	0.2539
Visit 4	Mean (SD)	36.16 (0.36)	36.34 (0.28)	36.24 (0.33)	0.2539

Laboratory values:

The following laboratory values were collected: Hemoglobin, Hematocrit, Red Blood Count, Platelets, White Blood Count, INR, aPTT, Fibrinogen, Antithrombin III, total protein, glucose, alkaline phosphatase, uric acid, urea, creatinine, AST, ALT, GGT, Sodium, Potassium, Alpha amylase, Bilirubin, Creatinine Clearance.

There were occasional statistical significant differences between the treatment groups at single visits. However, they could be classified as irrelevant. The following table shows the INR and the AST values during the course of the study which seem to be the most interesting laboratory parameters. The INR differences might be caused by additional heparin intake during the switch from other anticoagulants to Marcumar® in the Marcumar® treatment group.

Report Synopsis of Study : Resolution of Left Atrial-Appendage Thrombus – Effects of Dabigatran in patients with AF (RE-LATED AF) – A Prospective, multicenter, randomized, open-label, controlled, explorative, blinded-endpoint (PROBE) trial to compare the efficacy of Dabigatran (150 mg bid) with Phenprocoumon for the resolution of left atrial appendage thrombus formation in patients with atrial fibrillation

EudraCT-Nr.: 2013-005364-26

Vorlage-Nr.: 4039811

Table 7: Selected courses of laboratory values

Variable/ Visit		Pradaxa® (N=30)	Marcumar® (N=32)	Total (N=62)	P (t-Test)
INR					
Visit 1 (Screening)	Mean (SD)	1.37 (0.49)	1.33 (0.52)	1.35 (0.50)	0.7926
Visit 2	Mean (SD)	1.27 (0.16)	3.04 (1.44)	2.19 (1.37)	<.0001
Visit 3	Mean (SD)	1.17 (0.13)	2.49 (0.51)	1.86 (0.77)	<.0001
Visit 4	Mean (SD)	1.22 (0.16)	2.81 (0.73)	2.09 (0.97)	<.0001
ALT					
Visit 1 (Screening)	Mean (SD)	34.73 (15.35)	47.22 (27.83)	41.21 (23.35)	0.0454
Visit 2	Mean (SD)	32.13 (17.97)	40.72 (12.61)	36.60 (15.85)	0.0646
Visit 3	Mean (SD)	26.11 (11.45)	44.14 (13.33)	34.59 (15.14)	0.0101
Visit 4	Mean (SD)	33.33 (8.66)	34.20 (11.72)	33.77 (10.01)	0.8608

Conclusion:

In the RE-LATED AF study, the desired number of patients could not be included, even though the patient enrolment period was extended and modifications of in- and exclusion criteria were amended to facilitate patient enrollment. This limitation was driven by the finding that the majority of screened patients met one or more exclusion criteria or could not comply with all inclusion criteria, which therefore reflects the significant co-morbidity of patients suffering from a LAA thrombus.

In the study cohort, no significant differences were observed in the number of and time to LAA thrombus resolution between patients randomized to the Pradaxa® or Marcumar® arm. However, there were more adverse events in the Marcumar® group as compared to patients treated with Pradaxa®.

No significant treatment difference in the Pradaxa® and Marcumar® group were apparent. Thus, Pradaxa® seems to be not worse than Marcumar® in respect of the efficacy of LAA thrombus resolution.

Referring to the occurrence of adverse events Pradaxa® shows a slightly favorable safety profile compared to Marcumar®.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** 08.06.2020

Print Name: Univ.-Prof. Dr. Thomas Rostock, MD

Signature: