Clinical trial results:
Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation with Dabigatran after Pulmonary Vein Isolation for Atrial Fibrillation

Summary

EudraCT number	2013-003492-35
Trial protocol	DE
Global end of trial date	15 September 2020

Results information

Result version number	v1 (current)
This version publication date	02 November 2022
First version publication date	02 November 2022
Summary attachment (see zip file)	221004_ODIn-AF_Final Study Report_V1.0_final (221004_ODIn-AF_Final Study Report_V1.0_final.pdf)

Trial information

Trial identification

Sponsor protocol code	MED2-201301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02067182
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Bonn
Sponsor organisation address	Venusberg Campus 1, Bonn, Germany, 53127
Public contact	Dr. Martin Coenen, Clinical Study Core Unit Study Center Bonn, +49 22828716045, martin.coenen@ukb.uni-bonn.de
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 September 2020
Global end of trial reached?	Yes
Global end of trial date	15 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the ODIn-AF study is to demonstrate that the continued administration of dabigatran for 12 months is superior in the prevention of silent cerebral embolism to discontinuation of OAC in patients free from symptomatic AF-episodes with an elevated stroke risk (CHA2DS2VASc score ≥2) after successful antral pulmonary vein ablation (and re-ablation if necessary) for paroxysmal and persistent AF.

Protection of trial subjects:

The study medication has already been authorized for the treatment of xxx. The investigator informed the patient about the study in detail and both signed the informed consent form. A patient insurance was in place. Adverse events were documented regularly

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	56
From 65 to 84 years	144

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The investigator examines whether all of the inclusion- and exclusion criteria are given and explains all study-related issues. The patient is included if he signs the informed consent form. Patients are included during the baseline visit prior to or until discharge after pulmonary vein ablation.

Pre-assignment

Screening details:

Written informed consent will be obtained and patients will be included in the study before or until discharge after first pulmonary vein ablation. The randomi-zation will be performed after a 3 months blanking period following antral pulmo-nary vein isolation or re-PVI for AF, followed by a 3 months observation period for AF-recurrences. During th

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	dabigatran

Arm description:

AF free patients after successful PVI receiving standard anticoagulation for 12 months with dabigatran as recommended by current guidelines

Arm type	Experimental
Investigational medicinal product name	pradaxa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

220 mg taken as one 110 mg capsule twice daily for patients aged 80 years or above or patients who receive concomitant verapamil
For the following groups, the daily dose of Pradaxa® of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:
• Patients aged between 75-79 years or above
• Patients with moderate renal impairment (Cr-Cl 30-50 ml/min)

Arm title	no OAC

Arm description:

AF free patients after successful PVI. Termination of OAC after 6 months (3 months blanking period and 3 months observation period) after first or second PVI. Resumption of OAC with dabigatran in case of recurrent AF during follow up, as assessed by AF related symptoms and ECGrecording including 72h Holter ECG.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	dabigatran	no OAC
Started	99	101
Completed	99	101

Baseline characteristics

Reporting groups	
Reporting group title	dabigatran
Reporting group description:	
AF free patients after successful PVI receiving standard anticoagulation for 12 months with dabigatran as recommended by current guidelines	
Reporting group title	no OAC
Reporting group description:	
AF free patients after successful PVI. Termination of OAC after 6 months (3 months blanking period and 3 months observation period) after first or second PVI. Resumption of OAC with dabigatran in case of recurrent AF during follow up, as assessed by AF related symptoms and ECGrecording including 72h Holter ECG.	

Reporting group values	dabigatran	no OAC	Total
Number of subjects	99	101	200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	28	56
From 65-84 years	71	73	144
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	43	45	88
Male	56	56	112

End points

End points reporting groups

Reporting group title	dabigatran

Reporting group description:

AF free patients after successful PVI receiving standard anticoagulation for 12 months with dabigatran as recommended by current guidelines

Reporting group title	no OAC

Reporting group description:

AF free patients after successful PVI. Termination of OAC after 6 months (3 months blanking period and 3 months observation period) after first or second PVI. Resumption of OAC with dabigatran in case of recurrent AF during follow up, as assessed by AF related symptoms and ECGrecording including 72h Holter ECG.

Primary: incidence of new micro- and macro-embolic lesions on cerebral MRI imaging incl. flare and diffusion weighted imaging

End point title	incidence of new micro- and macro-embolic lesions on cerebral MRI imaging incl. flare and diffusion weighted imaging

End point description:

The primary endpoint is assessed after a 12 months period of study therapy that begins after a postinterventional 3 months blanking period and a subsequent 3 months observation period for AF-recurrences after a first or second PVI procedure before randomization. MRI are analysed by a blinded core laboratory, facilitating rater blinded reading to therapeutic regime

End point type	Primary

End point timeframe:

12 months after randomization compared to a baseline MRI at randomization.

End point values	dabigatran	no OAC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: whole	99	101		

Attachments (see zip file)	ODIn-AF_Statistical Analysis/220930_ODIn-AF_Statistics.pdf AE Listing/ODIn-AF_AE Listing.pdf

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The primary efficacy analysis was based on the occurrence of the primary endpoint at 12 months after the randomization visit, which is performed 6 months after PVI. The rate of occurrence of one of the events, which define the endpoint, was compared between the treatment groups with a Mantel-Haenszel test stratified for centres, at a level of 5%.

Comparison groups	dabigatran v no OAC
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 5
Method	Mantel-Haenszel

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Adverse Events (AE) that occur during the study treatment until the last study visit (Visit 3) will be collected throughout the study and documented in the subject's medical record using medical terminology and transferred to the CRF.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	dabigatran

Reporting group description:

AF free patients after successful PVI receiving standard anticoagulation for 12 months with dabigatran as recommended by current guidelines

Reporting group title	no OAC

Reporting group description:

AF free patients after successful PVI. Termination of OAC after 6 months (3 months blanking period and 3 months observation period) after first or second PVI. Resumption of OAC with dabigatran in case of recurrent AF during follow up, as assessed by AF related symptoms and ECGrecording including 72h Holter ECG.

Serious adverse events	dabigatran	no OAC	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	dabigatran	no OAC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 99 (0.00%)	0 / 101 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: see attached report

Experimental arm:
number of non-serious adverse events: 72
number of serious adverse events: 34

Control arm:

number of non-serious adverse events: 46
number of serious adverse events: 18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2016	Inclusion after PVI allowed, laser ablation added, additional site added (Cologne)
25 July 2016	Prolongation of interval until screening-TEE, additional sites added (Bielefeld, Ludwigshafen, Göttingen), sites removed (Rostock, Lübeck), prolongation of recruitment period
03 November 2016	Re-PVI can be included, linear ablation procedures for makro-reentry tachycardia allowed, electroanatomical mapping not compulsory anymore, MRI for exclusion contraindications for OAC at randomization added, additional site added (Wuppertal)
27 January 2017	Analysis of dispensable laboratory parameters removed (ANP, BNP, NTproBNP, CRP), additional sites added (Munich, Karlsruhe)
19 September 2017	Prolongation of time between Holter and randomization from 7 to 14 days, new sIMPD (changed colour of IMP-capsules), new SmPC (17.01.2013), site removed (Frankfurt)
30 July 2019	new SmPC (January 2018)
13 November 2019	new SmPC (May 2019)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported