Clinical trial results:
Does oral administration of dabigatran etexilate, a direct thrombin inhibitor, achieve clinical significant concentrations of dabigatran and thrombin inhibiting activity in vitreous and subretinal fluid?

Summary

EudraCT number	2014-000388-41
Trial protocol	NL
Global end of trial date	22 April 2015

Results information

Result version number	v2 (current)
This version publication date	27 July 2019
First version publication date	03 February 2016
Version creation reason	• Changes to summary attachments pubmed link attached

Trial information

Trial identification

Sponsor protocol code	OZR-2013-27

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register: NTR4825

Notes:

Sponsors

Sponsor organisation name	The Rotterdam Eye Hospital
Sponsor organisation address	PO Box 70030, Rotterdam, Netherlands, 3000LM
Public contact	Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, 31 104023430, r.wubbels@oogziekenhuis.nl
Scientific contact	Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, 31 104023430, r.wubbels@oogziekenhuis.nl

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	21 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2015
Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Quantifying dabigatran levels and thrombin inhibiting activity in the vitreous and subretinal fluid after oral administration of dabigatran etexilate in patiens with a retinal detachment.

Protection of trial subjects:

Patients at increased risk of bleeding were excluded.

Background therapy:

Coagulation factor thrombin is thought to play an important role in the development of proliferative vitreoretinopathy. The direct thrombin inhibitor dabigatran is, therefore, an interesting potential drug candidate. The objective of this study is to investigate whether oral administration of dabigatran etexilate in patients with a rhegmatogenous retinal detachment leads to clinical significant dabigatran levels and thrombin inhibiting activity in the vitreous and subretinal fluid.

Evidence for comparator: -	
Actual start date of recruitment	06 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

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)	17
From 65 to 84 years	11

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with a rhegmatogenous retinal detachment, scheduled for a vitrectomy or scleral buckle surgery, were invited to participate.

Pre-assignment

Screening details:

Use of anticoagulants or medication increasing the risk of gastro-intestinal bleeding.

Pre-assignment period milestones

Number of subjects started	28
Number of subjects completed	28

Period 1

Period 1 title	Overall trial. (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Intraocular dabigatran level.

Arm description:

All patients received 220 mg dabigatran. Depending on the type of surgery either a subretinal fluid sample (n=12) or a vitreous sample (n=16) could be taken for analysis.

Arm type	Experimental
Investigational medicinal product name	Dabigatran etexilate.
Investigational medicinal product code	EU/1/08/442
Other name	Pradaxa®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Single oral dose (220 mg) administered 2 to 8 hours prior to surgery.

Number of subjects in period 1	Intraocular dabigatran level.
Started	28
Completed	28

Baseline characteristics

Reporting groups

Reporting group title	Overall trial.

Reporting group description: -

Reporting group values	Overall trial.	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	60.8		
standard deviation	± 7.6	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	22	22	

Subject analysis sets

Subject analysis set title	Dabigatran level in the subretinal fluid.
Subject analysis set type	Full analysis

Subject analysis set description:

Dabigatran concentration in the subretinal fluid after oral administration of 220 mg dabigatran etexilate.

Subject analysis set title	Dabigatran level in the vitreous.
Subject analysis set type	Full analysis

Subject analysis set description:

Dabigatran concentration in the vitreous after oral administration of 220 mg dabigatran etexilate.

Reporting group values	Dabigatran level in the subretinal fluid.	Dabigatran level in the vitreous.	
Number of subjects	12	16	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	58.2	62.8	
standard deviation	± 8.1	± 6.8	
Gender categorical Units: Subjects			
Female	4	2	
Male	8	14	

End points

End points reporting groups

Reporting group title	Intraocular dabigatran level.
Reporting group description:	
All patients received 220 mg dabigatran. Depending on the type of surgery either a subretinal fluid sample (n=12) or a vitreous sample (n=16) could be taken for analysis.	
Subject analysis set title	Dabigatran level in the subretinal fluid.
Subject analysis set type	Full analysis
Subject analysis set description:	
Dabigatran concentration in the subretinal fluid after oral administration of 220 mg dabigatran etexilate.	
Subject analysis set title	Dabigatran level in the vitreous.
Subject analysis set type	Full analysis
Subject analysis set description:	
Dabigatran concentration in the vitreous after oral administration of 220 mg dabigatran etexilate.	

Primary: Intraocular dabigatran level.

End point title	Intraocular dabigatran level.
End point description:	
End point type	Primary
End point timeframe:	
A single dose of dabigatran etexilate (220 mg) is administered 2 to 8 hours prior to surgery.	

End point values	Dabigatran level in the subretinal fluid.	Dabigatran level in the vitreous.		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	16		
Units: Concentration.				
arithmetic mean (standard deviation)	5.8 (± 6)	1.8 (± 1)		

Statistical analyses

Statistical analysis title	Comparison of dabigatran levels.
Comparison groups	Dabigatran level in the subretinal fluid. v Dabigatran level in the vitreous.
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Postoperative period.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	All participants.

Reporting group description: -

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: No non-serious adverse events were reported.

Serious adverse events	All participants.		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 28 (10.71%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Eye disorders			
Retinal detachment (rhegmatogenous).	Additional description: The reported SAE (i.e. a recurrent retinal detachment) is a known complication of the initial condition.		
subjects affected / exposed	3 / 28 (10.71%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	All participants.		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This was a pilot study to demonstrate that dabigatran reaches the intraocular space.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28128536