Clinical trial results:
Risk of apoplexia cerebri in clopidogrel non-responders.

Summary

EudraCT number	2011-004748-23
Trial protocol	DK
Global end of trial date	11 November 2016

Results information

Result version number	v1 (current)
This version publication date	13 July 2018
First version publication date	13 July 2018

Trial information

Trial identification

Sponsor protocol code	2011080362

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02093299
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zealand University Hospital
Sponsor organisation address	Sygehusvej 10, Roskilde, Denmark, 4000
Public contact	Neurologisk ambulatorium, Neurologisk Afdeling, 0045 47322800, clra@regionsjaelland.dk
Scientific contact	Neurologisk ambulatorium, Neurologisk Afdeling, 0045 47322800, clra@regionsjaelland.dk

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	22 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 November 2016
Global end of trial reached?	Yes
Global end of trial date	11 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Assesment of risk og apoplexia cerebri in clopidogrel non-responders

Protection of trial subjects:

All patients were offered quick access by telephone to the study physician should any concerns about treatment occur.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2012
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	Denmark: 165
Worldwide total number of subjects	165
EEA total number of subjects	165

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)	63
From 65 to 84 years	102
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects recruited from the stroke unit at the Neurovascular center between December 2012 and November 2016.

Pre-assignment

Screening details:

179 subjects were screened for inclusion.
Inclusion criteria: age 18 and 90 years, acute ischemic stroke, treatment with clopidogrel 75 mg/day.
Exclusion criteria: treatment with other platelet inhibitor than clopidogrel, previous stroke, known cancer, increased bleeding risk.

Pre-assignment period milestones

Number of subjects started	179[1]
Number of subjects completed	165

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 14

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 179 patients were screened and 165 included

Period 1

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

Blinding implementation details:

Both subject and investigator were blinded for the Platelet Raction Unit (PRU)-result during the follow-up period. Blood samples were collected by the investigator, but analysis was performed by the study-nurse who had no contact with the subjects. The investigator did not have access to PRU-results.

Arms

Arm title	all patients

Arm description:

only one arm. Experimental.

Arm type	Experimental
Investigational medicinal product name	clopidogrel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Enteral use

Dosage and administration details:

75 mg/day

Number of subjects in period 1	all patients
Started	165
Completed	142
Not completed	23
Adverse event, non-fatal	19
Protocol deviation	4

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	165	165	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	63	63	
From 65-84 years	102	102	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	64		
standard deviation	± 9.2	-	
Gender categorical Units: Subjects			
Female	55	55	
Male	110	110	

End points

End points reporting groups

Reporting group title	all patients
Reporting group description: only one arm. Experimental.	

Primary: Composite vascular event

End point title	Composite vascular event[1]
End point description: Composite end point of stroke, acute myocardial infarction or vascular death	
End point type	Primary
End point timeframe: froim inclusion and through 24 months follow-up	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Too few patients in the HTPR- group to make statistical analysis. Underpowered study

Statistical analyses

No statistical analyses for this end point

Primary: Platelet Reaction Units

End point title	Platelet Reaction Units[2]
End point description: Platelet Reaction Units are dichotomized at PRU=208 to define subjects with high on treatment platelet reactivity (or non-responders) (PRU>208)	
End point type	Primary
End point timeframe: Platelet Reaction Units measured once during follow-up (preferrable at inclusion visit)	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As there is only 1 group, the form cannot be filled.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion and through 24 months follow-up

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	2011

Reporting groups

Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 165 (10.91%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsil cancer			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to liver			
subjects affected / exposed	2 / 165 (1.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Surgical and medical procedures			
Aneurysm repair			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transurethral incision of prostate			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileostomy closure			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Atrial fibrillation			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	3 / 165 (1.82%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			

subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Transient ischaemic attack			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Angioedema			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulcer haemorrhage			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Hip fracture			

subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 165 (1.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 165 (3.64%)		
Investigations			
Fatigue			
subjects affected / exposed	4 / 165 (2.42%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pain			
subjects affected / exposed	1 / 165 (0.61%)		
occurrences (all)	1		

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

None reported