Clinical trial results:
Platelet Function and Treatment with ASA in patients with Essential Thrombocytosis

Summary

EudraCT number	2015-002798-39
Trial protocol	DK
Global end of trial date	14 September 2016

Results information

Result version number	v1 (current)
This version publication date	22 September 2017
First version publication date	22 September 2017

Trial information

Trial identification

Sponsor protocol code	2015050991

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Coordinator, Aarhus University Hospital, +45 78450000, madslr@rm.dk
Scientific contact	Coordinator, Aarhus University Hospital, +45 78450000, madslr@rm.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	05 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 September 2016
Global end of trial reached?	Yes
Global end of trial date	14 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The project aims to examine why patients
with the disease essential
thrombocytosis (ET) are at increased risk of thrombosis, and then to examine if their treatment with ASA can be improved.

Protection of trial subjects:

The study was conducted in accordance with the Helsinki II Declaration and Guidelines for Good Clinical Practice (IHC-GCP). The study protocol was approved by the Central Denmark Region Committees on Biomedical Research Ethics, the Danish Medicines Agency and the Danish Data Protection Agency (EudraCT #2015-002798-39). The study was monitored by the Unit for Good Clinical Practice, Aarhus University, Denmark. Written informed consent was obtained from all participants.

Background therapy:

PPI: (Pantoprazol , Esomeprazol)
Cytoreductive therapy: (hydroxyurea)
Antihypertensive therapy: Ancosan comp, Cozaar, Amlodipin, enalapril, atenolol, Norvasc, corodil comp, Metropolol)
Statins: (simvastatin)
Other medication: Alendronat, Fish oil, allopurinol, Eltroxin, letrozol, estradiol, Fluicintin, Brikanyl, Kaleorid, noritren, Tramadol, Imozop, paracetamol)

Evidence for comparator: -

Actual start date of recruitment	30 March 2016
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	9
From 65 to 84 years	15
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were identified at the Department of Hematology, Aarhus University Hospital, Denmark in january 2016.

Pre-assignment

Screening details:

The screening were preformed in accordance with the in-and exclusions criteria. A total of 189 patients were eligible for inclusion. 129 patients did not meet the in - or exclusion criteria. 60 patients were invited to the study and 25 patients rejected, leaving a study population of 25 patients.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ET patients

Arm description:

All patients enrolled in the study went through all periods created except for the period heathy voulenteers. This was the most proper way to create this design in this interface. Thus all patient went through period 1 + 3 + 4. This study was non-randomised. Baseline data was compared with heathy voulenteers and period 3 + 4 was compared as paired data.

Arm type	No intervension
Investigational medicinal product name	ASS Gamma 75 mg Tablets
Investigational medicinal product code	ACT code: B01AC06
Other name	Aspirin/ASA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were asked to discontinue ASA for 14 days prior to blood sampling

Number of subjects in period 1	ET patients
Started	25
Completed	24
Not completed	1
Adverse event, non-fatal	1

Period 2	
Period 2 title	healthy indviduals
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	healthy individuals

Arm description:

These patients are not enrolled in the trial, but used to compare with enrolled patients in the endpoints

Arm type	Healthy

No investigational medicinal product assigned in this arm

Number of subjects in period 2	healthy individuals
Started	24
Completed	24

Period 3	
Period 3 title	Visit 2 (ASA 75 mg x 1)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ASA 75 mg x 1

Arm description:

All patients enrolled in the study went through all periods created except for the period heathy voulenteers. This was the most proper way to create this design in this interface. Thus all patient went through period 1 + 3 + 4.

Arm type	Experimental
Investigational medicinal product name	ASS Gamma 75 mg Tablets
Investigational medicinal product code	ACT code: B01AC06
Other name	Aspirin/ASA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were asked to take ASS gamma 75 mg once-daily for 7 days

Number of subjects in period 3	ASA 75 mg x 1
Started	24
Completed	22
Not completed	2
Protocol deviation	2

Period 4	
Period 4 title	visit 3 (ASA 37.5 mg x 2)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ASA 37.5 mg x 2

Arm description:

All patients enrolled in the study went through all periods created except for the period heathy voulenteers. This was the most proper way to create this design in this interface. Thus all patient went through period 1 + 3 + 4.

Arm type	Experimental
Investigational medicinal product name	ASS Gamma 75 mg Tablets
Investigational medicinal product code	ACT code: B01AC06
Other name	Aspirin/ASA
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

After 14 days washout, patients were asked to take ASS gamma 37.5 mg twice-daily for 7 days

Number of subjects in period 4	ASA 37.5 mg x 2
Started	22
Completed	22

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	25	25	
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)	10	10	
From 65-84 years	13	13	
85 years and over	1	1	
not recorded	1	1	
Age continuous Units: years			
median	67		
inter-quartile range (Q1-Q3)	55 to 69	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	12	12	

End points

End points reporting groups

Reporting group title	ET patients
Reporting group description:	
All patients enrolled in the study went through all periods created except for the period heathy voulenteers. This was the most proper way to create this design in this interface. Thus all patient went through period 1 + 3 + 4. This study was non-randomised. Baseline data was compared with heathy voulenteers and period 3 + 4 was compared as paired data.	
Reporting group title	healthy individuals
Reporting group description:	
These patients are not enrolled in the trial, but used to compare with enrolled patients in the endpoints	
Reporting group title	ASA 75 mg x 1
Reporting group description:	
All patients enrolled in the study went through all periods created except for the period heathy voulenteers. This was the most proper way to create this design in this interface. Thus all patient went through period 1 + 3 + 4.	
Reporting group title	ASA 37.5 mg x 2
Reporting group description:	
All patients enrolled in the study went through all periods created except for the period heathy voulenteers. This was the most proper way to create this design in this interface. Thus all patient went through period 1 + 3 + 4.	

Primary: Difference in the nadir value of TXB2 at the end of the dosing interval (24h blood sample) between the once-daily and twice-daily regimen.

End point title	Difference in the nadir value of TXB2 at the end of the dosing interval (24h blood sample) between the once-daily and twice-daily regimen.
End point description:	
We compared TXB2 values after intake of aspirin 75 mg once-daily for seven days with the values after intake of aspirin 37.5 mg twice-daily. Due to the interface of this website it is created as two arms (otherwise errors occured). But the statistical method used was a paired t-test, thus the same patients went though both regimens.	
End point type	Primary
End point timeframe:	
blood sampling after visit 2 and after visit 3.	

End point values	ASA 75 mg x 1	ASA 37.5 mg x 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: ng/mL				
arithmetic mean (standard deviation)	29.6 (± 19.1)	15.7 (± 12.6)		

Statistical analyses

Statistical analysis title	paired t-test

Statistical analysis description:

In this interface, the design of the study is created as arms suggesting different subjects for analysis in each arm. However, the intension was a paired analysis with 22 subjects going though the two different periods (period 3 and 4).

Comparison groups	ASA 75 mg x 1 v ASA 37.5 mg x 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.9
upper limit	27.7

Notes:

[1] - Paired t test with 22 subjects (not 44 as stated).

Primary: difference in IPC between ET patients and healthy individuals

End point title	difference in IPC between ET patients and healthy individuals

End point description:

End point type	Primary

End point timeframe:

Measured at the baseline blood sample

End point values	ET patients	healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: 10<9>/ L blood				
median (inter-quartile range (Q1-Q3))	12.3 (9.7 to 18.7)	6.9 (5.5 to 10.3)		

Statistical analyses

Statistical analysis title	unpaired t-test
Comparison groups	ET patients v healthy individuals

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	7.5

Secondary: difference in IPF between health and ET patients

End point title	difference in IPF between health and ET patients
End point description:	
End point type	Secondary
End point timeframe:	
From baseline period	

End point values	ET patients	healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: %				
median (inter-quartile range (Q1-Q3))	2.8 (2.3 to 3.4)	2.6 (2.1 to 3.9)		

Statistical analyses

Statistical analysis title	unpaired mann whitney
Comparison groups	ET patients v healthy individuals
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.6

Secondary: Difference in MPV between ET patients and healthy individuals

End point title	Difference in MPV between ET patients and healthy individuals
End point description:	
End point type	Secondary
End point timeframe:	
From baseline period	

End point values	ET patients	healthy individuals		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	24		
Units: fL				
median (inter-quartile range (Q1-Q3))	10.1 (9.4 to 10.5)	10.4 (10.1 to 10.8)		

Statistical analyses

Statistical analysis title	unpaired mann whitney
Comparison groups	ET patients v healthy individuals
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.9

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the whole study perioud between march and sebtember 2016	
Assessment type	Systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1.36.1

Reporting groups	
Reporting group title	All patients

Reporting group description:

Blood samples were obtained at baseline (off treatment blood sample), at visit 2 (after 7 days treatment of aspirin 75 mg once-daily) and at visit 3 (after 7 days treatment of aspirin 37.5 mg twice-daily).

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
TIA	Additional description: transient ischemic attack		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
Blood and lymphatic system disorders			
anemia			
subjects affected / exposed	1 / 25 (4.00%)		
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

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

During the study, we experienced difficulties with recruiting a sufficient number of patients and ended up with a study population of 22-24 patients.

Notes: