Clinical trial results:
The effect of clopidogrel and ticagrelor with and without acetylsalicylic acid (ASA) on hemostatic system activation at the site of plug formation in vivo in man

Summary

EudraCT number	2010-019643-19
Trial protocol	AT
Global end of trial date	19 December 2013
Results information	
Result version number	v1 (current)
This version publication date	25 April 2020
First version publication date	25 April 2020
Summary attachment (see zip file)	Effects of clopidogrel with or without aspirin on the generation of extracellular vesicles in the microcirculation and in venous blood: A randomized placebo controlled trial. (Traby-2018-Effects of clopidogrel with or without aspirin.pdf) Effects of P2Y12 receptor inhibition with or without aspirin on hemostatic system activation: a randomized trial in healthy subjects. (publicaton_top_2016 effect of P2Y12 receptor inhibition with or without aspirin on hemostatic system activatio traby et al.pdf) Differential Effects of Ticagrelor With or Without Aspirin on Platelet Reactivity and Coagulation Activation: A Randomized Trial in Healthy Volunteers (Traby_et_al-2019-Clinical_Pharmacology_&_Therapeutics_.pdf)

Trial information

Trial identification	
Sponsor protocol code	9/27/2012
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02120092
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Waehringerguertel 18-20, Vienna, Austria, 1090
Public contact	Medical University of Vienna Department of Medicine I, Medical University of Vienna Department of Medicine I, +43 14040044100, sabine.eichinger@meduniwien.ac.at
Scientific contact	Ao. Univ. Prof. Dr. Sabine Eichinger, Medical University of Vienna Department of Medicine I, +43 14040044100, sabine.eichinger@meduniwien.ac.at

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	19 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2013
Global end of trial reached?	Yes
Global end of trial date	19 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- to compare the effects of clopidogrel and ticagrelor on in vivo and ex vivo hemostatic system activation
- to investigate the additional effect of ASA to clopidogrel or ticagrelor with regard to their effects on in vivo and ex vivo hemostatic system activation

Protection of trial subjects:

subjects were encouraged to report any discomfort, pain, or other change to their physical intactness. subjects were particularly instructed to record any bleeding (including nose bleeds, hematoma, wet purpura, blood in stool or urine).

Background therapy:

none

Evidence for comparator: -

Actual start date of recruitment	19 October 2010
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	Austria: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	88
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted as a randomized, parallelgroup, double-blind, placebo-controlled trial between November 2011 and December 2013 at the Departments of Medicine I and Clinical Pharmacology, Medical University of Vienna, Vienna, Austria.

Pre-assignment

Screening details:

Inclusion criteria: healthy, male, non-smoking volunteers (18–50 yrs)
Exclusion criteria: history of bleeding, bleeding risk, obesity, allergy to IP, known GI disease, significant finding in physical or
laboratory examination, alcohol abuse, medication use within 2 weeks before study start

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Randomization
was performed by the method of permuted blocks with a block size of four. A person not directly involved in study-related procedures performed concealment of the respective drugs. Investigators involved in the study were not aware of the randomization code, which was broken after finalizing the study and all laboratory analyses were completed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Clopidogrel + aspirin

Arm description:

On day 1, volunteers received 600 mg clopidogrel (Plavix; Sanofi Pharma Bristol-Myers Squibb, Paris, France) together
with 100 mg aspirin followed by 150 mg clopidogrel together with 100 mg aspirin
from day 2 until day 7.

Arm type	Active comparator
Investigational medicinal product name	Clopidogrel + aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Clopidogrel 600 mg + Aspirin 100 mg
Day 2 - day 7: Clopidogrel 150 mg + Aspirin 100 mg

Arm title	Clopidogrel + placebo

Arm description:

On day 1, volunteers received 600 mg clopidogrel (Plavix; Sanofi Pharma Bristol-Myers Squibb, Paris, France) together
with placebo followed by 150 mg clopidogrel together with placebo from day 2 until day 7.

Arm type	Placebo

Investigational medicinal product name	Clopidogrel + placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Clopidogrel 600 mg + placebo
Day 2-7: Clopidogrel 150 mg + placebo

Arm title	Ticagrelor + aspirin

Arm description:

Day 1: Ticagrelor 180 mg + aspirin 300 mg

Arm type	Active comparator
Investigational medicinal product name	Ticagrelor + aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Ticagrelor 180 mg + aspirin 300 mg

Arm title	Ticagrelor + placebo

Arm description:

Day 1: Ticagrelor 180 mg + placebo

Arm type	Placebo
Investigational medicinal product name	Ticagrelor + placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Ticagrelor 180 mg + placebo

Number of subjects in period 1	Clopidogrel + aspirin	Clopidogrel + placebo	Ticagrelor + aspirin
Started	23	21	22
Completed	23	21	22

Number of subjects in period 1	Ticagrelor + placebo
Started	22
Completed	22

Baseline characteristics

Reporting groups	
Reporting group title	Clopidogrel + aspirin
Reporting group description:	
On day 1, volunteers received 600 mg clopidogrel (Plavix; Sanofi Pharma Bristol-Myers Squibb, Paris, France) together with 100 mg aspirin followed by 150 mg clopidogrel together with 100 mg aspirin from day 2 until day 7.	
Reporting group title	Clopidogrel + placebo
Reporting group description:	
On day 1, volunteers received 600 mg clopidogrel (Plavix; Sanofi Pharma Bristol-Myers Squibb, Paris, France) together with placebo followed by 150 mg clopidogrel together with placebo from day 2 until day 7.	
Reporting group title	Ticagrelor + aspirin
Reporting group description:	
Day 1: Ticagrelor 180 mg + aspirin 300 mg	
Reporting group title	Ticagrelor + placebo
Reporting group description:	
Day 1: Ticagrelor 180 mg + placebo	

Reporting group values	Clopidogrel + aspirin	Clopidogrel + placebo	Ticagrelor + aspirin
Number of subjects	23	21	22
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
adults (18 - 50 years)	23	21	22
Gender categorical			
young, healthy, male volunteers			
Units: Subjects			
Female	0	0	0
Male	23	21	22

Reporting group values	Ticagrelor + placebo	Total	
Number of subjects	22	88	
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
adults (18 - 50 years)	22	88	
Gender categorical			
young, healthy, male volunteers			
Units: Subjects			
Female	0	0	
Male	22	88	

End points

End points reporting groups

Reporting group title	Clopidogrel + aspirin
Reporting group description:	
On day 1, volunteers received 600 mg clopidogrel (Plavix; Sanofi Pharma Bristol-Myers Squibb, Paris, France) together with 100 mg aspirin followed by 150 mg clopidogrel together with 100 mg aspirin from day 2 until day 7.	
Reporting group title	Clopidogrel + placebo
Reporting group description:	
On day 1, volunteers received 600 mg clopidogrel (Plavix; Sanofi Pharma Bristol-Myers Squibb, Paris, France) together with placebo followed by 150 mg clopidogrel together with placebo from day 2 until day 7.	
Reporting group title	Ticagrelor + aspirin
Reporting group description:	
Day 1: Ticagrelor 180 mg + aspirin 300 mg	
Reporting group title	Ticagrelor + placebo
Reporting group description:	
Day 1: Ticagrelor 180 mg + placebo	

Primary: beta-thromboglobulin in microvascular blood

End point title	beta-thromboglobulin in microvascular blood
End point description:	
End point type	Primary
End point timeframe:	
Difference between baseline levels and levels 2 hours after first intake of study medication	

End point values	Clopidogrel + aspirin	Clopidogrel + placebo	Ticagrelor + aspirin	Ticagrelor + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	21	22	22
Units: international unit(s)/litre				
median (inter-quartile range (Q1-Q3))	2.6 (2.3 to 4.5)	2.6 (1.8 to 3.4)	1.7 (1.2 to 2.9)	1.8 (1.2 to 2.6)

Statistical analyses

Statistical analysis title	unpaired t-test
Statistical analysis description:	
the unpaired t-test was used comparing baseline measurements with values after 2 hours.	
Comparison groups	Clopidogrel + aspirin v Clopidogrel + placebo v Ticagrelor + aspirin v Ticagrelor + placebo

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Clopdidogrel + aspirin: 8 days Clopidogrel + placebo: 8 days Ticagrelor + aspirin: 2 days Ticagrelor + placebo: 2 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	ICD
Dictionary version	10

Reporting groups	
Reporting group title	Clopdidogrel + aspirin: 8 days
Reporting group description: Clopdidogrel + aspirin: 8 days	

Serious adverse events	Clopdidogrel + aspirin: 8 days		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Clopdidogrel + aspirin: 8 days		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)		
Blood and lymphatic system disorders			
Epistaxis	Additional description: One volunteer had nose bleeding for ~1 min and a hematoma on the thigh ~7 cm in diameter. He was treated with clopidogrel and aspirin, reported to the study center on day 8, completed treatment, and did not receive a specific therapy.		
subjects affected / exposed	1 / 23 (4.35%)		
occurrences (all)	1		
Haematoma	Additional description: One volunteer had nose bleeding for ~1 min and a hematoma on the thigh ~7 cm in diameter. He was treated with clopidogrel and aspirin, reported to the study center on day 8, completed treatment, and did not receive a specific therapy.		

subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 September 2012	Change of one tested substance: ticagrelor instead of prasugrel

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26663880

http://www.ncbi.nlm.nih.gov/pubmed/29857271

http://www.ncbi.nlm.nih.gov/pubmed/31442298