Clinical trial results:
Does acetylsalicylic acid reduce the mortality of patients admitted to an Intensive Care Unit

Summary

EudraCT number	2012-002235-29
Trial protocol	AT
Global end of trial date	05 September 2017

Results information

Result version number	v1
This version publication date	02 February 2018
First version publication date	02 February 2018

Trial information

Trial identification

Sponsor protocol code	1.0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02285153
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Waehringer Guertel 18-20, Vienna, Austria, 1090
Public contact	Medizinische Universität Wien - Uni, Medizinische Universität Wien - Universitätsklinik für klinische Pharmakologie, 0043 01404002980, klin-pharmakologie@meduniwien.ac.at
Scientific contact	Medizinische Universität Wien - Uni, Medizinische Universität Wien - Universitätsklinik für klinische Pharmakologie, 0043 01404002980, klin-pharmakologie@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	10 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the 28-/90-day mortality of patients treated with ASA vs. placebo;

Protection of trial subjects:

Daily blood samples were drawn on a routine basis. Furthermore physical examinations were performed every day by trained physicians.

Background therapy:

Participation in this trial did not affect background therapy of patients. Placebo or acetylsalicylic acid were add-on therapy to the usual treatment of the patients.

Evidence for comparator:

This was a placebo controlled trial. We investigated whether acetylsalicylic acid reduced the mortality of critically ill patients compared to placebo. Since this was an add-on treatment the use of an active comparator was not indicated.

Actual start date of recruitment	15 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 Patients participated in this trial. The first patient was included on November 15th 2012. The last patient on March 13th 2014. All were recruited in the General Hospital of Vienna, Austria.

Pre-assignment

Screening details:

Patients admitted to an ICU without platelet inhibitors, with no recent or planned invasive procedures or surgeries, with no active bleeding, no coagulation disorders, no low platelet counts, no terminal illness (anticipated life expectancy < 3 months), at the discretion of the treating physician were eligible for inclusion.

Pre-assignment period milestones

Number of subjects started	15
Number of subjects completed	15

Period 1

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

Blinding implementation details:

Patients were randomized by a trained person not otherwise involved in the conduct of the trial. Treatment was prepared and the ICU ward received the study drug on each day. Verum/Placebo were not distinguishable by its physical appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo Arm

Arm type	Placebo
Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100ml 0.9% sodium chloride solution

Arm title	Verum

Arm description:

100mg Acetylsalicylic Acid per day

Arm type	Experimental
Investigational medicinal product name	Acetylsalicylic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intracavernous use

Dosage and administration details:

1 Infusion of 100mg Acetylsalicylic Acid in 100ml 0.9% sodium chloride solution

Number of subjects in period 1	Placebo	Verum
Started	8	7
Completed	8	6
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo Arm	
Reporting group title	Verum
Reporting group description:	
100mg Acetylsalicylic Acid per day	

Reporting group values	Placebo	Verum	Total
Number of subjects	8	7	15
Age categorical			
Age at Inclusion			
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)	4	5	9
From 65-84 years	4	2	6
85 years and over	0	0	0
Age continuous			
Age at inclusion			
Units: years			
median	63	61	
standard deviation	± 10	± 15	-
Gender categorical			
Gender			
Units: Subjects			
Female	2	4	6
Male	6	3	9
SAPS III score			
stratification variable			
Units: Subjects			
<50	1	1	2
>50	7	6	13
Age			
stratification variable			
Units: Subjects			
>60	4	3	7
<60	4	4	8
SAPS III			
Disease score			
Units: points			

arithmetic mean	63	64	
standard deviation	± 13	± 19	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo Arm	
Reporting group title	Verum
Reporting group description:	
100mg Acetylsalicylic Acid per day	

Primary: day 28 mortality	
End point title	day 28 mortality
End point description:	
primary endpoint Due to the early termination of the trial due to recruitment problems no formal statistical analysis was performed.	
End point type	Primary
End point timeframe:	
28 days after ICU inclusion	

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: deaths				
dead	1	1		
alive	7	6		

Statistical analyses

Statistical analysis title	Mortality
Statistical analysis description:	
Day 28/90 Mortality	
Comparison groups	Placebo v Verum
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.57 [2]
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	0.434

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	4.792
Variability estimate	Standard error of the mean
Dispersion value	1.225

Notes:
[1] - Chi2
[2] - There is no significant difference in mortality between the two groups.

Primary: 90-day mortality

End point title	90-day mortality

End point description:
Deaths within 90 days of inclusion

End point type	Primary

End point timeframe:
day 90 mortality

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: deaths				
dead	1	2		
alive	7	5		

Statistical analyses

Statistical analysis title	Mortality

Statistical analysis description:
Day 90 mortality between two groups

Comparison groups	Placebo v Verum
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.57 [4]
Method	Chi-squared
Parameter estimate	Cox proportional hazard
Point estimate	0.434
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	4.792
Variability estimate	Standard error of the mean
Dispersion value	1.225

Notes:
[3] - Chi2
[4] - There is no difference between the two groups.

Secondary: Major bleeding

End point title	Major bleeding

End point description:
Major bleedings during the Treatment phase of the trial

End point type	Secondary

End point timeframe:
Duration of the Treatment phase

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: Major bleedings				
Major bleeding	8	1		

Statistical analyses

Statistical analysis title	Major bleeding

Statistical analysis description:
major bleeding in both groups.

Comparison groups	Placebo v Verum
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.467 [6]
Method	Chi-squared

Notes:
[5] - Chi2 Test
[6] - There is no significant difference between the two groups with regards to bleeding incidences.

Secondary: Thromboembolic events

End point title	Thromboembolic events

End point description:

End point type	Secondary

End point timeframe:
Duration of Treatment

End point values	Placebo	Verum		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	7		
Units: Thromboembolic events				
Thromboembolic events	1	0		

Statistical analyses

Statistical analysis title	Thromboembolic Events

Statistical analysis description:

Thromboembolic Events during the treatment phase

Comparison groups	Placebo v Verum
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 1 [8]
Method	Chi-squared

Notes:

[7] - Chi2 Test

[8] - There was no significant difference in the number of thromboembolic events between the two groups.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: The duration of the ICU Stay	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20

Reporting groups	
Reporting group title	Verum
Reporting group description: Patients who received 100mg Acetylsalicylic acid	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 7 (28.57%)	3 / 8 (37.50%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Asystolia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
hypoxic brain damage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colon Perforation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Aspiration Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	6 / 8 (75.00%)	
Vascular disorders			
Bleeding	Additional description: minor bleeding according to the TIMI-bleeding criteria		
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
atrial fibrillation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Delirium			
subjects affected / exposed	2 / 7 (28.57%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Nausea			

subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Obstipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Liver function test increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Catheter infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
herpes virus infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

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.

The trial was terminated after 15 patients due to recruitment difficulties. Thus, any statistical analysis and interpretation of trial results should only be done with caution.

Notes: