Clinical trial results:
ASsessment of Platelet function and Inhibition in patients Recovering from a severe INfection

Summary

EudraCT number	2016-004303-32
Trial protocol	NL
Global end of trial date	10 February 2021

Results information

Result version number	v1 (current)
This version publication date	30 December 2023
First version publication date	30 December 2023
Summary attachment (see zip file)	Statement (Eudract statement-resultaten.pdf)

Trial information

Trial identification

Sponsor protocol code	ASPIRIN-17

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Amsterdam Umc, location VUmc
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands, De Boelelaan 1117
Public contact	Jeske van Diemen, Amsterdam Umc, location VUmc, 0031 630179557, jj.vandiemen@amsterdamumc.nl
Scientific contact	Jeske van Diemen, Amsterdam Umc, location VUmc, 0031 630179557, jj.vandiemen@amsterdamumc.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	12 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Measuring the efficacy of aspirin in inhibiting platelet activity in patients during (recovery from) a severe infection.

Protection of trial subjects:

The protocol was approved by the medical ethical committee of the VU University Medical Center Amsterdam. Written informed consent was obtained from all participants.

Background therapy:

Observational epidemiological studies have confirmed what experienced clinicians suspected for many years: cardiovascular events can be triggered by a variety of common non-cardiovascular clinical conditions, particularly those that are associated with systemic inflammation. Acute systemic infection, like pneumonia, raises risk of myocardial infarction by approximately fivefold , and risk of stroke by eightfold . This increased risk is confined to the first 90 days after the onset of illness. This phenomenon of cardiovascular events occurring in patients hospitalized for non-cardiovascular conditions is clearly important, but the causal mechanisms are unclear and, thus, so are targeted preventive strategies. Nevertheless, there is evidence which suggests that, at least, one of the mechanism lies in the platelets' response to the inflammation. Hence, targeting platelets with inhibitors could be used as a preventative strategy.

Evidence for comparator:

Aspirin has been the number one prophylaxis for the prevention of cardiovascular events since the 1980's . We hypothesize that aspirin can prevent or attenuate (post-)inflammatory platelet hyperaggregability.

Actual start date of recruitment	01 January 2018
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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	31
From 65 to 84 years	22
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This is a multi-center open label randomized trial, performed in four hospitals in Amsterdam and Amstelveen, the Netherlands (Amsterdam UMC location VUmc, OLVG location East and West, hospital Amstelland). Patients from the Internal and Pulmonary medicine wards were screened for inclusion between April 2017 and December 2020.

Pre-assignment

Screening details:

All patients who were newly admitted to the internal and pulmonary medicine wards of the above-named hospitals were screened for inclusion according to the following inclusion criteria: a primary clinical diagnosis of pneumonia, or an invasive urinary tract infection or a soft tissue infection; age above 18 years, hospitalisation for at least 24 h

Pre-assignment period milestones

Number of subjects started	61[1]
Number of subjects completed	54

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Protocol deviation: 5

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: The number of people that signed informed consent differs from the number of people in the baseline measurements, due to withdrawal of informed consent or not meeting the inclusion criteria in retrospect. We reported the number of people that were included in the baseline measurements as the worldwide number of people enrolled in the trial.

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	No intervention

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Aspirin

Arm description:

Received aspirin 80mg

Arm type	Active comparator
Investigational medicinal product name	acetylsalicylic acid, non-enteric-coated
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral, 80mg

Number of subjects in period 1	No intervention	Aspirin
Started	16	38
Completed	16	38

Baseline characteristics

Reporting groups	
Reporting group title	No intervention
Reporting group description: -	
Reporting group title	Aspirin
Reporting group description:	
Received aspirin 80mg	

Reporting group values	No intervention	Aspirin	Total
Number of subjects	16	38	54
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			
median	64	60	
inter-quartile range (Q1-Q3)	52 to 69	46 to 72	-
Gender categorical			
Units: Subjects			
Female	8	20	28
Male	8	18	26

End points

End points reporting groups

Reporting group title	No intervention
Reporting group description: -	
Reporting group title	Aspirin
Reporting group description: Received aspirin 80mg	

Primary: the Platelet Function Analyzer Closure Time (PFA-CT)

End point title	the Platelet Function Analyzer Closure Time (PFA-CT)
End point description: The Platelet Function Analyzer (PFA) measures platelet aggregation by simulating blood flow through an injured vessel. The closure time (CT) is the time needed for a blood plug to develop and occlude the hole in the cartridge. CT is inversely correlated with platelet aggregation; an increased or prolonged CT means decreased aggregation. A normal CT (< 193 seconds) despite aspirin use was determined aspirin resistant. TWe used the Collagen/Epinephrine Test Cartridge was used, which is sensitive to aspirin mediated effects. A CT greater than 300 seconds (the maximum) is reported as 301 for the data-analysis. In Amsterdam UMC location VUmc, the PFA-200® was used, the other hospitals used the PFA-100®.	
End point type	Primary
End point timeframe: prior to randomization (T1), after intervention (T2) and after recovery (day 90) (T3)	

End point values	No intervention	Aspirin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	38		
Units: second				
number (not applicable)	106	191		

Statistical analyses

Statistical analysis title	Linear mixed models
Statistical analysis description: Linear mixed models with measurements clustered within participants and with randomisation group as interaction term were performed to obtain changes with 95% confidence intervals between the different time points. Results were back-transformed for presentation and expressed as percentage.	
Comparison groups	No intervention v Aspirin
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 90 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25

Reporting groups	
Reporting group title	Bleeding
Reporting group description: -	

Serious adverse events	Bleeding		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Bleeding		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 54 (0.00%)		

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: There were no non-serious adverse events in our study

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 July 2019	Due to the COVID-19 pandemic and the exclusion of patients with suspected or confirmed Sars-Cov-2 infection, the inclusion rate radically decreased. We therefore halted the twice daily 40 mg group, and focused on the regular dosage regimen of once daily 80 mg. For analysis, we merged the two dosage groups together as the aspirin treatment group.

Notes:

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.

An important limitation is the early termination of the study, resulting in a small sample size and the inability to compare the two dosage regimens.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37294478