Clinical trial results:
Novel strategies of antithrombotic prophylaxis in patients with Essential Thrombocythemia (ET) at high risk of cardiovascular events: comparison of different dosing regimens of administration of low-dose acetylsalicylic acid. ARES

Summary

EudraCT number	2016-002885-30
Trial protocol	IT
Global end of trial date	31 December 2021
Results information	
Result version number	v1 (current)
This version publication date	20 October 2022
First version publication date	20 October 2022
Summary attachment (see zip file)	Report EMA (Report EMA.pdf) Appendix 1 (Appendix 1 - Investigators.docx) Appendix 4 (Appendix 4- SAE-AE.xlsx) Appendix 8 (Appendix 8 - rand_part A and B.xlsx)

Trial information

Trial identification	
Sponsor protocol code	FARM12Y8HH_ARES
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	FARM12Y8HH: ARES, EudraCT: 2016-002885-30

Notes:

Sponsors	
Sponsor organisation name	Fondazione Policlinico Gemelli
Sponsor organisation address	Largo A. Gemelli 1, Rome, Italy,
Public contact	Area di ematologia, FONDAZIONE POLICLINICO GEMELLI, 0039 0630154968, valerio.destefano@policlinicogemelli.it
Scientific contact	Area di ematologia, FONDAZIONE POLICLINICO GEMELLI, 0039 0630154968, valerio.destefano@policlinicogemelli.it

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	23 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2021
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1- To investigate whether low-dose (100 mg) aspirin regimens twice or three times daily are superior to the standard once-daily regimen in inhibiting platelet-derived thromboxane (TX)A2, as assessed by the measurement of serum TXB2, without significantly affecting in vivo PGI2 biosynthesis, as assessed by its urinary metabolite (PGIM). The comparison between aspirin 100 mg twice or 3 times daily vs. 100 mg od was hypothesized and tested as a superiority hypothesis. PGIM comparisons was hypothesized and assess based on a non-inferiority hypothesis of any multiple daily dosing vs standard od regimen.
2- To evaluate the long-term persistence of superior biochemical efficacy of an optimized, multiple daily dosing regimen of aspirin, as compared to the standard 100 mg od regimen and its safety.

Protection of trial subjects:

The Investigators conducted the study in compliance with the 2004 revision of the 1964 declaration of Helsinki and in accordance with Good Clinical Practice requirements described in the ICH guidelines included in the protocol. Prior to undergoing any study-specific procedure, all subjects gave their consent in writing to participate. The process of obtaining the informed consent was conducted in compliance with the Italian regulations. The ICF incorporated privacy working that complied with relevant data protection and privacy legislation.
All possible measures to minimize pain and distress were adopted along the trial timeframe, although the IMP is a well-known drug with a known safety profile.
Patients were prescribed proton pump inhibitors (PPI) according to current regulatory indications approved in Italy, when deemed necessary to reduce upper gastrointestinal symptoms. In case of occasional need of anti-inflammatory, antipyretic or analgesic drugs, patients were instructed to take paracetamol (up to 2000 mg daily) and avoid ibuprofen or naproxen of NSAIDs in general which have a known pharmacodynamic interaction with aspirin and may also potentiate its bleeding risk at the gastrointestinal level.

Background therapy:

During the study all cytoreductive drugs were allowed as background therapy (i.e. hydroxyurea, pipobroman, busulphan, interferon, anagrelide) to control platelet count, according to the judgement of the referring Hematologist. and current international guidelines Patients were also prescribed proton pump inhibitors (PPI) according to current regulatory indications approved in Italy. In case of occasional need of anti-inflammatory/antipyretic drugs, patients were instructed to take paracetamol (up to 2000 mg daily) and avoid ibuprofen or naproxen and NSAIDs in general.

Evidence for comparator:

Part A: all patients were treated with the current standard of care for cardiovascular prevention in ET, i.e. aspirin 100 mg once-daily. In part A placebo was used as comparator on top of aspirin once daily so that all patients took study medication 3 times daily, i.e. 1 aspirin plus 2 placebo pills or 2 aspirin plus one placebo pills or 3 aspirin pills daily.
Part B: the comparator was the standard of care for the disease, eg aspirin 100 mg once-daily and no placebo was used.

Actual start date of recruitment	27 July 2017
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	Italy: 268
Worldwide total number of subjects	268
EEA total number of subjects	268

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)	164
From 65 to 84 years	104
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

ET patients were recuited from up to 11 Italian hematological Centers: 3 General (Bergamo, Pescara, Vicenza) and 8 Academic (Bari, Bologna, Firenze, Milano Bicocca, Milano Ospedale Maggiore, Padova, Roma, Torino) Hospitals. Recruitment was competitive. Randomization was centralized. FPFV of part A to LPLV of part B dates: 12/12/2017 to 24/10/2020

Pre-assignment

Screening details:

Following a 6-week screening period, all patients fulfilling the eligibility criteria and giving their informed consent underwent a run-in phase, where patients were instructed to take their aspirin tablet at breakfast (7-9 am) for 7-10 consecutive days to allow synchronizing of aspirin intake. After runin patients entered the trial.

Period 1

Period 1 title	Run in
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	single arm

Arm description: -

Arm type	standard of care
Investigational medicinal product name	acetylsalycilic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily

Number of subjects in period 1[1]	single arm
Started	245
Completed	245

Notes:

[1] - The number of subjects reported to be in the baseline 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 trial consisted in two parts with different number of arms

Period 2

Period 2 title	part A
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

All patients had a 5-digit ID code which was sequential and not associated with the randomized arm, thus the laboratories measurements of the primary and secondary biomarker endpoints were performed by personnel who was blinded with regards of the randomized assignement.
Patients were randomized to 3 arms in a 1:1:1 fashion: 100 mg of aspirin once, twice or three times daily with matching placebo tablets to achieve 3 tablet's intake per day.

Arms

Are arms mutually exclusive?	Yes
Arm title	standard of care

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	acetylsalycilic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily

Arm title	twice daily

Arm description: -

Arm type	Experimental
Investigational medicinal product name	acetylsalycilic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg twice daily

Arm title	third daily

Arm description: -

Arm type	Experimental
Investigational medicinal product name	acetylsalycilic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg three times daily

Number of subjects in period 2[2]	standard of care	twice daily	third daily
Started	85	79	79
Completed	85	79	79

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: the trial consisted in two parts with different number of arms

Period 3

Period 3 title	Part B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Part B was open-label. However the laboratory measurements were performed by personnel who was blinded regarding the assigned randomized arm, since patients were sequentially identified with a 5-digit code.

Arms

Arm title	two arm protocol

Arm description: -

Arm type	Experimental
Investigational medicinal product name	acetylsalycilic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg once daily

Number of subjects in period 3[3]	two arm protocol
Started	242
Completed	242

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: the trial consisted in two parts with different number of arms

Baseline characteristics

Reporting groups	
Reporting group title	Run in

Reporting group description: -

Reporting group values	Run in	Total	
Number of subjects	245	245	
Age categorical Units: Subjects			
Adults (18-64 years)	158	158	
From 65-84 years	87	87	
Gender categorical			
Male, n (%) 112 (45.7) Female, n (%) 133 (54.3)			
Units: Subjects			
Female	133	133	
Male	112	112	

End points

End points reporting groups

Reporting group title	single arm
Reporting group description: -	
Reporting group title	standard of care
Reporting group description: -	
Reporting group title	twice daily
Reporting group description: -	
Reporting group title	third daily
Reporting group description: -	
Reporting group title	two arm protocol
Reporting group description: -	
Subject analysis set title	Part A
Subject analysis set type	Intention-to-treat

Subject analysis set description:

251 eligible, aspirin-treated, consenting ET patients started the run-in phase, 6 patients withdrew their consent for personal reasons, 245 patients underwent randomization. There were no statistically significant differences of patient's characteristics across the 3 treatment arms. One patient assigned to aspirin 100 mg od exited the study for abdominal pain, and 1 patient had no serum sample available; 243 patients were evaluable and included in the analyses. Compliance: 218 out of 243 patients (90%) took all nine pills in the three days preceding visit 3 and were considered fully compliant. After two weeks of randomized aspirin treatment, serum TXB2 values of patients assigned to either the 100 mg bid or tid regimen were reduced by 80 to 90% versus their baseline values and were significantly lower than serum TXB2 values of patients assigned to 100 mg od.

Subject analysis set title	Part B
Subject analysis set type	Intention-to-treat

Subject analysis set description:

242 aspirin-treated patients with essential thrombocythemia, were randomized to 100 mg aspirin twice- versus once-daily in addition to standard care. The primary endpoint was serum thromboxane B2, a biomarker of antithrombotic efficacy.
On 10 visits during 20-month follow-up, serum thromboxane B2 was consistently lower in the twice-daily versus once-daily arm (median 3.9 ng/mL versus 19.2 ng/mL, respectively; P<0.001; median relative reduction 80%, 95% confidence interval, 74 to 85%).
No major bleeding occurred. No statistically significant difference was found between the twice- and once-daily treatment groups regarding clinically relevant, non-major bleedings (6.6% versus 1.7%, p=ns), and major thromboses (0.8% versus 2.5%, p=ns). Severe hand and foot microvascular pain was consistently less frequent in the twice-daily arm, while upper gastrointestinal pain scores were comparable in the two arms.

Primary: Serum thromboxane-TX B2

End point title	Serum thromboxane-TX B2

End point description:

Part A and B: platelet thromboxane (TX)A2 production ex vivo, as reflected by serum TXB2 measured in samples collected in a fasting state, in the morning, before the next aspirin intake

Part A: vascular PGI2 biosynthesis in vivo, as reflected by urinary 2,3-dinor-6-keto-PGF1alfa (PGIM) excretion in a urine sample collected in the morning before the next aspirin intake.
Both biomarkers will be measured at baseline and after 14±2 days of randomized treatment

End point type	Primary

End point timeframe:

Applicable for both Part A and part B .
Values were measured over 2 visits in part A and over 11 visits in part B

End point values	Part A	Part B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	251	242		
Units: ng/ml				
number (not applicable)				
Urinary prostacyclin metabolite PGIM	245	242		
Urinary thromboxane metabolite	245	242		

Statistical analyses

Statistical analysis title	major outcome

Statistical analysis description:

Part A. Based on previous findings (3, 7) we assumed a mean±SD serum TXB2 in ET patients on aspirin 100 mg od and 100 mg bid of 22±33 and 5.0±6.0 ng/ml respectively.Anticipating a 30% dropout over the entire study duration (i.e. between part A and part B, and during part B), 100 patients were planned to be enrolled in each study arm to ensure adequate statistical power.Statistical hypothesis and sample size for Part B. The same ET patients were planned to be randomized in part B of the study.

Comparison groups	Part B v Part A
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	15
Confidence interval	
level	Other: 85 %
sides	2-sided
lower limit	5
upper limit	20

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From FPFV of part A to LPLV of part B: 12/12/2017-24/10/2020

Adverse event reporting additional description:

Part A: no serior adverse events recorded
Part B: tthrombotic complications: 1 and 3, in the twice- and once-daily aspirin regimen, respectively; No major bleeding; clinically relevant non-major bleedings were 8 and 2 in the twice- and once-daily aspirin regimen, respectively (p=ns). Other NSAE: 97 and 84 in the od and bid arms in 20 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	adverse events

Reporting group description: -

Serious adverse events	adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 268 (5.60%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
pulmonary cancer			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
major arterial thrombosis			
subjects affected / exposed	8 / 268 (2.99%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CORONARY REVASCULARIZATION FOR ANGINA AND WORSENING OF CHRONIC CORONARY SYNDROME			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
DIAGNOSIS OF ACUTE MYELOID LEUKEMIA			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myeloid leukaemia			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ACUTE PANCREATITIS			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
tyroid cancer			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	adverse events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 268 (36.57%)		
Vascular disorders			
Erythromelalgia			
subjects affected / exposed	47 / 268 (17.54%)		
occurrences (all)	47		
Gastrointestinal disorders			

gastric pain subjects affected / exposed occurrences (all)	30 / 268 (11.19%) 30		
Infections and infestations flu subjects affected / exposed occurrences (all)	23 / 268 (8.58%) 23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2017	#1: included one new trial site (Unit 13) and a prolongation of the study overall from 36 to 40 months to accommodate possible delays of the Centers in recruiting patients, importantly the time on treatment for the patients in part A and B was not changed and remained as in the protocol
02 July 2020	# 2: the Amendment included the change of PIs in Units 8 and 9 as well as a better definition of the time frame for 'breakfast' and 'after dinner' on the basis of part A experience to increase feasibility for the patients and ensure a 12 h interval intake for the bid regimen.

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.

NA

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29880847

http://www.ncbi.nlm.nih.gov/pubmed/32266380

http://www.ncbi.nlm.nih.gov/pubmed/34743317