Clinical trial results:
Clinical non-inferiority study between Micronized purified flavonoid fraction 1000 mg, one chewable tablet per day and Micronized Purified Flavonoid Fraction 500 mg, 2 tablets daily after eight weeks of treatment in patients suffering from symptomatic Chronic Venous Disease (CVD). International, multicenter, double-blind, randomized, parallel group study.

Summary

EudraCT number	2017-003633-28
Trial protocol	HU AT RO
Global end of trial date	07 October 2019

Results information

Result version number	v1 (current)
This version publication date	25 September 2020
First version publication date	25 September 2020

Trial information

Trial identification

Sponsor protocol code	CL3-05682-109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1209-6049

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Institut de Recherches Internationales Servier, Cardiovascular and Metabolism Centre of Therapeutic Innovation, +33 155724366, clinicaltrials@servier.com
Scientific contact	Institut de Recherches Internationales Servier, Cardiovascular and Metabolism Centre of Therapeutic Innovation, +33 155724366, clinicaltrials@servier.com

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	07 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2019
Global end of trial reached?	Yes
Global end of trial date	07 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical non-inferiority of efficacy between micronised purified flavonoid fraction (MPFF) 1000 mg, 1 chewable tablet, and MPFF 500 mg, 2 tablets, in improving lower limb discomfort assessed by a 10 cm electronic visual analogue scale (eVAS) after 8 weeks of treatment in patients suffering from CVD.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 July 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	Turkey: 14
Country: Number of subjects enrolled	Thailand: 55
Country: Number of subjects enrolled	Vietnam: 32
Country: Number of subjects enrolled	Argentina: 125
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Brazil: 78
Country: Number of subjects enrolled	Hungary: 43
Country: Number of subjects enrolled	Romania: 87
Country: Number of subjects enrolled	Russian Federation: 173
Worldwide total number of subjects	611
EEA total number of subjects	134

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)	549
From 65 to 84 years	62
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Male or female outpatients, aged from 20 to 75 years old (inclusive) with 18 kg/m² ≤ body mass index ≤ 35 kg/m², suffering from primary CVD with lower limb discomfort ≥ 4 cm on eVAS and belonging to the Clinical Etiological Anatomic Pathophysiologic (CEAP) class C0s to C4s on the most affected leg.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MPFF chewable tablet 1000 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	MPFF chewable tablet 1000 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

One chewable tablet of MPFF 1000 mg taken daily (in the morning) per os during the meal.

Arm title	MPFF tablet 2 x 500 mg

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	MPFF tablet 500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 tablets of MPFF 500 mg daily (one at midday and one in the evening) taken per os during meals

Number of subjects in period 1	MPFF chewable tablet 1000 mg	MPFF tablet 2 x 500 mg
Started	309	302
Completed	291	293
Not completed	18	9
Adverse event, serious fatal	-	1
non-medical reason	7	5

Adverse event, non-fatal	5	1
Protocol deviation	6	2

Baseline characteristics

Reporting groups	
Reporting group title	MPFF chewable tablet 1000 mg
Reporting group description: -	
Reporting group title	MPFF tablet 2 x 500 mg
Reporting group description: -	

Reporting group values	MPFF chewable tablet 1000 mg	MPFF tablet 2 x 500 mg	Total
Number of subjects	309	302	611
Age categorical Units: Subjects			
Adults (18-64 years)	278	271	549
From 65-84 years	31	31	62
Age continuous Units: years			
arithmetic mean	47.7	47.7	
standard deviation	± 12.3	± 12.5	-
Gender categorical Units: Subjects			
Female	256	246	502
Male	53	56	109

End points

End points reporting groups

Reporting group title	MPFF chewable tablet 1000 mg
Reporting group description: -	
Reporting group title	MPFF tablet 2 x 500 mg
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

In accordance with the intention-to-treat principle and the Section 5.2.1 of ICH E9 guideline, all patients of the randomised set having taken at least one dose of Investigational Medicinal Product (IMP) and having a value at baseline and at least one post-baseline value for the lower limb discomfort assessed by eVAS.

Primary: Lower limb discomfort (eVAS): change from baseline to W8

End point title	Lower limb discomfort (eVAS): change from baseline to W8

End point description:

Lower limb discomfort defined by the evaluation of the overall symptoms of lower limbs: lack pain, leg heaviness, tiredness and feeling of swelling. On the eVAS scale: 0 = no discomfort and 10-cm = extreme discomfort.

End point type	Primary

End point timeframe:

Discomfort assessed by the patient on an electronic device (auto-evaluation) at site during selection, then weekly at home at same time and same day in the evening (except week-end) and before visits W000, W004 and W008 (evening) in the same conditions.

End point values	MPFF chewable tablet 1000 mg	MPFF tablet 2 x 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	266	253		
Units: cm				
arithmetic mean (standard deviation)	-3.6 (± 2.4)	-3.6 (± 2.5)		

Statistical analyses

Statistical analysis title	Non-inferiority analysis
Comparison groups	MPFF chewable tablet 1000 mg v MPFF tablet 2 x 500 mg
Number of subjects included in analysis	519
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANCOVA

Notes:

[1] - Non-inferiority margin was set at 1.0 cm. One-sided type I error rate = 0.025. Missing data was imputed by treatment group, using centre and baseline, using multiple imputation approach based on the regression method (after MCMC monotone-data imputation).
The analysis included the fixed, categorical effect of treatment, the random categorical effect of centre, as well as the continuous, fixed covariate of baseline.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events which occurred or worsened or became serious according to investigator opinion, between the first IMP intake date, corresponding to the double-blind treatment period (included) and the last IMP intake date + 3 days (included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	MPFF chewable tablet 1000 mg
Reporting group description: -	
Reporting group title	MPFF tablet 2 x 500 mg

Reporting group description: -

Serious adverse events	MPFF chewable tablet 1000 mg	MPFF tablet 2 x 500 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	MPFF chewable tablet 1000 mg	MPFF tablet 2 x 500 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 307 (10.75%)	31 / 301 (10.30%)	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast dysplasia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Menstruation delayed			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	3 / 307 (0.98%)	1 / 301 (0.33%)	
occurrences (all)	5	1	
Fall			

subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Road traffic accident			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 307 (0.98%)	7 / 301 (2.33%)	
occurrences (all)	3	8	
Hypoaesthesia			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			

subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	2 / 307 (0.65%)	0 / 301 (0.00%)	
occurrences (all)	2	0	
Aphthous ulcer			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Dental caries			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	3 / 307 (0.98%)	1 / 301 (0.33%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	0 / 307 (0.00%)	2 / 301 (0.66%)	
occurrences (all)	0	2	
Faeces soft			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	7 / 307 (2.28%)	3 / 301 (1.00%)	
occurrences (all)	7	3	
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Skin hyperpigmentation			
subjects affected / exposed	1 / 307 (0.33%)	1 / 301 (0.33%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Limb discomfort			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 307 (0.33%)	1 / 301 (0.33%)	
occurrences (all)	1	1	
Bronchitis			

subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	2	
Conjunctivitis viral			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	2 / 307 (0.65%)	2 / 301 (0.66%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	2 / 307 (0.65%)	1 / 301 (0.33%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	0 / 307 (0.00%)	2 / 301 (0.66%)	
occurrences (all)	0	2	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 307 (0.00%)	1 / 301 (0.33%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 307 (0.33%)	0 / 301 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2019	One substantial amendment to protocol (applicable in all centres in all countries), was issued to add a precision concerning excipients to non-selection criterion No. 32 and clarifications concerning non authorised pharmacological treatments. Moreover, minor modifications were added: implementation of a new procedure related to the archiving of participants' e-CRF data at the study file, addition of a short name for the study, modification of archiving time of the information relevant to the study after the end of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported