Clinical trial results:
Evaluation of the clinical efficacy and safety of perindopril 10 mg/indapamide 2.5 mg/amlodipine 5 or 10 mg/bisoprolol 5 mg in single-pill combination after 8 weeks of treatment versus the free combination of perindopril 10 mg, indapamide 2.5 mg and amlodipine 5 or 10 mg in patients with uncontrolled essential hypertension. An international, multicentre, randomised, double-blind, 16-week study.

Summary

EudraCT number	2020-004891-16
Trial protocol	PL PT LT IT LV SK HU CZ BG HR
Global end of trial date	14 December 2023

Results information

Result version number	v1 (current)
This version publication date	09 November 2024
First version publication date	09 November 2024

Trial information

Trial identification

Sponsor protocol code	CL3-05179-002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S.)
Sponsor organisation address	22, route 128, Gif-sur-Yvette, France, 91190
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55724366, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1 55724366, 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	14 December 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of S05179 over Free [Per + Ind + Aml] (a tritherapy) on the lowering of office sitting SBP after 8 weeks of treatment (following a tritherapy run-in period).

Protection of trial subjects:

The study was initiated only after the Ethics Committee’s approval, in accordance with the local regulations in each of the countries. Amendments to the protocol were applied only after the Ethics Committee's approval and in accordance with the local regulatory requirements.
The study was conducted in accordance with the protocol and with the following:
• Consensus ethical principles derived from international guidelines including the Declaration of Helsinki, 1964, as revised in Fortaleza, 2013.
• Applicable Good Clinical Practice (GCP) guidelines.
• Applicable laws and regulations.
In addition to the main study information and consent form (ICF) for study participation, this study also used a separate ICF for optional assessments (24-hour Ambulatory Blood Pressure Monitoring (ABPM) post-W008 visit and HBPM post-W000 visit) and for the consent of a pregnant partner of a study participant (for Italy).

Background therapy:

99 patients (54.1%) were reported with concomitant therapy during the treatment period: mainly lipid lowering agents (36.6%) and diabetes drugs (26.2%).

Evidence for comparator:

Tritherapy free combination of: Perindopril, Indapamine and Amlodipine

Actual start date of recruitment	12 February 2022
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	Armenia: 56
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Kazakhstan: 7
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Bulgaria: 5

Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Latvia: 10
Country: Number of subjects enrolled	Lithuania: 4
Worldwide total number of subjects	183
EEA total number of subjects	55

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)	135
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study planned to enroll 968 patients. 183 patients in 13 countries were included. In July 2023, the sponsor decided to close patient selections before reaching the planned number of included patients due to recruitment difficulties.

Pre-assignment

Screening details:

All patients were adults aged 18+ years. Patients were eligible for selection if they had uncontrolled BP despite treatment with 3 antihypertensive drugs at the optimal tolerated dose (including a diuretic) for at least 1 month prior to the selection visit.

Pre-assignment period milestones

Number of subjects started	469[1]
Number of subjects completed	183

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failure: 267
Reason: Number of subjects	Adverse event, non-fatal: 5
Reason: Number of subjects	Consent withdrawn by subject: 14

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 pre-assignment period is a run-in period (8 weeks): from ASS1 selection visit (8 weeks before the inclusion visit) to inclusion visit (W000). The Run-in period was dedicated to confirming the essential uncontrolled HT on tritherapy free combination perindopril 10 mg, indapamide 2.5 mg and amlodipine 5 or 10 mg. The presented numbers are the numbers of all selected patients included in the Run-in period with uncontrolled essential hypertension.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm S05179

Arm description:

Patients randomized to receive 1 capsule of quadritherapy drug S05179, 1 capsule of placebo and 1 tablet of placebo once daily for 8 weeks according to randomized treatment.

Arm type	Experimental
Investigational medicinal product name	S05179
Investigational medicinal product code	
Other name	Per/Ind/Aml/Biso; Perindpril/Indapamine/Amlodipine/Bisoprolol
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of S05179 single-pill combination (SPC) at one of the following strengths: Per/Ind/Aml/Biso 10/2.5/5/5 mg or 10/2.5/10/5 mg was taken once daily. The dose of amlodipine in the combination 5 mg or 10 mg was defined at ASS1 for each patient.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One capsule of placebo was taken once daily for purpose of maintain the blinding of the study.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet of placebo was taken once daily for purpose of maintain the blinding of the study.

Arm title	Arm Tritherapy free combination

Arm description:

Patients randomized to receive tritherapy free combination of perindopril, indapamide and amlodipine once daily for 8 weeks.

Arm type	Active comparator
Investigational medicinal product name	Per 10 mg
Investigational medicinal product code	
Other name	perindopril
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 10 mg capsule was taken once daily for 8 week.

Investigational medicinal product name	Ind 2.5 mg
Investigational medicinal product code	
Other name	indapamide
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 2.5 mg tablet was taken once daily for 8 week.

Investigational medicinal product name	Aml 5 or 10 mg
Investigational medicinal product code	
Other name	amlodipine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One 5 mg or 10 mg capsule was taken once daily for 8 week. The dose of amlodipine of 5 mg or 10 mg was defined at ASS1 (first selection visit) for each patient and remained unchanged for the whole study duration.

Number of subjects in period 1	Arm S05179	Arm Tritherapy free combination
Started	89	94
Completed	89	93
Not completed	0	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm S05179
Reporting group description:	
Patients randomized to receive 1 capsule of quadritherapy drug S05179, 1 capsule of placebo and 1 tablet of placebo once daily for 8 weeks according to randomized treatment.	
Reporting group title	Arm Tritherapy free combination
Reporting group description:	
Patients randomized to receive tritherapy free combination of perindopril, indapamide and amlodipine once daily for 8 weeks.	

Reporting group values	Arm S05179	Arm Tritherapy free combination	Total
Number of subjects	89	94	183
Age categorical Units: Subjects			
Adults (18-64 years)	64	71	135
From 65-84 years	25	23	48
Age continuous Units: years			
arithmetic mean	56.9	57.8	
standard deviation	± 11.4	± 9.8	-
Gender categorical Units: Subjects			
Female	37	49	86
Male	52	45	97

End points

End points reporting groups

Reporting group title	Arm S05179
Reporting group description:	
Patients randomized to receive 1 capsule of quadritherapy drug S05179, 1 capsule of placebo and 1 tablet of placebo once daily for 8 weeks according to randomized treatment.	
Reporting group title	Arm Tritherapy free combination
Reporting group description:	
Patients randomized to receive tritherapy free combination of perindopril, indapamide and amlodipine once daily for 8 weeks.	

Primary: Office sitting Systolic Blood Pressure (SBP)

End point title	Office sitting Systolic Blood Pressure (SBP)
End point description:	
End point type	Primary
End point timeframe:	
From baseline (Week 000) to Week 008	

End point values	Arm S05179	Arm Tritherapy free combination		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80[1]	82[2]		
Units: number				
arithmetic mean (standard deviation)				
Change in SBP from Baseline to week 008	-20.67 (± 15.37)	-11.32 (± 14.77)		

Notes:

[1] - Only randomized patients considered non-controlled at baseline are included in the analysis

[2] - Only randomized patients considered non-controlled at baseline are included in the analysis.

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Arm S05179 v Arm Tritherapy free combination
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
Method	General Linear Model
Parameter estimate	Adjusted difference from baseline - W008
Point estimate	-8.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.99
upper limit	-4.09
Variability estimate	Standard error of the mean
Dispersion value	2.02

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected during the period Week 000 - Week 008	
Adverse event reporting additional description:	
Safety Set (SS) consisted of 183 patients (100%) according to actual treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	S05179 arm
Reporting group description:	
Patients receiving actually 1 capsule of quadritherapy drug S05179, 1 capsule of placebo and 1 tablet of placebo once daily for 8 weeks.	
Reporting group title	Tritherapy free combination arm
Reporting group description:	
Patients receiving actually tritherapy free combination of perindopril, indapamide and amlodipine once daily for 8 weeks.	

Serious adverse events	S05179 arm	Tritherapy free combination arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 88 (0.00%)	0 / 95 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	S05179 arm	Tritherapy free combination arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 88 (11.36%)	8 / 95 (8.42%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Heart rate increased			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	

Human chorionic gonadotropin increased			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	3 / 88 (3.41%)	1 / 95 (1.05%)	
occurrences (all)	3	1	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 88 (1.14%)	0 / 95 (0.00%)	
occurrences (all)	1	0	

Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 88 (0.00%)	2 / 95 (2.11%)	
occurrences (all)	0	2	
Acute sinusitis			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 88 (2.27%)	0 / 95 (0.00%)	
occurrences (all)	2	0	
Dyslipidaemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 88 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2021	Amendment No. 1 - Addition of a paragraph regarding benefit-risk assessment, dose and duration in the background information. - Addition of a blood pregnancy test at the inclusion visit and at the last study visit or withdrawal visit. - Update of several non-selection criteria. - Update of the period used to measure the BP uncontrolled status on the planned 24h-ABPM assessment (from real daytime period to 24h-period). - Update of the 24h ABPM validity criteria. - Addition of the possibility to perform a blinded sample size reassessment.
21 June 2022	Amendment No. 3 - Addition of a urine home (or on site) pregnancy test the day before ASS2 visit and W004 phone contact in order to have a pregnancy test at every visit. - Clarification on sites' internal organisation regarding ABPM/HBPM results and/or blood results assessments by the investigator. - Imaging methods used to evaluate the function and structure of the kidneys were extended. - Change renal echography by renal imagery. - Change real daytime by 24-hour period. - Update of selection criteria: the upper age limit was deleted (criterion 1); the criterion 2a. regarding patient with very high cardiovascular risk was clarified. - imaging modalities to document absence of renal secondary HT were extended. - Update of non-selection criteria: addition of a urine home (or on site) pregnancy test the day before ASS2; clarification of the type of (i.e. symptomatic) bradycardia and other diseases and the severity of asthma histories; harmonisation of non-selection criteria N° 25 and N° 26 with selection criterion N° 2; clarification of criterion N° 30: patients having a moderate or severe renal failure. - Update of inclusion criteria: clarification of criterion 55a. regarding 12-lead ECG and an exemption for AV block Grade consistent with Bisoprolol SmPC. - Update of exclusion criteria: criterion 69a. (imaging modalities to document absence of renal secondary HT were extended.); criteria 71a. (clarification of the criterion about abnormal results of TSH.) - Clarification of withdrawal criteria and procedure during the run-in period. - Clarification of Office BP measurements. - The documentation of the adverse event was aligned with ICH E6 R2. - The procedure for ERIN was clarified. - Renal arteries assessments were clarified. - e-CRF signature was clarified. - Blind-reviews and database managements were clarified. - Update of the section "printing the data" of the Appendix 3 was updated.
17 October 2022	Amendment No. 4 - Update of the non-selection criteria 13a in order to exclude patients with the most severe obesity forms (BMI > 35 kg/m2). Consequently, Background information and References were updated. - Procedure for an ERIN was updated: addition of the 24-hour phone line (outside working hours).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported