



Clinical trial results:

Open-label, multicenter, multinational, interventional Clinical Trial to assess Efficacy and Safety of the extemporaneous combination of Nebivolol and Ramipril in hypertensive patients - ARTEMISIA study Summary

EudraCT number	2022-003060-25
Trial protocol	HU BG
Global end of trial date	19 February 2024

Results information

Result version number	v1 (current)
This version publication date	20 February 2025
First version publication date	20 February 2025

Trial information

Trial identification

Sponsor protocol code	MEIN/22/NeRam-Hyp/001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT06104423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Menarini International Operation Luxembourg SA
Sponsor organisation address	1, Avenue de la Gare, Luxembourg L-1611, Luxembourg, Luxembourg,
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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	29 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 February 2024
Global end of trial reached?	Yes
Global end of trial date	19 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antihypertensive efficacy of the extemporaneous combination of Nebivolol (NEB) 5 mg with Ramipril (RAM) 2.5 mg, 5 mg or 10 mg in lowering sitting Systolic blood pressure (SBP) between Visit 2 (Week 0) and Visit 5 (Week 12) in patients with uncontrolled blood pressure (BP) previously treated with NEB 5 mg or RAM 5 mg monotherapies for at least 30 days.

For the purpose of this study, uncontrolled BP is defined as sitting Systolic blood pressure (SBP)/Diastolic blood pressure (DBP):

- $\geq 130/80$ mmHg in patients < 65 years old
- $\geq 140/80$ mmHg in patients ≥ 65 years old

Protection of trial subjects:

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP), including the archiving of essential documents as well as the ethical principles of the Declaration of Helsinki.

Background therapy:

All Patients are in therapy with anti hypertensive monotherapy treatment either with Beta blockers (BBs) (NEB 5 mg or any dose if other BB) or Angiotensin-converting enzyme inhibitors (ACE-i) (RAM 5 mg or any dose if other ACE-i) for at least 30 days before Visit 1 (screening)

Evidence for comparator: -

Actual start date of recruitment	02 October 2023
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	Poland: 52
Country: Number of subjects enrolled	Bulgaria: 213
Country: Number of subjects enrolled	Hungary: 1
Worldwide total number of subjects	266
EEA total number of subjects	266

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)	202
From 65 to 84 years	64
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study started 02Oct2023 and terminated 19Feb2024. 270 patients (pts) were screened of which 266 pts entered the Run-In phase and were assigned monotherapy with NEB 5mg or RAM 5mg; 4 pts were screen failures. Out of these 266 pts, 11 pts were dropped during Run-In. 255 pts completed the trial (Run-In and combination therapy phase)

Pre-assignment

Screening details:

270 patients (pts) male and female uncontrolled hypertensive patients ≥ 18 years of age on monotherapy either with ACE-i or BBs since at least 1 month and with mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg and / or mean sitting DBP ≥ 90 mmHg and ≤ 109 mmHg, were screened.

Period 1

Period 1 title	Run-In Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open- label study, not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nebivolol 5 mg

Arm description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit (Visit 1, Week - 4).

Patients previously receiving Neb 5 mg continued the same treatment, while patients receiving any other BBs were switched to Neb 5 mg

Arm type	Active comparator
Investigational medicinal product name	Nebivolol 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study drug was administered with a glass of water once daily

Arm title	Ramipril 5 mg
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Arm description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit (Visit 1, Week - 4).

Patients previously receiving RAM 5 mg continued the same treatment, while patients receiving any other ACE-i were switched to RAM 5 mg

Arm type	Active comparator
Investigational medicinal product name	Ramipril 5mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study drug was administered with a glass of water once daily

Number of subjects in period 1	Nebivolol 5 mg	Ramipril 5 mg
Started	128	138
Completed	124	131
Not completed	4	7
Not compliant with eligibility criteria	3	6
Lab abnormal results	1	1

Period 2

Period 2 title	Assessment
Is this the baseline period?	Yes ^[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Arm title	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg
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Arm description:

Visit2 (V2) Week0 (W0): Patients (pts) having uncontrolled BP (BP $\geq$ 130/80mmHg in pt<65y old/BP $\geq$ 140/80mmHg in pt $\geq$ 65y old) were assigned to the extemporaneous combination of NEB5mg and RAM2.5mg.

V3 W4: After 4 Weeks $\pm$ 2 days controlled pt (BP<130/80mmHg in pt<65y old/ BP<140/80mmHg in pt $\geq$ 65y old) continued the same combination of V2 while for pt with uncontrolled BP the RAM dose was up-titrated to 5mg and the pt received the combination NEB/RAM 5/5mg for next 4 weeks.

V4 W8: After 4 Weeks $\pm$ 2 days controlled pt continued the same combination of V3 for next 4 weeks $\pm$ 2 days till V5 (W12).

Pt with uncontrolled BP: on NEB/RAM 5/2.5mg were up-titrated to NEB/RAM 5/5mg; on NEB/RAM 5/5mg were up-titrated to NEB/RAM 5/10mg for next 4 weeks $\pm$ 2 days till V5.

To correctly evaluate additional effect of the combination therapy, the number of pts with uncontrolled BP needed to be balanced at V2 (max 5% difference). Weekly evaluations were performed to maintain a 1:1 during period 2.

Arm type	Experimental
Investigational medicinal product name	Nebivolol 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study medication was administered with a glass of water once daily

Investigational medicinal product name	Ramipril 2.5/5/10mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet of study medication was administered with a glass of water once daily

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the Run-in period. The objective of the study is to evaluate the effectiveness and safety of the combination therapy (Nebivolol/Ramipril) versus the monotherapy. Hence the baseline period starts on Period 2 (Assessment), with the assessment of blood pressure after the run-in period and the intake of the combination therapy.

Number of subjects in period 2^[2]	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg
Started	255
Completed	255

Notes:

[2] - 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: 270 patients are enrolled patients that are included in the study and start the Run-in period (Period 1). Period 1 is not the baseline period. The baseline period is Period 2 (Assessment) where patients start to take the combination therapy NEB 5 mg/RAM 2.5mg.

Baseline characteristics

Reporting groups

Reporting group title	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg
Reporting group description:	
Visit2 (V2) Week0 (W0): Patients (pts) having uncontrolled BP (BP $\geq$ 130/80mmHg in pt<65y old/BP $\geq$ 140/80mmHg in pt $\geq$ 65y old) were assigned to the extemporaneous combination of NEB5mg and RAM2.5mg.	
V3 W4: After 4 Weeks $\pm$ 2 days controlled pt (BP<130/80mmHg in pt<65y old/ BP<140/80mmHg in pt $\geq$ 65y old) continued the same combination of V2 while for pt with uncontrolled BP the RAM dose was up-titrated to 5mg and the pt received the combination NEB/RAM 5/5mg for next 4 weeks.	
V4 W8: After 4 Weeks $\pm$ 2 days controlled pt continued the same combination of V3 for next 4 weeks $\pm$ 2 days till V5 (W12).	
Pt with uncontrolled BP: on NEB/RAM 5/2.5mg were up-titrated to NEB/RAM 5/5mg; on NEB/RAM 5/5mg were up-titrated to NEB/RAM 5/10mg for next 4 weeks $\pm$ 2 days till V5.	
To correctly evaluate additional effect of the combination therapy, the number of pts with uncontrolled BP needed to be balanced at V2 (max 5% difference). Weekly evaluations were performed to maintain a 1:1 during period 2.	

Reporting group values	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg	Total	
Number of subjects	255	255	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	195	195	
From 65-84 years	60	60	
85 years and over	0	0	
Not recorded	0	0	
Age continuous Units: years			
arithmetic mean	55.1		
standard deviation	$\pm$ 12.77	-	
Gender categorical Units: Subjects			
Female	133	133	
Male	122	122	

End points

End points reporting groups

Reporting group title	Nebivolol 5 mg
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Reporting group description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit (Visit 1, Week - 4).

Patients previously receiving Neb 5 mg continued the same treatment, while patients receiving any other BBs were switched to Neb 5 mg

Reporting group title	Ramipril 5 mg
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Reporting group description:

Eligible patients entered a 4 week run-in period on the same day of the screening visit (Visit 1, Week - 4).

Patients previously receiving RAM 5 mg continued the same treatment, while patients receiving any other ACE-i were switched to RAM 5 mg

Reporting group title	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg
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Reporting group description:

Visit2 (V2) Week0 (W0): Patients (pts) having uncontrolled BP ($BP \geq 130/80$ mmHg in $pt < 65y$ old/ $BP \geq 140/80$ mmHg in $pt \geq 65y$ old) were assigned to the extemporaneous combination of NEB5mg and RAM2.5mg.

V3 W4: After 4 Weeks $\pm$ 2 days controlled pt ($BP < 130/80$ mmHg in $pt < 65y$ old/ $BP < 140/80$ mmHg in $pt \geq 65y$ old) continued the same combination of V2 while for pt with uncontrolled BP the RAM dose was up-titrated to 5mg and the pt received the combination NEB/RAM 5/5mg for next 4 weeks.

V4 W8: After 4 Weeks $\pm$ 2 days controlled pt continued the same combination of V3 for next 4 weeks $\pm$ 2 days till V5 (W12).

Pt with uncontrolled BP: on NEB/RAM 5/2.5mg were up-titrated to NEB/RAM 5/5mg; on NEB/RAM 5/5mg were up-titrated to NEB/RAM 5/10mg for next 4 weeks $\pm$ 2 days till V5.

To correctly evaluate additional effect of the combination therapy, the number of pts with uncontrolled BP needed to be balanced at V2 (max 5% difference). Weekly evaluations were performed to maintain a 1:1 during period 2.

Subject analysis set title	Efficacy Population
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

All study participants who signed informed consent, met all screening criteria, were enrolled and received at least one dose of the assigned treatment during run-in period, completed the 4-week run-in period and met criteria at Visit 2 (Week 0) [uncontrolled BP (sitting BP $\geq 130/80$ mmHg in patients < 65 years old/sitting BP $\geq 140/80$ mmHg in patients ≥ 65 years old) at Visit 2, with adequate treatment adherence (ranging between 80% to 120%)], tolerated treatment, had treatment adherence between 80 – 120 %, had at least one dose of combination therapy and had at least baseline [Visit 2 (Week 0)] and Visit 5 (Week 12) assessments with primary efficacy data. 239 pts were included in Modified intention to treat (mITT) for primary efficacy analysis.

Primary: Change in mean sitting SBP

End point title	Change in mean sitting SBP
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End point description:

End point type	Primary
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End point timeframe:

12 weeks of combination therapy treatment. From study Visit 2 (Week 0) to study Visit 5 (Week 12)

End point values	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg	Efficacy Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	239	239		
Units: mmHG				
arithmetic mean (standard deviation)	-19.2 (± 8.62)	-19.2 (± 8.62)		

Statistical analyses

Statistical analysis title	SBP at Visit 2 (Week 0) vs Visit 5 (Week 12)
Statistical analysis description:	
Change from Baseline in the Systolic Blood Pressure (SBP). Primary endpoint, verified on the single cohort of patients who completed the run-in period, is calculated as the mean difference in sitting SBP between V2 (W0, Baseline) and V5 (W12, End of Study Visit). This is not a comparison of two different arms, but a comparison of two measurements taken from the same patient treated with combination therapy (single arm paired pre- vs. post-combination therapy comparison)	
Comparison groups	Combination Therapy Neb 5mg/ Ram 2.5 or 5 or 10 mg v Efficacy Population
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon
Parameter estimate	Signed Rank Test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Informed Consent signed to final visit

Adverse event reporting additional description:

Safety population: Patients who are in the Enrolled population and receive at least 1 dose of monotherapy (either followed by combination therapy or not). For the purpose of safety analyses concerning the combination therapy period, 255, 170, and 71 patients were exposed to at least 1 dose of the NEB/RAM 5/2.5 mg, 5 mg, 10 mg, respectively.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Monotherapy
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Reporting group description:

Safety Population that received Monotherapy

Reporting group title	Combination therapy Neb5mg/RAM2.5mg
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Reporting group description:

Safety Population that received Combination therapy Neb5mg/RAM2.5mg (the actual number of patients who received NEB 5 mg/RAM 2.5 mg for the entire combination period, patients who were up-titrated to NEB 5 mg/RAM 5 mg at Visit 3 (Week 4) and who were up-titrated to NEB 5 mg/RAM 5 mg or NEB 5 mg/RAM 10 mg at Visit 4 (Week 8), respectively).

Reporting group title	Combination therapy Neb5mg/RAM5mg
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Reporting group description:

Safety Population that received Combination therapy Neb5mg/RAM5mg (the actual number of patients who were up-titrated to NEB 5 mg/RAM 5 mg at Visit 3 (Week 4) and who were up-titrated to NEB 5 mg/RAM 5 mg or NEB 5 mg/RAM 10 mg at Visit 4 (Week 8), respectively).

Reporting group title	Combination therapy Neb5mg/RAM10mg
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Reporting group description:

Safety Population that received Combination therapy Neb5mg/RAM10mg (the actual number of patients who were up-titrated to NEB 5 mg/RAM 10 mg at Visit 4 (Week 8)).

Serious adverse events	Monotherapy	Combination therapy Neb5mg/RAM2.5mg	Combination therapy Neb5mg/RAM5mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	1 / 170 (0.59%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	1 / 170 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Combination therapy Neb5mg/RAM10mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 71 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Monotherapy	Combination therapy Neb5mg/RAM2.5mg	Combination therapy Neb5mg/RAM5mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 266 (0.00%)	14 / 255 (5.49%)	18 / 170 (10.59%)
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	0 / 170 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 266 (0.00%)	1 / 255 (0.39%)	0 / 170 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	5 / 170 (2.94%)
occurrences (all)	0	0	5
Sciatica			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	2 / 170 (1.18%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	1 / 170 (0.59%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Dyspepsia subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	1 / 255 (0.39%) 1	1 / 170 (0.59%) 1
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	1 / 255 (0.39%) 1	0 / 170 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	0 / 255 (0.00%) 0	0 / 170 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	1 / 255 (0.39%) 1	0 / 170 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	1 / 255 (0.39%) 1	3 / 170 (1.76%) 3
Back pain subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	0 / 255 (0.00%) 0	1 / 170 (0.59%) 1
Spinal pain subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	0 / 255 (0.00%) 0	1 / 170 (0.59%) 1
Myalgia subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	0 / 255 (0.00%) 0	0 / 170 (0.00%) 0
Infections and infestations Influenza subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	4 / 255 (1.57%) 4	0 / 170 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	3 / 255 (1.18%) 3	3 / 170 (1.76%) 3
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 266 (0.00%) 0	1 / 255 (0.39%) 1	0 / 170 (0.00%) 0

Pharyngitis			
subjects affected / exposed	0 / 266 (0.00%)	1 / 255 (0.39%)	0 / 170 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	1 / 170 (0.59%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	1 / 170 (0.59%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	0 / 170 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	0 / 170 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 266 (0.00%)	0 / 255 (0.00%)	1 / 170 (0.59%)
occurrences (all)	0	0	1

Non-serious adverse events	Combination therapy Neb5mg/RAM10mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 71 (8.45%)		
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Sciatica			

subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all) Gastroesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0 0 / 71 (0.00%) 0 1 / 71 (1.41%) 1		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Spinal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0 0 / 71 (0.00%) 0 0 / 71 (0.00%) 0 1 / 71 (1.41%) 1		
Infections and infestations			

Influenza			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
COVID-19			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2023	Affected Section(s): 2,4,5,7,12 Summary of Revisions Made: For the purpose of this study, uncontrolled BP is amended as follows: sitting SBP/DBP: $\geq 130/80$ mmHg in patients < 65 years old sitting SBP/DBP: $\geq 140/80$ mmHg in patients ≥ 65 years old. The optimal BP goal is modified accordingly, as follows: sitting BP $< 130/80$ mmHg in patients < 65 years old sitting BP $< 140/80$ mmHg in patients ≥ 65 years old. Minor editorial and document formatting revisions: 1) In the following sentence "and" has been replaced by "and/or" for further clarification: "Hypertensive patients with Systolic blood pressure (SBP) ranging from ≥ 140 to ≤ 179 mmHg and/or Diastolic blood pressure (DBP) ranging from ≥ 90 to ≤ 109 mmHg on treatment." 2) The following sentence has been updated as below for following visits by removing the word first dose: "Intake of the dispensed study medication at the site at the end of all other procedures/assessments" • Screening and start of Run-in period (Visit 1, Week -4) • Assessment period (Visit 2, Week 0) • Assessment period (Visit 3, Week 4) • Assessment period (Visit 4, Week 8) Rationale: Thresholds and target BP goals have been amended by age groups according to 2018 ESC/ESH guidelines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported