



Clinical trial results:

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of BHV-3241 in Subjects with Multiple System Atrophy (M-STAR Study)

Summary

EudraCT number	2019-001100-38
Trial protocol	FR DE GB AT IT
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	13 July 2023
First version publication date	13 July 2023

Trial information

Trial identification

Sponsor protocol code	BHV3241-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03952806
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biohaven Pharmaceuticals, Inc
Sponsor organisation address	215 Church Street, New Haven, Connecticut, United States, 06510
Public contact	Chief Medical Officer, Biohaven Pharmaceuticals Inc, +1 203-404-0410, clinicaltrials@biohavenpharma.com
Scientific contact	Chief Medical Officer, Biohaven Pharmaceuticals Inc, +1 203-404-0410, clinicaltrials@biohavenpharma.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	28 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2021
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of verdiperstat (BHV-3241), compared to placebo, as measured by a change from baseline in a modified Unified Multiple System Atrophy (MSA) Rating Scale (UMSARS), consisting of a subset of items from Part I and Part II, at Week 48.

To assess the safety and tolerability of verdiperstat relative to placebo in participants with MSA.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice, as defined by the International Council on Harmonisation and in accordance with the ethical principles underlying European Union Directive 2001/20/EC, and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 2019
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	United Kingdom: 5
Country: Number of subjects enrolled	United States: 214
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Italy: 29
Worldwide total number of subjects	336
EEA total number of subjects	117

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)	227
From 65 to 84 years	109
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 3, randomized, double-blind, placebo-controlled study was conducted in participants with MSA at 48 centers.

Pre-assignment

Screening details:

This study consists of a screening period (up to 6 weeks) and double-blind treatment phase (48 weeks) followed by open-label extension (OLE) phase (48 weeks). A total of 336 participants were enrolled in this study.

Period 1

Period 1 title	Randomization Phase (Weeks 1 Through 48)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Verdiperstat

Arm description:

Randomization Phase (Randomization through Week 48): Participants received verdiperstat 300 milligrams (mg) tablet orally once daily for 1 week, followed by 300 mg twice daily for 1 week, and then 600 mg twice daily for the remaining 46 weeks of the double-blind phase.

Arm type	Experimental
Investigational medicinal product name	Verdiperstat
Investigational medicinal product code	BHV-3241
Other name	AZD3241
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Verdiperstat 300 mg tablet administered orally once daily for 1 week, followed by 300 mg twice daily for 1 week, and then 600 mg twice daily for the remaining 46 weeks of the double-blind phase.

Arm title	Placebo
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Arm description:

Randomization Phase (Randomization through Week 48): Participants received placebo matching with verdiperstat for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching with verdiperstat administered orally once daily for 1 week, followed by twice daily for the remaining 47 weeks of the double-blind phase.

Number of subjects in period 1	Verdiperstat	Placebo
Started	168	168
Completed	127	146
Not completed	41	22
Consent withdrawn by subject	4	2
Disease progression	5	-
Adverse event, non-fatal	26	15
Participant request	5	5
Unspecified	1	-

Period 2

Period 2 title	OLE Phase (48 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Verdiperstat/Verdiperstat

Arm description:

OLE phase (48 weeks): Participants who completed the double-blind phase were offered the opportunity to enroll in an OLE phase to continue verdiperstat 600 mg orally twice daily for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Verdiperstat
Investigational medicinal product code	BHV-3241
Other name	AZD3241
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants continued verdiperstat 600 mg twice daily for 48 weeks in OLE phase.

Arm title	Placebo/Verdiperstat
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Arm description:

OLE phase (48 weeks): Participants who completed the double-blind phase were offered the opportunity to enroll in an OLE phase to receive verdiperstat 600 mg tablet orally twice daily for 48 weeks.

Arm type	Placebo
Investigational medicinal product name	Verdiperstat
Investigational medicinal product code	BHV-3241
Other name	AZD3241
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received verdiperstat 600 mg twice daily for 48 weeks in OLE phase.

Number of subjects in period 2 ^[1]	Verdiperstat/Verdiperstat	Placebo/Verdiperstat
Started	123	140
Completed	44	46
Not completed	79	94
Consent withdrawn by subject	4	5
Disease progression	6	9
Adverse event, non-fatal	18	29
Participant request to discontinue	35	38
Unspecified	16	13

Notes:

[1] - 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: Participants who continued into the extension phase.

Baseline characteristics

Reporting groups

Reporting group title	Verdiperstat
Reporting group description:	
Randomization Phase (Randomization through Week 48): Participants received verdiperstat 300 milligrams (mg) tablet orally once daily for 1 week, followed by 300 mg twice daily for 1 week, and then 600 mg twice daily for the remaining 46 weeks of the double-blind phase.	
Reporting group title	Placebo
Reporting group description:	
Randomization Phase (Randomization through Week 48): Participants received placebo matching with verdiperstat for 48 weeks.	

Reporting group values	Verdiperstat	Placebo	Total
Number of subjects	168	168	336
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.4	60.1	
standard deviation	± 7.12	± 6.68	-
Gender categorical Units: Subjects			
Female	83	83	166
Male	85	85	170
Ethnicity Units: Subjects			
Hispanic or Latino	5	5	10
Not Hispanic or Latino	163	163	326
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	3	1	4
Asian	5	7	12
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	3	2	5
White	155	156	311
More than one race	0	0	0
Unknown or Not Reported	1	2	3
UMSARS Modified Score Units: unit on a scale			
arithmetic mean	6.1	5.8	
standard deviation	± 4.24	± 3.74	-

End points

End points reporting groups

Reporting group title	Verdiperstat
Reporting group description: Randomization Phase (Randomization through Week 48): Participants received verdiperstat 300 milligrams (mg) tablet orally once daily for 1 week, followed by 300 mg twice daily for 1 week, and then 600 mg twice daily for the remaining 46 weeks of the double-blind phase.	
Reporting group title	Placebo
Reporting group description: Randomization Phase (Randomization through Week 48): Participants received placebo matching with verdiperstat for 48 weeks.	
Reporting group title	Verdiperstat/Verdiperstat
Reporting group description: OLE phase (48 weeks): Participants who completed the double-blind phase were offered the opportunity to enroll in an OLE phase to continue verdiperstat 600 mg orally twice daily for 48 weeks.	
Reporting group title	Placebo/Verdiperstat
Reporting group description: OLE phase (48 weeks): Participants who completed the double-blind phase were offered the opportunity to enroll in an OLE phase to receive verdiperstat 600 mg tablet orally twice daily for 48 weeks.	

Primary: Change From Baseline in the Modified UMSARS Score at Week 48

End point title	Change From Baseline in the Modified UMSARS Score at Week 48
End point description: The UMSARS is a clinician-rated 5-point scale of items graded 0 (no impairment) to 4 (complete impairment) comprised of 4 parts: Part I, Historical Review, is an assessment of functioning across various areas. Part II is a Motor Examination. Part III is an Autonomic Examination and includes supine and standing vital signs, orthostatic change, and orthostatic symptoms. Part IV is a Global Disability Scale. The primary outcome variable for the study was the Modified UMSARS, which is composed of a subset of 9 items from UMSARS Part I and Part II. The Modified UMSARS Part I and Part II responses are measured on a 4-point scale ranging from 0 to 3, where, 0=no/mild impairment, 1=moderate impairment, 2=severe impairment, and 3=complete impairment. Higher scores indicate greater impairment. Modified Intent to Treat (mITT) population included randomized participants who received at least 1 dose of blinded study therapy and provided a baseline and at least 1 post-baseline efficacy assessment.	
End point type	Primary
End point timeframe: Baseline and Week 48	

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	140		
Units: unit on a scale				
least squares mean (confidence interval 95%)	5.20 (4.52 to 5.89)	4.85 (4.19 to 5.51)		

Statistical analyses

Statistical analysis title	Treatment difference in modified UMSARS score
Comparison groups	Verdiperstat v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4656
Method	Mixed models analysis
Parameter estimate	Least Square mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.48

Primary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs ^[1]
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End point description:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in participants or clinical investigation participants administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. A serious AE (SAE) is defined as any event that met any of the following criteria at any dose: death; life-threatening; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect in the offspring of a participant who received study drug; other important medical events that may not have resulted in death, be life-threatening, or required hospitalization, or, based upon appropriate medical judgment, they may have jeopardized the participant and may have required medical or surgical intervention to prevent one of the other serious outcomes. Treated population.

End point type	Primary
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End point timeframe:

Up to 100 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistical analysis was performed for the primary end point.

End point values	Verdiperstat	Placebo	Verdiperstat/Verdiperstat	Placebo/Verdiperstat
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	168	168	123	140
Units: participants				
TEAE	160	156	95	112
Serious TEAE	44	29	30	27

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Improvement (CGI-I) Score at Week 48

End point title	Clinical Global Impression of Improvement (CGI-I) Score at Week 48
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End point description:

The CGI-I is a clinician-rated scale measuring the change in the participant's clinical status from a specific point in time. It is scored on a 7- point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. Higher scores indicate greater impairment. mITT population.

End point type	Secondary
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End point timeframe:

Week 48

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	142		
Units: unit on a scale				
least squares mean (confidence interval 95%)	5.07 (4.92 to 5.21)	5.14 (5.00 to 5.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple System Atrophy Quality of Life (MSA-QoL) Motor Subscale at Week 48

End point title	Change From Baseline in Multiple System Atrophy Quality of Life (MSA-QoL) Motor Subscale at Week 48
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End point description:

The MSA-QoL is a participant-rated scale that was designed to measure health-related quality of life specifically in MSA. It assesses activities of daily living and has subscales for motor, nonmotor, and emotional/social domains. The MSA-QoL includes 40 items and has three subscales: (1) motor (14 items), (2) nonmotor (12 items), and (3) emotional/social (14 items). Scores on each of the subscales are derived by summing the respective items with higher scores on each scale indicating a higher impact of the disease on the aspect measured by each subscale. mITT population.

End point type	Secondary
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End point timeframe:

Baseline and Week 48

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	130		
Units: unit on a scale				
least squares mean (confidence interval 95%)	13.83 (10.97 to 16.69)	13.45 (10.72 to 16.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Multiple System Atrophy Quality of Life (MSA-QoL) Non-motor Subscale at Week 48

End point title	Change From Baseline in Multiple System Atrophy Quality of Life (MSA-QoL) Non-motor Subscale at Week 48
End point description:	
The MSA-QoL is a participant-rated scale that was designed to measure health-related quality of life specifically in MSA. It assesses activities of daily living and has subscales for motor, nonmotor, and emotional/social domains. The MSA-QoL includes 40 items and has three subscales: (1) motor (14 items), (2) nonmotor (12 items), and (3) emotional/social (14 items). Scores on each of the subscales are derived by summing the respective items with higher scores on each scale indicating a higher impact of the disease on the aspect measured by each subscale. mITT population.	
End point type	Secondary
End point timeframe:	
Baseline and Week 48	

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	128		
Units: unit on a scale				
least squares mean (confidence interval 95%)	7.52 (4.93 to 10.11)	5.56 (3.07 to 8.04)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UMSARS Part I and Part II Total Score at Week 48

End point title	Change From Baseline in UMSARS Part I and Part II Total Score at Week 48
End point description:	
The UMSARS is a clinician-rated 5-point scale of items graded 0 (no impairment) to 4 (complete impairment) comprised of 4 parts: Part I, Historical Review, is an assessment of functioning across various areas. Part II is a Motor Examination. The UMSARS Part I and Part II responses are measured on a 4-point scale ranging from 0 to 3, where, 0 = no/mild impairment, 1 = moderate impairment, 2 = severe impairment, and 3 = complete impairment. Higher scores indicate greater impairment. mITT population.	

End point type	Secondary
End point timeframe:	
Baseline and Week 48	

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	139		
Units: unit on a scale				
least squares mean (confidence interval 95%)	12.00 (10.37 to 13.63)	11.34 (9.77 to 12.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Patient Global Impression of Severity (PGI-S) at Week 48

End point title	Change From Baseline in Patient Global Impression of Severity (PGI-S) at Week 48
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End point description:

The PGI-S is a participant-rated scale which measures how participants perceive the severity of their illness. The PGI-S is a 1- item questionnaire on a 4-point scale ranging from 1 to 4, where, 1 = normal, 2 = mild, 3 = moderate, 4 = severe. Higher scores indicate greater impairment. mITT population.

End point type	Secondary
End point timeframe:	
Baseline and Week 48	

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	142		
Units: unit on a scale				
least squares mean (confidence interval 95%)	0.33 (0.23 to 0.42)	0.27 (0.18 to 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression of Severity (CGI-S) at Week 48

End point title	Change From Baseline in Clinical Global Impression of Severity (CGI-S) at Week 48
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End point description:

The CGI-S is a clinician-rated scale measuring the severity of the participant's illness. It is scored on a 7- point scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill participants). Higher scores indicate greater impairment. mITT population.

End point type	Secondary
End point timeframe:	
Baseline and Week 48	

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	142		
Units: unit on a scale				
least squares mean (confidence interval 95%)	0.79 (0.66 to 0.92)	0.78 (0.66 to 0.90)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UMSARS Part III at Week 48

End point title	Change From Baseline in UMSARS Part III at Week 48
End point description:	
The UMSARS is a clinician-rated 5-point scale of items graded 0 (no impairment) to 4 (complete impairment) comprised of 4 parts: Part III is an Autonomic Examination, and includes supine and standing vital signs, orthostatic change, and orthostatic symptoms. mITT population. Here, n= number of participants analyzed for each parameter.	
End point type	Secondary
End point timeframe:	
Baseline and Week 48	

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	132		
Units: unit on a scale				
least squares mean (confidence interval 95%)				
Systolic blood pressure (BP) (n=118, 132)	-2.18 (-5.90 to 1.55)	-3.09 (-6.63 to 0.44)		
Diastolic BP (n=118, 131)	-2.87 (-5.13 to -0.61)	-2.54 (-4.70 to -0.38)		
Heart rate (n=119, 132)	0.20 (-1.48 to 1.87)	-0.68 (-2.27 to 0.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UMSARS Part IV at Week 48

End point title	Change From Baseline in UMSARS Part IV at Week 48
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End point description:

The UMSARS is a clinician-rated 5-point scale of items graded 0 (no impairment) to 4 (complete impairment) comprised of 4 parts: Part IV is a Global Disability Scale. The UMSARS Part IV measured on a 5-point scale ranging from 0 to 4, where, 0 = Completely independent, 1 = Not completely independent, 2 = More dependent, 3 = Very dependent, and 4 = Totally dependent and helpless. Higher scores indicate greater impairment. mITT population.

End point type	Secondary
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End point timeframe:

Baseline and Week 48

End point values	Verdiperstat	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	140		
Units: unit on a scale				
least squares mean (confidence interval 95%)	0.82 (0.69 to 0.96)	0.85 (0.72 to 0.99)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

TEAEs were reported from first dose of study drug and prior to 30 days after the last dose of study drug, maximum of 100 weeks.

Adverse event reporting additional description:

Treated population included enrolled participants who received at least 1 dose of blinded study therapy (verdiperstat or placebo).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Verdiperstat - Randomization Phase
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Reporting group description:

Participants received verdiperstat 300 mg tablet orally once daily for 1 week, followed by 300 mg twice daily for 1 week, and then 600 mg twice daily for the remaining 46 weeks of the double-blind phase.

Reporting group title	Placebo - Randomization Phase
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Reporting group description:

Participants received placebo matching with verdiperstat for 48 weeks.

Reporting group title	Verdiperstat - Randomization Phase/ Verdiperstat - OLE Phase
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Reporting group description:

Participants who completed the double-blind phase were offered the opportunity to enroll in an OLE phase to continue verdiperstat 600 mg orally twice daily for 48 weeks.

Reporting group title	Placebo - Randomization Phase/ Verdiperstat - OLE Phase
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Reporting group description:

Participants who completed the double-blind phase were offered the opportunity to enroll in an OLE phase to receive verdiperstat 600 mg tablet orally twice daily for 48 weeks.

Serious adverse events	Verdiperstat - Randomization Phase	Placebo - Randomization Phase	Verdiperstat - Randomization Phase/ Verdiperstat - OLE Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 168 (26.19%)	29 / 168 (17.26%)	30 / 123 (24.39%)
number of deaths (all causes)	11	5	12
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 168 (0.00%)	2 / 168 (1.19%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			

subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			
Vulva cyst			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Increased bronchial secretion			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis aspiration			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	3 / 168 (1.79%)	1 / 168 (0.60%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	1 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	3 / 123 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device occlusion			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood creatine phosphokinase abnormal			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 168 (0.00%)	2 / 168 (1.19%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 168 (0.60%)	2 / 168 (1.19%)	2 / 123 (1.63%)
occurrences causally related to treatment / all	1 / 1	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	2 / 168 (1.19%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	2 / 123 (1.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Hip fracture			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	2 / 123 (1.63%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 2
Cardiac failure			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	3 / 123 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Pericarditis constrictive			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Bradykinesia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dorsal ramus syndrome			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 168 (0.00%)	2 / 168 (1.19%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple system atrophy			

subjects affected / exposed	3 / 168 (1.79%)	2 / 168 (1.19%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 1
Oromandibular dystonia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 168 (1.19%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 168 (1.19%)	1 / 168 (0.60%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Decubitus ulcer			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	1 / 168 (0.60%)	4 / 168 (2.38%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Clostridial sepsis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			

subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 168 (2.98%)	2 / 168 (1.19%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	1 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 168 (1.19%)	2 / 168 (1.19%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 168 (1.79%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	7 / 168 (4.17%)	1 / 168 (0.60%)	4 / 123 (3.25%)
occurrences causally related to treatment / all	0 / 11	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	4 / 168 (2.38%)	2 / 168 (1.19%)	1 / 123 (0.81%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Wound infection			
subjects affected / exposed	0 / 168 (0.00%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 168 (0.60%)	1 / 168 (0.60%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 168 (0.60%)	0 / 168 (0.00%)	0 / 123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo - Randomization Phase/ Verdiperstat - OLE Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 140 (19.29%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive urgency			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Oedema peripheral			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vulva cyst			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic respiratory failure			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Hypoxia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Increased bronchial secretion			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis aspiration			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	2 / 140 (1.43%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			

Device occlusion			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine phosphokinase abnormal			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			

subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Overdose			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Radius fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin laceration			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			

subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Cardiac failure			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery disease			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis constrictive			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Bradykinesia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dorsal ramus syndrome			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial paresis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			

subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple system atrophy			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oromandibular dystonia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paralysis recurrent laryngeal nerve			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vocal cord paralysis			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Volvulus			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder pain			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal pain			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
COVID-19 pneumonia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridial sepsis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Herpes zoster				
subjects affected / exposed	0 / 140 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected skin ulcer				
subjects affected / exposed	0 / 140 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 140 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	0 / 140 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumococcal sepsis				
subjects affected / exposed	0 / 140 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 140 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	3 / 140 (2.14%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pyelonephritis acute				
subjects affected / exposed	0 / 140 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	3 / 140 (2.14%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 140 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 140 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 140 (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: 5 %

Non-serious adverse events	Verdiperstat - Randomization Phase	Placebo - Randomization Phase	Verdiperstat - Randomization Phase/ Verdiperstat - OLE Phase
Total subjects affected by non-serious adverse events subjects affected / exposed	125 / 168 (74.40%)	130 / 168 (77.38%)	55 / 123 (44.72%)
Investigations Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all)	9 / 168 (5.36%) 13	1 / 168 (0.60%) 1	6 / 123 (4.88%) 6
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	37 / 168 (22.02%) 66	39 / 168 (23.21%) 53	21 / 123 (17.07%) 27
Vascular disorders Hypertension subjects affected / exposed occurrences (all) Orthostatic hypotension subjects affected / exposed occurrences (all)	3 / 168 (1.79%) 3 7 / 168 (4.17%) 7	9 / 168 (5.36%) 9 11 / 168 (6.55%) 12	1 / 123 (0.81%) 1 4 / 123 (3.25%) 4
Nervous system disorders Balance disorder subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Syncope subjects affected / exposed occurrences (all)	17 / 168 (10.12%) 20 13 / 168 (7.74%) 16 21 / 168 (12.50%) 25 3 / 168 (1.79%) 4	14 / 168 (8.33%) 15 22 / 168 (13.10%) 22 23 / 168 (13.69%) 28 9 / 168 (5.36%) 11	3 / 123 (2.44%) 4 3 / 123 (2.44%) 3 3 / 123 (2.44%) 4 2 / 123 (1.63%) 5
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	7 / 168 (4.17%) 7	6 / 168 (3.57%) 7	5 / 123 (4.07%) 5

Fatigue subjects affected / exposed occurrences (all)	15 / 168 (8.93%) 15	14 / 168 (8.33%) 17	6 / 123 (4.88%) 6
Gait disturbance subjects affected / exposed occurrences (all)	12 / 168 (7.14%) 12	12 / 168 (7.14%) 12	2 / 123 (1.63%) 2
Oedema peripheral subjects affected / exposed occurrences (all)	12 / 168 (7.14%) 12	7 / 168 (4.17%) 8	6 / 123 (4.88%) 6
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	19 / 168 (11.31%) 21	12 / 168 (7.14%) 13	7 / 123 (5.69%) 7
Nausea subjects affected / exposed occurrences (all)	17 / 168 (10.12%) 19	8 / 168 (4.76%) 8	1 / 123 (0.81%) 1
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	9 / 168 (5.36%) 12	4 / 168 (2.38%) 5	1 / 123 (0.81%) 1
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	10 / 168 (5.95%) 11	7 / 168 (4.17%) 7	3 / 123 (2.44%) 3
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 168 (3.57%) 6	9 / 168 (5.36%) 9	3 / 123 (2.44%) 3
Back pain subjects affected / exposed occurrences (all)	7 / 168 (4.17%) 7	9 / 168 (5.36%) 10	3 / 123 (2.44%) 3
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	2 / 168 (1.19%) 2	11 / 168 (6.55%) 11	3 / 123 (2.44%) 3
Urinary tract infection			

subjects affected / exposed	44 / 168 (26.19%)	54 / 168 (32.14%)	26 / 123 (21.14%)
occurrences (all)	71	77	38

Non-serious adverse events	Placebo - Randomization Phase/ Verdiperstat - OLE Phase		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 140 (50.71%)		
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	7 / 140 (5.00%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	21 / 140 (15.00%)		
occurrences (all)	38		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 140 (2.14%)		
occurrences (all)	3		
Orthostatic hypotension			
subjects affected / exposed	4 / 140 (2.86%)		
occurrences (all)	4		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	4 / 140 (2.86%)		
occurrences (all)	5		
Dizziness			
subjects affected / exposed	5 / 140 (3.57%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	11 / 140 (7.86%)		
occurrences (all)	12		
Syncope			
subjects affected / exposed	8 / 140 (5.71%)		
occurrences (all)	8		
General disorders and administration site conditions			

<p>Asthenia</p> <p>subjects affected / exposed</p> <p>7 / 140 (5.00%)</p> <p>occurrences (all)</p> <p>8</p>			
<p>Fatigue</p> <p>subjects affected / exposed</p> <p>4 / 140 (2.86%)</p> <p>occurrences (all)</p> <p>4</p>			
<p>Gait disturbance</p> <p>subjects affected / exposed</p> <p>2 / 140 (1.43%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>4 / 140 (2.86%)</p> <p>occurrences (all)</p> <p>4</p>			
<p>Gastrointestinal disorders</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>4 / 140 (2.86%)</p> <p>occurrences (all)</p> <p>6</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>8 / 140 (5.71%)</p> <p>occurrences (all)</p> <p>9</p>			
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>4 / 140 (2.86%)</p> <p>occurrences (all)</p> <p>5</p>			
<p>Psychiatric disorders</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>2 / 140 (1.43%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>2 / 140 (1.43%)</p> <p>occurrences (all)</p> <p>2</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>3 / 140 (2.14%)</p> <p>occurrences (all)</p> <p>3</p>			
<p>Infections and infestations</p>			

COVID-19			
subjects affected / exposed	5 / 140 (3.57%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	29 / 140 (20.71%)		
occurrences (all)	40		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2020	Modification of UMSARS analysis, refinement of eligibility criteria and clarification of prohibited/restricted concomitant medications /timing of required washout for prohibited medications to address limitations in this rare disease population of very ill participants with multiple comorbidities, specification of option to Rescreen participants, incorporation of Administrative Letters 1, 2 and 3 to update ICON medical monitor information and clarify IP storage temperature and excursion reporting, and administrative clarifications/updates.
16 July 2020	Due to restrictions intended to minimize COVID-19 public health emergency resurgence potential hazards to study participants, that impact conduct of study assessments and visits, provisions were added/implemented to allow alternatives to in-person study visits if needed, including remote safety visits and expansion of window for Week 48 visit to proactively account for any visits that may be delayed. In addition, sample size was increased to proactively account for potential loss of subjects due to COVID-19 and to increase the power to 90%. Addition of Open-Label Extension to provide participants who complete the double-blind portion of the study with access to treatment with open-label BHV-3241.
20 January 2021	Addition of exploratory objectives and clarification of eligibility criteria related to Open Label Extension phase of study and correction of typographical error in Section 4.5.2 to correspond to text correctly presented in Table 2 Schedule of Assessments and Events – Open Label Phase, Footnote 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported