



Clinical trial results:

Opened phase II controlled and randomized clinical trial to evaluate the efficacy in the intra-arterial infusion with mononuclear autologous bone marrow stem cells in patients with ischemic stroke

Summary

EudraCT number	2013-002135-15
Trial protocol	ES
Global end of trial date	14 April 2023

Results information

Result version number	v1 (current)
This version publication date	25 March 2026
First version publication date	25 March 2026
Summary attachment (see zip file)	Resumen del Informe Clínico Final (CMMo-Ictus-2013_Resumen informe clínico final_1.0_17Dic2025.pdf)

Trial information

Trial identification

Sponsor protocol code	CMMo/ICTUS/2013
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02178657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Red Andaluza De Diseno Y Traslacion De Terapias Avanzadas Fundacion Publica Andaluza Progreso Y Salud
Sponsor organisation address	Edificio S-2 Calle Americo Vesputio Nº 15 Parque Cientifico Y Tecnologico Cartuja 93 Sevilla 41092 S, Sevilla, Spain, 41092
Public contact	UNIDAD DE COORDINACIÓN-INVESTIGACIÓN CLÍNICA , Red Andaluza De Diseno Y Traslacion De Terapias Avanzadas Fundacion Publica Andaluza Progreso Y Salud, 0034 955048366, ensayosclinicos.radytta.fps@juntadeandalucia.es
Scientific contact	UNIDAD DE COORDINACIÓN-INVESTIGACIÓN CLÍNICA , Red Andaluza De Diseno Y Traslacion De Terapias Avanzadas Fundacion Publica Andaluza Progreso Y Salud, 0034 955048366, ensayosclinicos.radytta.fps@juntadeandalucia.es

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	04 September 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2023
Global end of trial reached?	Yes
Global end of trial date	14 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy in the intra-arterial infusion with mononuclear autologous bone marrow stem cells in patients with ischemic stroke, by the evaluation of the functional recovering after infusion

Protection of trial subjects:

Trial subject protection measures included prior written informed consent, predefined inclusion and exclusion criteria to minimise risk, close safety monitoring throughout the trial, follow-up of adverse events, and civil liability insurance coverage in accordance with Spanish legislation (Royal Decree 1090/2015) to compensate subjects in the event of trial-related harm.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2015
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	Spain: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	37

From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was conducted between 29 April 2015 and 6 May 2021 at participating hospitals. Most patients were enrolled at Hospital Universitario Virgen del Rocío, followed by Hospital Reina Sofía. Hospital Universitario Virgen Macarena and Hospital Puerta del Mar enrolled smaller numbers of patients.

Pre-assignment

Screening details:

Screening failures (n = 2)

Did not meet eligibility criteria (n = 1)

Other (n = 1): Inability to perform bone marrow extraction and processing on the same day.

Period 1

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

Blinding implementation details:

This is a double-blind clinical trial, meaning that neither the patient nor the medical team will be aware of the treatment group assignment.

Once the 6-month follow-up period of the last enrolled patient has been completed, and under the conditions previously described, unblinding will be authorised. At that point, all patients who were randomised to the control group may be treated under a compassionate use programme.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental group 1

Arm description:

Non-expanded autologous adult bone marrow mononuclear cells (CMMo/CMN-BM) at a dose of $2 \times 10 \pm 10\%$ cells/kg body weight.

Arm type	Experimental
Investigational medicinal product name	Autologous bone marrow adult mononuclear cells not expanded
Investigational medicinal product code	PRD11475388
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Infusion

Dosage and administration details:

Non-expanded autologous adult bone marrow mononuclear cells (CMMo/CMN-BM) at a dose of $2 \times 10 \pm 10\%$ cells/kg body weight.

After inclusion in the trial and randomisation, all patients will undergo a catheterisation procedure during which baseline haemodynamic parameters will be assessed and, as appropriate, the cellular product or placebo will be administered via the three main coronary arteries: the left anterior descending, the circumflex, and the right coronary artery, using a microcatheter positioned in the proximal segment of each artery. Fifty percent of the total cell dose will be administered via the left anterior descending artery, and the remaining 50% will be administered via either the right coronary artery or the circumflex artery, depending on coronary dominance. In cases where no clear dominance is present, the cell suspension will be distributed equally between the right coronary and circumflex arteries (25% each). Exceptionally, if the left anterior descending arteries

Arm title	Experimental group 2
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Arm description:

Non-expanded autologous adult bone marrow mononuclear cells (CMMo/CMN-BM) at a dose of $5 \times 10 \pm 10\%$ cells/kg body weight

Arm type	Experimental
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Investigational medicinal product name	Autologous bone marrow adult mononuclear cells not expanded
Investigational medicinal product code	PRD11475388
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Infusion

Dosage and administration details:

Non-expanded autologous adult bone marrow mononuclear cells (CMMo/CMN-BM) at a dose of $2 \times 10 \pm 10\%$ cells/kg body weight.

After inclusion in the trial and randomisation, all patients will undergo a catheterisation procedure during which baseline haemodynamic parameters will be assessed and, as appropriate, the cellular product or placebo will be administered via the three main coronary arteries: the left anterior descending, the circumflex, and the right coronary artery, using a microcatheter positioned in the proximal segment of each artery. Fifty percent of the total cell dose will be administered via the left anterior descending artery, and the remaining 50% will be administered via either the right coronary artery or the circumflex artery, depending on coronary dominance. In cases where no clear dominance is present, the cell suspension will be distributed equally between the right coronary and circumflex arteries (25% each). Exceptionally, if the left anterior descending arteries

Arm title	Control group
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Arm description:

Without intervention.

Arm type	No intervention
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No investigational medicinal product assigned in this arm

Number of subjects in period 1	Experimental group 1	Experimental group 2	Control group
Started	20	19	38
Completed	20	19	38

Baseline characteristics

End points

End points reporting groups

Reporting group title	Experimental group 1
Reporting group description: Non-expanded autologous adult bone marrow mononuclear cells (CMMo/CMN-BM) at a dose of $2 \times 10 \pm 10\%$ cells/kg body weight.	
Reporting group title	Experimental group 2
Reporting group description: Non-expanded autologous adult bone marrow mononuclear cells (CMMo/CMN-BM) at a dose of $5 \times 10 \pm 10\%$ cells/kg body weight	
Reporting group title	Control group
Reporting group description: Without intervention.	

Primary: Primary endpoint. Modified Rankin Scale score 0–2.

End point title	Primary endpoint. Modified Rankin Scale score 0–2.
End point description: To evaluate the efficacy of bone marrow stem cell treatment in patients with acute ischemic stroke by assessing functional recovery following the procedure. The primary study endpoint will be the proportion of patients achieving functional independence (modified Rankin Scale score 0–2) at 6 months of follow-up	
End point type	Primary
End point timeframe: At 6 months of follow-up.	

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Number of subjects	10	8	14	

Statistical analyses

Statistical analysis title	Proportion of Subjects Achieving mRS 0–2. 6 Month
Statistical analysis description: The primary efficacy variable is binary (success: mRS 0–2 vs failure: mRS 3–6). The comparison between treatment groups was performed using binary logistic regression with an identity link at 6 months. The common difference in success proportions between groups was calculated with its 95% confidence interval (Wald method) as the measure of clinical effect. In addition, the odds ratio between groups was estimated with its 95% confidence interval using standard logistic regression with a logit link	
Comparison groups	Experimental group 1 v Experimental group 2 v Control group

Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wald test

Secondary: Secondary end point. NIH Stroke Scale (NIHSS) - 3 months

End point title	Secondary end point. NIH Stroke Scale (NIHSS) - 3 months
End point description: Change in NIHSS score from baseline to 3 and 6 months, and comparison of this change between the control and experimental groups.	
End point type	Secondary
End point timeframe: From baseline to 3 and 6 months	

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: NIHSS points				
least squares mean (confidence interval 95%)	5.7 (4.3 to 7.2)	9 (7.5 to 10.5)	7 (5.9 to 8.1)	

Statistical analyses

Statistical analysis title	NIH Stroke Scale (NIHSS)
Statistical analysis description: The improvement in the NIHSS score from baseline to 3 and 6 months was evaluated as a quantitative variable using generalized linear mixed models (GLMM), which incorporated the baseline measurement and the posttreatment assessments, accounting for the distribution and correlation between repeated measures. The treatment effect was expressed as the adjusted mean difference between groups, with 95% confidence intervals and statistical significance evaluated using the Wald method.	
Comparison groups	Experimental group 1 v Experimental group 2 v Control group
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	> 0.05 ^[2]
Method	Wald test within GLMM

Notes:

[1] - Analysis of adjusted mean differences using generalized linear mixed models (GLMM)

[2] - Wald test from generalized linear mixed model (GLMM) comparing adjusted means.

Secondary: Secondary end point. NIH Stroke Scale (NIHSS) - 6 months

End point title	Secondary end point. NIH Stroke Scale (NIHSS) - 6 months
End point description: Change in NIHSS score from baseline to 3 and 6 months, and comparison of this change between the	

control and experimental groups.

End point type	Secondary
End point timeframe:	
From baseline to 3 and 6 months	

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: NIHSS points				
least squares mean (confidence interval 95%)	4.6 (3.2 to 6.1)	7.9 (6.4 to 9.4)	6.5 (5.4 to 7.5)	

Statistical analyses

Statistical analysis title	NIH Stroke Scale (NIHSS)
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Statistical analysis description:

The improvement in the NIHSS score from baseline to 3 and 6 months was evaluated as a quantitative variable using generalized linear mixed models (GLMM), which incorporated the baseline measurement and the posttreatment assessments, accounting for the distribution and correlation between repeated measures. The treatment effect was expressed as the adjusted mean difference between groups, with 95% confidence intervals and statistical significance evaluated using the Wald method.

Comparison groups	Experimental group 1 v Experimental group 2 v Control group
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	> 0.05 ^[4]
Method	Wald test within GLMM

Notes:

[3] - Analysis of adjusted mean differences using generalized linear mixed models (GLMM).

[4] - Wald test from generalized linear mixed model (GLMM) comparing adjusted means.

Secondary: Secondary end point. Barthel Index (Barthel >90) - 3 months

End point title	Secondary end point. Barthel Index (Barthel >90) - 3 months
End point description:	

End point type	Secondary
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End point timeframe:

Independence on the Barthel Index (Barthel >90) between baseline and 3 and 6 months, and between the control and experimental groups.

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Subjects				
number (confidence interval 95%)	8 (4 to 12)	6 (2 to 10)	7 (2 to 12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary end point. Barthel Index (Barthel >90) - 6 months

End point title	Secondary end point. Barthel Index (Barthel >90) - 6 months
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End point description:

End point type	Secondary
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End point timeframe:

Independence on the Barthel Index (Barthel >90) between baseline and 3 and 6 months, and between the control and experimental groups.

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Subjects				
number (confidence interval 95%)	3 (0 to 6)	9 (5 to 13)	9 (4 to 14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary end point. Final infarct volume (FLAIR MRI) at 180 days

End point title	Secondary end point. Final infarct volume (FLAIR MRI) at 180 days
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End point description:

Final infarct volume measured on FLAIR MRI at 180 days. Baseline infarct was characterized on diffusionweighted MRI (DWI). Given the quantitative nature and high dispersion with potential outliers, between group comparisons were performed using quantile regression, reporting adjusted median (and quartile) differences with 95% confidence intervals.

End point type	Secondary
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End point timeframe:

Baseline (DWI MRI) and Day 180 ($\pm$ X days) FLAIR MRI

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: mL				
median (confidence interval 95%)	44.9 (25.4 to 64.4)	41.9 (18.5 to 65.3)	42.3 (30.5 to 54.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint. Longterm neurological maintenance. Modified Rankin Scale 0–2 (12)

End point title	Secondary endpoint. Longterm neurological maintenance. Modified Rankin Scale 0–2 (12)
End point description: Analysis of the modified Rankin Scale 0–2 and the Barthel Index (>90) at 12 and 24 months to assess longterm neurological maintenance. Modified Rankin Scale 0–2 at 12 months.	
End point type	Secondary
End point timeframe: 12 months.	

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Number of subjects	12	6	16	

Statistical analyses

Statistical analysis title	Proportion of Subjects Achieving mRS 0–2. 12 Month
Statistical analysis description: Neurological maintenance, evaluated using mRS 0–2 and Barthel >90 at 12 and 24 months, was analyzed following the same methodology applied to the primary variable. (The primary efficacy variable is binary (success: mRS 0–2 vs failure: mRS 3–6). The comparison between treatment groups was performed using binary logistic regression with an identity link at 6 months. The common difference in success proportions between groups was calculated with its 95% confidence interval (Wald method)).	
Comparison groups	Experimental group 1 v Experimental group 2 v Control group
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wald test

Secondary: Secondary endpoint. Longterm neurological maintenance. Modified Rankin Scale 0–2 (24)

End point title	Secondary endpoint. Longterm neurological maintenance. Modified Rankin Scale 0–2 (24)
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End point description:

Analysis of the modified Rankin Scale 0–2 and the Barthel Index (>90) at 12 and 24 months to assess longterm neurological maintenance.

Modified Rankin Scale 0–2 at 12 months.

End point type	Secondary
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End point timeframe:

At 24 months.

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Number of subjects	11	6	18	

Statistical analyses

Statistical analysis title	Proportion of Subjects Achieving mRS 0–2. 24Months
Comparison groups	Experimental group 1 v Experimental group 2 v Control group
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Wald test

Secondary: Secondary endpoint. Longterm neurological maintenance. Barthel index (>90) (12)

End point title	Secondary endpoint. Longterm neurological maintenance. Barthel index (>90) (12)
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End point description:

Neurological maintenance, assessed using mRS 0–2 and Barthel >90 at 12 and 24 months, was analyzed following the same methodology applied to the primary variable.

End point type	Secondary
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End point timeframe:

At 12 months

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Subjects				
number (confidence interval 95%)	10 (6 to 14)	4 (1 to 7)	13 (7 to 19)	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint. Longterm neurological maintenance. Barthel index (>90) (24)

End point title	Secondary endpoint. Longterm neurological maintenance. Barthel index (>90) (24)
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End point description:

Neurological maintenance, assessed using mRS 0–2 and Barthel >90 at 12 and 24 months, was analyzed following the same methodology applied to the primary variable.

End point type	Secondary
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End point timeframe:

At 24 months

End point values	Experimental group 1	Experimental group 2	Control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	19	38	
Units: Subjects				
number (confidence interval 95%)	11 (7 to 16)	4 (1 to 8)	13 (7 to 19)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events occurring at any time after patient inclusion in the study must be reported, that is, from the signing of the informed consent by the subject until 30 days after the patient has completed or withdrawn from the study. A subject is co

Adverse event reporting additional description:

The investigator / their collaborators will question and/or examine the patient for any signs of adverse events. Patient questioning regarding the possible occurrence of adverse events will be conducted in a general manner. Patients should not be specifically questioned about the presence or absence of particular adverse events.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Control
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Reporting group description: -

Reporting group title	Treated, Dose 2 × 10 ±10%
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Reporting group description: -

Reporting group title	Treated, Dose 5 × 10 ±10%
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Reporting group description: -

Serious adverse events	Control	Treated, Dose 2 × 10 ±10%	Treated, Dose 5 × 10 ±10%
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 39 (35.90%)	5 / 19 (26.32%)	10 / 19 (52.63%)
number of deaths (all causes)	4	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gallbladder cancer			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
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			
Femur fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Post angioplasty restenosis			

subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Vascular disorders			
Fibromuscular dysplasia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
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			
Angina pectoris			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Myocardial ischemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Acute coronary syndrome			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Transient ischemic attack			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischemic stroke			
subjects affected / exposed	3 / 39 (7.69%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Vascular stent stenosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Social circumstances			
Postmenopause			

subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric volvulus			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (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
Infections and infestations			
Respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Control	Treated, Dose 2 × 10 ±10%	Treated, Dose 5 × 10 ±10%
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 39 (92.31%)	16 / 19 (84.21%)	19 / 19 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gallbladder cancer			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vulval cancer			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Fibromuscular dysplasia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haematoma			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 39 (2.56%)	1 / 19 (5.26%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Hypotension			
subjects affected / exposed	1 / 39 (2.56%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hypovolemic shock			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Polypectomy subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
General disorders and administration site conditions			
Gait disturbance subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Stent stenosis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0
Social circumstances			
Postmenopause	Additional description: Counts by treatment received: Control (N = 39); Treated, Dose 2 × 10 ±10% (N = 19); Treated, Dose 5 × 10 ±10% (N = 19)		
subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Weight decreased subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 19 (5.26%) 2	0 / 19 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Catarrh subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Pleural effusion subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Respiratory failure			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Orthopnea			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Allergic rhinitis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Choking sensation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Hypertensive crisis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	3 / 39 (7.69%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Mood altered			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Visual hallucination			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0

Anxiety			
subjects affected / exposed	2 / 39 (5.13%)	2 / 19 (10.53%)	1 / 19 (5.26%)
occurrences (all)	2	2	1
Apathy			
subjects affected / exposed	0 / 39 (0.00%)	3 / 19 (15.79%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Depression			
subjects affected / exposed	3 / 39 (7.69%)	1 / 19 (5.26%)	2 / 19 (10.53%)
occurrences (all)	3	1	2
Depressed mood			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Middle insomnia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	1 / 39 (2.56%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Depressive symptom			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 39 (0.00%)	3 / 19 (15.79%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 39 (0.00%)	3 / 19 (15.79%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 39 (0.00%)	2 / 19 (10.53%)	0 / 19 (0.00%)
occurrences (all)	0	3	0
Transaminases increased			

subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 19 (5.26%) 1	1 / 19 (5.26%) 1
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Post procedural haematoma			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Lesion			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Post angioplasty restenosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Lupus endocarditis			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Atrial fibrillation			
subjects affected / exposed	2 / 39 (5.13%)	1 / 19 (5.26%)	3 / 19 (15.79%)
occurrences (all)	2	2	3
Myocardial ischaemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Palpitations			

subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Acute coronary syndrome			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	3
Supraventricular tachycardia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Amnesia			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	1 / 39 (2.56%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Memory impairment			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Epilepsy			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Muscle spasticity			
subjects affected / exposed	1 / 39 (2.56%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Cerebral artery stenosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cerebral haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Ischaemic stroke subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Dizziness subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 19 (0.00%) 0	2 / 19 (10.53%) 2
Syncope subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Shaking subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Balance disorder subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Blood and lymphatic system disorders			
Anemia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 19 (0.00%) 0	5 / 19 (26.32%) 5
Anemia normocytic subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Anemia iron deficiency subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Lymphadenitis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 2	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	4 / 39 (10.26%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	4	0	0
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Lower abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Upper abdominal pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hematochezia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Gastric haemorrhage			
subjects affected / exposed	0 / 39 (0.00%)	0 / 19 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Short bowel syndrome			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastric volvulus			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hypertransaminaemia			
subjects affected / exposed	2 / 39 (5.13%)	0 / 19 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 39 (0.00%)	1 / 19 (5.26%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			

Hematuria subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Urinary incontinence subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0
Kidney failure subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Urinary retention subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	2 / 19 (10.53%) 2
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0
Rotator cuff syndrome subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Urinary tract infection bacterial subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1

Urinary tract infection subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6	2 / 19 (10.53%) 3	4 / 19 (21.05%) 5
Dental infection subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	1 / 19 (5.26%) 2	1 / 19 (5.26%) 1
Pneumonia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	0 / 19 (0.00%) 0	2 / 19 (10.53%) 4
Otitis externa subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Iron deficiency subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0
Vitamin B12 decreased subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 19 (5.26%) 1	1 / 19 (5.26%) 1
Hypercholesterolaemia subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2014	Substantial Modification 1 – Protocol version dated 11 March 2014
02 June 2015	Substantial Modification 2 – Protocol version dated 25 February 2015
01 June 2016	Substantial Modification 3 – Protocol version dated 18 January 2016
23 May 2017	Substantial Modification 4 – Protocol version dated 27 March 2017
04 November 2019	Substantial Modification 5 – Protocol version dated 29 April 2019
22 November 2021	Substantial Modification 6 – Protocol version dated 11 June 2021
08 July 2022	Substantial Modification 7 – Protocol version dated 10 June 2022.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36681446>