Clinical trial results:
A randomized, double-blind, placebo-controlled study of the usefulness of the probiotic 'Lactobacillus reuteri' in the therapy of quadruple eradication of Helicobacter pylori infection in usual clinical practice

Summary

EudraCT number	2017-000342-22
Trial protocol	ES
Global end of trial date	01 August 2018

Results information

Result version number	v1 (current)
This version publication date	17 April 2020
First version publication date	17 April 2020

Trial information

Trial identification

Sponsor protocol code	VALACT-2017-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dr. Luis Fernández-Dr. Jesus Barrio
Sponsor organisation address	Hosp Clín Univ Valladolid-Hosp Univ Río Hortega Valladolid, Valladolid, Spain,
Public contact	Dr. Jesus Barrio Hosp Univ Río Hortega Valladolid, Dr. Luis Fernández Hosp Clín Univ Valladolid , +34 9999999, jbarrioa95@gmail.com
Scientific contact	Dr. Jesus Barrio Hosp Univ Río Hortega Valladolid, Dr. Luis Fernández Hosp Clín Univ Valladolid , +34 9999999, jbarrioa95@gmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2018
Global end of trial reached?	Yes
Global end of trial date	01 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To know if supplementation with Gastrus (food supplement) vs Placebo is able of lowering the gastrointestinal adverse effects of quadruple eradication therapy determined by the GSRS gastrointestinal symptom scale in routine clinical practice.

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

Eradicator treatment with quadruple therapy (at the discretion of the responsible physician):
- Quadruple with bismuth: Pylera (three in one tablets: bismuth, tetracyclines and metronidazole): 3 tablets every 6 hours and omeprazole of 20 mg 1 tablet every 12 hours for 10 consecutive days.
- Quadruple without bismuth: Esomeprazole 40 mg 1 tablet every 12 hours, Amoxicillin 1 g every 12 hours, Clarithromycin 500 mg every 12 hours, Metronidazole 500 mg every 12 hours, all for 14 consecutive days.

Evidence for comparator:

Placebo-controlled study to confirm the usefulness of the probiotic 'Lactobacillus reuteri'

Actual start date of recruitment	01 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 86
Worldwide total number of subjects	86
EEA total number of subjects	86

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)	79
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Two centers involved and 86 subjects participated in the study. Data collection began in January 2017 and ended in August 2018. Seven subjects did not meet the age inclusion criteria and two subjects did not meet the exclusion criterion 3 "Patient treated with NSAIDs", so their data is not analysed. 77 subjects were declared valid for analysis.

Pre-assignment

Screening details:

Aged 18-65 years; Positive diagnosis of H pylori infection.

Period 1

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

Blinding implementation details:

All study treatments were supplied in a way in that they are indistinguishable from each other, in order to maintain the masking of the clinical trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Gastrus

Arm description:

Gastrus (a dietary supplement containing Lactobacillus reuteri DSM 17938 and Lactobacillus reuteri ATCC PTA 6475).
The daily Gastrus dose was one tablet per day (2x108 UFC). It was administered from the first day of the eradicator treatment until completing 30 days of treatment.

Arm type	Experimental
Investigational medicinal product name	Gastrus
Investigational medicinal product code	
Other name	Lactobacillus reuteri DSM 17938 and Lactobacillus reuteri ATCC PTA 6475
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The daily Gastrus dose was one tablet per day (2x108 UFC). It was administered from the first day of the eradicator treatment until completing 30 days of treatment.

Arm title	Placebo

Arm description:

The daily placebo dose was one tablet per day. It was administered from the first day of the eradicator treatment until completing 30 days of treatment.

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

Dosage and administration details:

The daily placebo dose was one tablet per day. It was administered from the first day of the eradicator treatment until completing 30 days of treatment.

Number of subjects in period 1[1]	Gastrus	Placebo
Started	36	41
Completed	36	41

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Seven subjects did not meet the age inclusion criteria, not exceeding 65 years, so their data is not analysed. In a subject, the exclusion criterion 3 "The patient is treated with NSAIDs" was not specified, so that subject is not considered valid for analysis either. Another patient was treated with NSAIDs, which is also excluded from the analysis. 77 subjects were declared valid for analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Gastrus
Reporting group description:	
Gastrus (a dietary supplement containing Lactobacillus reuteri DSM 17938 and Lactobacillus reuteri ATCC PTA 6475). The daily Gastrus dose was one tablet per day (2x108 UFC). It was administered from the first day of the eradicator treatment until completing 30 days of treatment.	
Reporting group title	Placebo
Reporting group description:	
The daily placebo dose was one tablet per day. It was administered from the first day of the eradicator treatment until completing 30 days of treatment.	

Reporting group values	Gastrus	Placebo	Total
Number of subjects	36	41	77
Age categorical Units: Subjects			
Age continuous Units: years			
median	51.5	44	
full range (min-max)	23 to 64	19 to 63	-
Gender categorical Units: Subjects			
Female	20	28	48
Male	16	13	29
Received therapy Units: Subjects			
Quadruple therapy with bismuth	24	27	51
Quadruple therapy without bismuth	12	14	26
GSRS total score			
The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).			
Units: points (range: 0-45)			
arithmetic mean	6.69	6.46	
standard deviation	± 4.28	± 4.21	-
GSRS score: Pain syndrome			
The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).			
Units: points (range: 0-3)			
arithmetic mean	0.31	0.34	
standard deviation	± 0.47	± 0.58	-
GSRS score: Dyspeptic syndrome			
The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more			

discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).			
Units: points (range: 0-12)			
arithmetic mean	2.47	1.78	
standard deviation	± 1.95	± 1.64	-
GSRS score: Indigestion syndrome			
The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).			
Units: points (range: 0-12)			
arithmetic mean	2.92	2.78	
standard deviation	± 2.1	± 2.2	-
GSRS score: Colon disfunction syndrome			
The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).			
Units: points (range: 0-18)			
arithmetic mean	1.0	1.56	
standard deviation	± 1.45	± 1.61	-

End points

End points reporting groups

Reporting group title	Gastrus
Reporting group description:	
Gastrus (a dietary supplement containing Lactobacillus reuteri DSM 17938 and Lactobacillus reuteri ATCC PTA 6475). The daily Gastrus dose was one tablet per day (2x108 UFC). It was administered from the first day of the eradicator treatment until completing 30 days of treatment.	
Reporting group title	Placebo
Reporting group description:	
The daily placebo dose was one tablet per day. It was administered from the first day of the eradicator treatment until completing 30 days of treatment.	

Primary: Change GSRS at day 15 from baseline: Total score

End point title	Change GSRS at day 15 from baseline: Total score
End point description:	
The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).	
End point type	Primary
End point timeframe:	
At day 15 of treatment	

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: points				
arithmetic mean (standard deviation)				
Total score	0.11 (± 4.51)	-0.57 (± 4.68)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v Gastrus
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.532
Method	ANOVA

Secondary: Change GSRS at day 15 from baseline: Pain syndrome	
End point title	Change GSRS at day 15 from baseline: Pain syndrome

End point description:

End point type	Secondary

End point timeframe:

At day 15

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: points				
arithmetic mean (standard deviation)	0.14 (± 0.65)	0.11 (± 0.84)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.846
Method	ANOVA

Secondary: Change GSRS at day 15 from baseline: Dyspeptic syndrome	
End point title	Change GSRS at day 15 from baseline: Dyspeptic syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

At day 15

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: points				
arithmetic mean (standard deviation)	-0.89 (± 2.26)	-0.24 (± 2.14)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.219
Method	ANOVA

Secondary: Change GSRS at day 15 from baseline: Indigestion syndrome

End point title	Change GSRS at day 15 from baseline: Indigestion syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

At day 15

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: points				
arithmetic mean (standard deviation)	-0.60 (± 1.96)	-0.95 (± 2.11)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Placebo v Gastrus

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.474
Method	ANOVA

Secondary: Change GSRS at day 15 from baseline: Colon dysfunction syndrome

End point title	Change GSRS at day 15 from baseline: Colon dysfunction syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

At dat 15

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: points				
arithmetic mean (standard deviation)	1.45 (± 1.77)	0.51 (± 2.05)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	ANOVA

Secondary: Change GSRS at day 31 from baseline: Total score

End point title	Change GSRS at day 31 from baseline: Total score

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

Overall period

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	36		
Units: points				
arithmetic mean (standard deviation)	-1.82 (± 3.59)	-2.36 (± 4.48)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.583
Method	ANOVA

Secondary: Change GSRS at day 31 from baseline: Pain syndrome

End point title	Change GSRS at day 31 from baseline: Pain syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

Overall period

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	36		
Units: points				
arithmetic mean (standard deviation)	-0.12 (± 0.48)	-0.11 (± 0.67)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.963
Method	ANOVA

Secondary: Change GSRS at day 31 from baseline: Dyspeptic syndrome

End point title	Change GSRS at day 31 from baseline: Dyspeptic syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

Overall period

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	36		
Units: points				
arithmetic mean (standard deviation)	-1.23 (± 2.24)	-0.83 (± 1.59)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.389
Method	ANOVA

Secondary: Change GSRS at day 31 from baseline: Indigestion syndrome

End point title	Change GSRS at day 31 from baseline: Indigestion syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms

associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

Overall period

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	36		
Units: points				
arithmetic mean (standard deviation)	-0.79 (± 1.70)	-1.17 (± 2.26)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.441
Method	ANOVA

Secondary: Change GSRS at day 31 from baseline: Colon dysfunction syndrome

End point title	Change GSRS at day 31 from baseline: Colon dysfunction syndrome

End point description:

The Gastrointestinal Symptom Rating Scale (GSRS) is a specific questionnaire for patients with gastrointestinal symptoms. The GSRS is a 15-item instrument designed to assess the symptoms associated with common GI disorders. Each item range from 1 to 3 and higher scores represent more discomfort. It has 4 subscales (Pain Syndrome, Dyspeptic syndrome, Indigestion Syndrome, Colon dysfunction syndrome).

End point type	Secondary

End point timeframe:

Overall period

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	36		
Units: points				
arithmetic mean (standard deviation)	0.323 (± 1.57)	-0.25 (± 1.85)		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169
Method	ANOVA

Secondary: Eradication rates

End point title	Eradication rates

End point description:

Porcentaje de pacientes que hayan erradicado mediante el test diagnóstico del test del aliento entre 4 y 8 semanas semanas tras la terminación del tratamiento con el probiótico o placebo.

End point type	Secondary

End point timeframe:

At day 59

End point values	Gastrus	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	41		
Units: subjects				
Positive	32	36		
Negative	4	5		

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Gastrus v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8745
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Gastrus
Reporting group description:	
Gastrus (a dietary supplement containing Lactobacillus reuteri DSM 17938 and Lactobacillus reuteri ATCC PTA 6475). The daily Gastrus dose was one tablet per day (2x108 UFC). It was administered from the first day of the eradicator treatment until completing 30 days of treatment	
Reporting group title	Placebo
Reporting group description:	
The daily placebo dose was one tablet per day. It was administered from the first day of the eradicator treatment until completing 30 days of treatment.	

Serious adverse events	Gastrus	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 41 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Gastrus	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 36 (25.00%)	5 / 41 (12.20%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 36 (2.78%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 36 (5.56%)	1 / 41 (2.44%)	
occurrences (all)	2	1	
Abdominal pain			

subjects affected / exposed	1 / 36 (2.78%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Breath odour			
subjects affected / exposed	1 / 36 (2.78%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 36 (2.78%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 36 (2.78%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	2 / 36 (5.56%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Vulvovaginal candidiasis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 41 (0.00%)	
occurrences (all)	2	0	
Fungal infection			
subjects affected / exposed	0 / 36 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 36 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported