Clinical trial results:
A randomised, double-blind, double-dummy, multi-site, phase III, single dose, 4-way cross-over pharmacodynamic study evaluating the efficacy of Bricanyl Turbuhaler M3 compared to Bricanyl Turbuhaler M2 by studying the protective effect on methacholine induced bronchoconstriction in patients with stable, mild to moderate asthma

Summary

EudraCT number	2014-001457-16
Trial protocol	SE NL
Global end of trial date	05 November 2015

Results information

Result version number	v1 (current)
This version publication date	02 October 2016
First version publication date	02 October 2016

Trial information

Trial identification

Sponsor protocol code	D4711C00001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca R&D Gothenburg
Sponsor organisation address	SE-431 83, Mölndal, Sweden,
Public contact	Göran Eckerwall, MD, PhD, AstraZeneca R&D, goran.eckerwall@astrazeneca.com
Scientific contact	Göran Eckerwall, MD, PhD, AstraZeneca R&D, goran.eckerwall@astrazeneca.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	25 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2015
Global end of trial reached?	Yes
Global end of trial date	05 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate therapeutic equivalence between Bricanyl Turbuhaler M3 and Bricanyl Turbuhaler M2 using bronchoprotective effect as outcome measure.
Outcome measurements: PC20 (Methacholine provocative concentration causing a 20% drop in FEV1)

Protection of trial subjects:

Prior methacholine challenge a stable asthma condition was ensured by FEV1 at every visit. Signs and symptoms were recorded and the challenge stopped after a 20% fall in FEV1 was reached. Ipratroprium was given post challenge.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2015
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	Canada: 35
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Sweden: 15
Worldwide total number of subjects	60
EEA total number of subjects	25

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)	60
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with stable, mild to moderate asthma were enrolled. The first patient entered the study on 10 March 2015 and the last patient completed the study on 5 November 2015. Subjects were recruited from: Site 1001 and 1002 in Canada, Site 7201 in Sweden,and Site 5001 in the Netherlands.

Pre-assignment

Screening details:

Of the 95 patients enrolled 34 were screen failures mainly due to not fulfilling specific randomization criteria on stability in asthma or sensitivity to methacholine challenge; 1 was withdrawal by subject; 72 entered run in period. A total of 60 patients were randomized to the 4 single-dose treatments with terbutaline in a crossover design.

Period 1

Period 1 title	Visit 3
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	M2 0.5 mg

Arm description:

0.5 mg terbutaline sulphate administered via Turbuhaler M2

Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

0.5 mg M2 Turbuhaler

Arm title	M2 1.5 mg

Arm description:

1.5 mg terbutaline sulphate administered via Turbuhaler M2

Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1.5 mg M2 Turbuhaler

Arm title	M3 0.5 mg

Arm description:

0.5 mg terbutaline sulphate administered via Turbuhaler M3

Arm type	Active comparator

Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
0.5 mg M3 Turbuhaler

Arm title	M3 1.5 mg

Arm description:
1.5 mg terbutaline sulphate administered via Turbuhaler M3

Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
1.5 mg M3 Turbuhaler

Number of subjects in period 1	M2 0.5 mg	M2 1.5 mg	M3 0.5 mg
Started	15	15	14
Completed	15	15	14

Number of subjects in period 1	M3 1.5 mg
Started	16
Completed	16

Period 2

Period 2 title	Visit 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	M2 0.5 mg
Arm description:	
0.5 mg terbutaline sulphate administered via Turbuhaler M2	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
0.5 mg M2 Turbuhaler	
Arm title	M2 1.5 mg
Arm description:	
1.5 mg terbutaline sulphate administered via Turbuhaler M2	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
1.5 mg M2 Turbuhaler	
Arm title	M3 0.5 mg
Arm description:	
0.5 mg terbutaline sulphate administered via Turbuhaler M3	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
0.5 mg M3 Turbuhaler	
Arm title	M3 1.5 mg
Arm description:	
1.5 mg terbutaline sulphate administered via Turbuhaler M3	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
1.5 mg M3 Turbuhaler	

Number of subjects in period 2	M2 0.5 mg	M2 1.5 mg	M3 0.5 mg
Started	15	14	16
Completed	15	14	16

Number of subjects in period 2	M3 1.5 mg
Started	15
Completed	15

Period 3	
Period 3 title	Visit 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	M2 0.5 mg
Arm description: 0.5 mg terbutaline sulphate administered via Turbuhaler M2	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 0.5 mg M2 Turbuhaler	
Arm title	M2 1.5 mg
Arm description: 1.5 mg terbutaline sulphate administered via Turbuhaler M2	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details: 1.5 mg M2 Turbuhaler	
Arm title	M3 0.5 mg
Arm description: 0.5 mg terbutaline sulphate administered via Turbuhaler M3	
Arm type	Active comparator

Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
0.5 mg M3 Turbuhaler

Arm title	M3 1.5 mg

Arm description:
1.5 mg terbutaline sulphate administered via Turbuhaler M3

Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:
1.5 mg M3 Turbuhaler

Number of subjects in period 3	M2 0.5 mg	M2 1.5 mg	M3 0.5 mg
Started	16	15	15
Completed	16	15	15

Number of subjects in period 3	M3 1.5 mg
Started	14
Completed	14

Period 4	
Period 4 title	Visit 6
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms	
Are arms mutually exclusive?	Yes

Arm title	M2 0.5 mg
Arm description:	
0.5 mg terbutaline sulphate administered via Turbuhaler M2	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
0.5 mg M2 Turbuhaler	
Arm title	M2 1.5 mg
Arm description:	
1.5 mg terbutaline sulphate administered via Turbuhaler M2	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
1.5 mg M2 Turbuhaler	
Arm title	M3 0.5 mg
Arm description:	
0.5 mg terbutaline sulphate administered via Turbuhaler M3	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
0.5 mg M3 Turbuhaler	
Arm title	M3 1.5 mg
Arm description:	
1.5 mg terbutaline sulphate administered via Turbuhaler M3	
Arm type	Active comparator
Investigational medicinal product name	terbutaline sulphate via Turbuhaler M3
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use
Dosage and administration details:	
1.5 mg M3 Turbuhaler	

Number of subjects in period 4	M2 0.5 mg	M2 1.5 mg	M3 0.5 mg
Started	14	16	15
Completed	14	16	15

Number of subjects in period 4	M3 1.5 mg
Started	15
Completed	15

Baseline characteristics

Reporting groups

Reporting group title	Visit 3

Reporting group description: -

Reporting group values	Visit 3	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	60	60	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous | Units: years			
median	26		
full range (min-max)	18 to 64	-	
Gender, Male/Female			
Gender			
Units: Participants			
Female	40	40	
Male	20	20	
Race/Ethnicity, Customized			
Race			
Units: Subjects			
White	57	57	
Black or African American	1	1	
Asian	2	2	

Subject analysis sets

Subject analysis set title	Efficacy Analysis Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients who have at least two values of the primary endpoints in the efficacy analysis set.

Reporting group values	Efficacy Analysis Set		
Number of subjects	60		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	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)	60		
From 65-84 years	0		
85 years and over	0		
Age Continuous |			
Units: years			
median	26		
full range (min-max)	18 to 64		
Gender, Male/Female			
Gender			
Units: Participants			
Female	40		
Male	20		
Race/Ethnicity, Customized			
Race			
Units: Subjects			
White	57		
Black or African American	1		
Asian	2		

End points

End points reporting groups

Reporting group title	M2 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M2 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M3 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M3 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M2 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M2 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M3 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M3 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M2 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M2 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M3 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M3 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M2 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M2 1.5 mg

Reporting group description:
1.5 mg terbutaline sulphate administered via Turbuhaler M2

Reporting group title	M3 0.5 mg

Reporting group description:
0.5 mg terbutaline sulphate administered via Turbuhaler M3

Reporting group title	M3 1.5 mg

Reporting group description:

1.5 mg terbutaline sulphate administered via Turbuhaler M3

Subject analysis set title	Efficacy Analysis Set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients who have at least two values of the primary endpoints in the efficacy analysis set.

Primary: PC20

End point title	PC20

End point description:

End point type	Primary

End point timeframe:

During treatment period from Visit 3 to Visit 6

End point values	M2 0.5 mg	M2 0.5 mg	M2 0.5 mg	M2 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	16	14
Units: mg/mL				
geometric mean (geometric coefficient of variation)	5.43 (± 302.49)	10.03 (± 185.14)	11.21 (± 160.36)	23.06 (± 341.4)

End point values	M2 1.5 mg	M2 1.5 mg	M2 1.5 mg	M2 1.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	14	15	16
Units: mg/mL				
geometric mean (geometric coefficient of variation)	22.76 (± 255.89)	37.39 (± 306.96)	10.99 (± 164.29)	18.01 (± 132.9)

End point values	M3 0.5 mg	M3 0.5 mg	M3 0.5 mg	M3 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	16	15	15
Units: mg/mL				
geometric mean (geometric coefficient of variation)	17.8 (± 319.32)	8.63 (± 106.66)	12 (± 237.01)	5.44 (± 215.56)

End point values	M3 1.5 mg	M3 1.5 mg	M3 1.5 mg	M3 1.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	15	14	15
Units: mg/mL				
geometric mean (geometric coefficient	19.34 (±	10.22 (±	29.04 (±	17.93 (±

of variation)	178.83)	199.6)	253.8)	250.8)

Statistical analyses

Statistical analysis title	PC20 mixed effect model analysis: M2 1.5 vs M2 0.5

Statistical analysis description:

A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect.

Comparison groups	M2 0.5 mg v M2 1.5 mg v M2 0.5 mg v M2 1.5 mg v M2 0.5 mg v M2 1.5 mg v M2 0.5 mg v M2 1.5 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Estimated mean ratio
Point estimate	1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	2.29

Statistical analysis title	PC20 mixed effect model analysis: M3 1.5 vs M3 0.5

Statistical analysis description:

A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect.

Comparison groups	M3 0.5 mg v M3 1.5 mg v M3 0.5 mg v M3 1.5 mg v M3 0.5 mg v M3 1.5 mg v M3 0.5 mg v M3 1.5 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Estimated mean ratio
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	2.2

Statistical analysis title	PC20 mixed effect model analysis: M3 0.5 vs M2 0.5

Statistical analysis description:

A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect.

Comparison groups	M2 0.5 mg v M3 0.5 mg v M2 0.5 mg v M3 0.5 mg v M2 0.5 mg v M3 0.5 mg v M2 0.5 mg v M3 0.5 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	equivalence
Method	Mixed models analysis
Parameter estimate	Estimated mean ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.13

Statistical analysis title	PC20 mixed effect model analysis: M3 1.5 vs M2 1.5

Statistical analysis description:

A linear mixed effect model based on restricted maximum likelihood analysis is used to estimate the treatment effect. PC20 in natural log scale is the response variable, treatment and period are the fixed effects, and patient within sequence is a random effect.

Comparison groups	M2 1.5 mg v M3 1.5 mg v M2 1.5 mg v M3 1.5 mg v M2 1.5 mg v M3 1.5 mg v M2 1.5 mg v M3 1.5 mg
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	equivalence
Method	Mixed models analysis
Parameter estimate	Estimated mean ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.08

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During randomized treatment period from Visit 3 to Visit 6	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	M2 0.5 mg
Reporting group description:	
0.5 mg terbutaline sulphate administered via Turbuhaler M2	
Reporting group title	M3 0.5 mg
Reporting group description:	
0.5 mg terbutaline sulphate administered via Turbuhaler M3	
Reporting group title	M3 1.5 mg
Reporting group description:	
1.5 mg terbutaline sulphate administered via Turbuhaler M3	
Reporting group title	M2 1.5 mg
Reporting group description:	
1.5 mg terbutaline sulphate administered via Turbuhaler M2	

Serious adverse events	M2 0.5 mg	M3 0.5 mg	M3 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 60 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	M2 1.5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	M2 0.5 mg	M3 0.5 mg	M3 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 60 (20.00%)	7 / 60 (11.67%)	13 / 60 (21.67%)
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	2 / 60 (3.33%)
occurrences (all)	0	2	2
Tachycardia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 60 (10.00%)	5 / 60 (8.33%)	7 / 60 (11.67%)
occurrences (all)	6	5	7
Headache			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	1 / 60 (1.67%)
occurrences (all)	1	1	1
Sciatica			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	2 / 60 (3.33%)	1 / 60 (1.67%)	5 / 60 (8.33%)
occurrences (all)	2	1	5
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Pyrexia			

subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Dry mouth			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Restlessness			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	1 / 60 (1.67%)
occurrences (all)	2	0	1
Sinusitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	0 / 60 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	M2 1.5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 60 (16.67%)		
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Cardiac disorders			

Palpitations			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 60 (0.00%)		
occurrences (all)	0		

Dry mouth subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Psychiatric disorders Restlessness subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0 0 / 60 (0.00%) 0		

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