Clinical trial results:
A randomized, subject- and Investigator-blinded, placebo-controlled, parallel-group study to investigate whether AFQ056 reduces cocaine use in patients diagnosed with Cocaine Use Disorder (CUD)

Summary

EudraCT number	2017-000736-33
Trial protocol	ES
Global end of trial date	16 December 2019

Results information

Result version number	v1 (current)
This version publication date	31 December 2020
First version publication date	31 December 2020

Trial information

Trial identification

Sponsor protocol code	CAFQ056X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03242928
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG , 41 613241111, Novartis.email@Novartis.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	16 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate treatment effect of 98-day mavoglurant administration in reducing cocaine us

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 December 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	Argentina: 37
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Switzerland: 16
Worldwide total number of subjects	68
EEA total number of subjects	15

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)	68
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 71 patients randomized but 3 patients did not receive study treatment

Period 1

Period 1 title	Overall Study (overall period)
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	AFQ056

Arm description:

Mavoglurant was up titrated on a bid regimen followed by fixed-dose bid regimen: 50 mg bid from Day 1 to Day 7, 100 mg bid from Day 8 to Day 14, and then fixed-dose 200 mg bid for 84 days

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

Dosage and administration details:

Mavoglurant: up-titration bid regimen followed by fixed-dose bid regimen (50 mg bid from Day 1 to Day 7 followed by 100 mg bid from Day 8 to Day 14, and then fixed-dose 200 mg bid for 84 days)

Arm title	Placebo

Arm description:

Matching tablet of placebo taken orally BID

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

Dosage and administration details:

Matching placebo doses and regimen to AFQ056 arm

Number of subjects in period 1	AFQ056	Placebo
Started	31	37
Completed	22	32
Not completed	9	5
Consent withdrawn by subject	5	3
Physician decision	-	1
Adverse event, non-fatal	2	1
Lost to follow-up	2	-

Baseline characteristics

Reporting groups	
Reporting group title	AFQ056
Reporting group description:	
Mavoglurant was up titrated on a bid regimen followed by fixed-dose bid regimen: 50 mg bid from Day 1 to Day 7, 100 mg bid from Day 8 to Day 14, and then fixed-dose 200 mg bid for 84 days	
Reporting group title	Placebo
Reporting group description:	
Matching tablet of placebo taken orally BID	

Reporting group values	AFQ056	Placebo	Total
Number of subjects	31	37	68
Age Categorical Units: participants			
18 - 65 years	31	37	68
Sex: Female, Male Units:			
Female	5	7	12
Male	26	30	56
Race/Ethnicity, Customized Units: Subjects			
Asian	0	1	1
White	31	36	67

End points

End points reporting groups

Reporting group title	AFQ056
Reporting group description:	
Mavoglurant was up titrated on a bid regimen followed by fixed-dose bid regimen: 50 mg bid from Day 1 to Day 7, 100 mg bid from Day 8 to Day 14, and then fixed-dose 200 mg bid for 84 days	
Reporting group title	Placebo
Reporting group description:	
Matching tablet of placebo taken orally BID	

Primary: Proportion of cocaine use days

End point title	Proportion of cocaine use days
End point description:	
The cocaine consumption was recorded once daily (Yes/No) by the subject using the Timeline Follow-Back (TLFB) cocaine assessment tool during the treatment period. For each patient, the proportion of cocaine use days was calculated by dividing the number of days of cocaine use during the treatment period, i.e. 98 days for completers and number of days between Day 1 and day of last dose in case of premature discontinuation of study treatment.	
End point type	Primary
End point timeframe:	
Day 1 up to day 98	

End point values	AFQ056	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	36		
Units: cocaine use days				
arithmetic mean (standard error)	0.122 (± 0.027)	0.209 (± 0.024)		

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	Placebo v AFQ056
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.021
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.087

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.161
upper limit	-0.013
Variability estimate	Standard error of the mean
Dispersion value	0.037

Secondary: Proportion of positive urine measuremebnts of benzoylecgonine (BE)

End point title	Proportion of positive urine measuremebnts of benzoylecgonine (BE)

End point description:

Urine samples were analyzed for the presence of cocaine's metabolite benzoylecgonine (BE) which is the main metabolite of cocaine present in urine. Two urine samples were provided per week to provide a quantitative measure.

End point type	Secondary

End point timeframe:

Day 1 up to day 98

End point values	AFQ056	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	36		
Units: positive urine samples				
arithmetic mean (standard error)	0.666 (± 0.057)	0.843 (± 0.051)		

Statistical analyses

Statistical analysis title	ANOVA analysis
Comparison groups	AFQ056 v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.025
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.331
upper limit	-0.023
Variability estimate	Standard error of the mean
Dispersion value	0.077

Secondary: Proportion of days of alcohol consumption

End point title	Proportion of days of alcohol consumption

End point description:

Alcohol consumption was recorded by the subjects using the Timeline Follow-Back (TLFB) alcohol self report. The number of standard drinks were recorded daily. The proportion of days of alcohol consumption during the study treatment period was was compared using an ANCOVA model with treatment as factor and past alcohol consumption as covariate. The past consumption of alcohol was the proportion of alcohol over the 28 days preceding the screening visit, which was assessed retrospectively using the TLFB.

End point type	Secondary

End point timeframe:

Day 1 up to day 98

End point values	AFQ056	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	36		
Units: alcohol consumption days				
arithmetic mean (standard error)	0.233 (± 0.030)	0.303 (± 0.026)		

Statistical analyses

Statistical analysis title	ANCOVA analysis
Comparison groups	AFQ056 v Placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.072
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.146
upper limit	0.006
Variability estimate	Standard error of the mean
Dispersion value	0.038

Secondary: AFQ056 plasma concentrations

End point title	AFQ056 plasma concentrations[1]

End point description:

Plasma samples were collected to assess pharmacokinetics (PK)

End point type	Secondary

End point timeframe:

Day 15 (0h, 2h), Day 29 (0, 2h), Day 57 (0h, 2h), Day 98 (0h,2h)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No analysis done

End point values	AFQ056			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 15 0 hour, n=21	41.2 (± 47.4)			
Day 15 2 hour,,n=21	78.0 (± 91.7)			
Day 29 0 hour, n=26	83.5 (± 116)			
Day 29 2 hour,,n=24	148 (± 131)			
Day 57 0 hour, n=22	108 (± 153)			
Day 57 2 hour, n=22	141 (± 153)			
Day 98 0 hour, n=21	89.8 (± 148)			
Day 98 2 hour, n=21	116 (± 86.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 14 days post treatment, up to maximum duration of approximately 16 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	AFQ056

Reporting group description:

Mavoglurant was up titrated on a bid regimen followed by fixed-dose bid regimen: 50 mg bid from Day 1 to Day 7, 100 mg bid from Day 8 to Day 14, and then fixed-dose 200 mg bid for 84 days

Reporting group title	Placebo

Reporting group description:

Matching tablet of placebo taken orally BID

Serious adverse events	AFQ056	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	AFQ056	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 31 (83.87%)	30 / 37 (81.08%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			

Haematoma			
subjects affected / exposed	1 / 31 (3.23%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Peripheral coldness			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Vasospasm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Discomfort			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 31 (6.45%)	3 / 37 (8.11%)	
occurrences (all)	4	3	
Influenza like illness			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	2 / 31 (6.45%)	1 / 37 (2.70%)	
occurrences (all)	4	1	
Pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Physical deconditioning			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Thirst			

subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 31 (3.23%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Nasal mucosal ulcer			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	2	2	
Rhinitis allergic			

subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 31 (9.68%)	4 / 37 (10.81%)	
occurrences (all)	4	5	
Aversion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Depressed mood			
subjects affected / exposed	1 / 31 (3.23%)	2 / 37 (5.41%)	
occurrences (all)	1	3	
Depression			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Depressive symptom			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Disorientation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	2	
Euphoric mood			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Feeling guilty			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Hallucination, auditory			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Hallucination, olfactory			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	3	0	

Hallucination, visual			
subjects affected / exposed	2 / 31 (6.45%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Ideas of reference			
subjects affected / exposed	0 / 31 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Illusion			
subjects affected / exposed	2 / 31 (6.45%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Initial insomnia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Insomnia			
subjects affected / exposed	5 / 31 (16.13%)	2 / 37 (5.41%)	
occurrences (all)	9	11	
Irritability			
subjects affected / exposed	1 / 31 (3.23%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Nightmare			
subjects affected / exposed	2 / 31 (6.45%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Paranoia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	3 / 31 (9.68%)	0 / 37 (0.00%)	
occurrences (all)	4	0	
Stress			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 31 (6.45%)	2 / 37 (5.41%)	
occurrences (all)	2	3	
Amylase increased			

subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 31 (6.45%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Blood creatinine abnormal			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	3 / 31 (9.68%)	2 / 37 (5.41%)	
occurrences (all)	3	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	2	
Lymphocyte count increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Neutrophil count increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Red blood cell count increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased			

subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Limb injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Skin laceration			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Toxicity to various agents			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 31 (22.58%)	4 / 37 (10.81%)	
occurrences (all)	17	4	
Headache			
subjects affected / exposed	6 / 31 (19.35%)	10 / 37 (27.03%)	
occurrences (all)	13	24	
Muscle contractions involuntary			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			

subjects affected / exposed	2 / 31 (6.45%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Resting tremor			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	4 / 31 (12.90%)	1 / 37 (2.70%)	
occurrences (all)	4	1	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Monocytosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Diplopia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Photopsia			
subjects affected / exposed	3 / 31 (9.68%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Photophobia			

subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	3 / 31 (9.68%)	7 / 37 (18.92%)	
occurrences (all)	6	12	
Constipation			
subjects affected / exposed	2 / 31 (6.45%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)	5 / 37 (13.51%)	
occurrences (all)	3	5	
Dyspepsia			
subjects affected / exposed	3 / 31 (9.68%)	2 / 37 (5.41%)	
occurrences (all)	3	2	
Dry mouth			
subjects affected / exposed	2 / 31 (6.45%)	0 / 37 (0.00%)	
occurrences (all)	4	0	
Gingival bleeding			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	6 / 31 (19.35%)	3 / 37 (8.11%)	
occurrences (all)	8	3	
Odynophagia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Paraesthesia oral			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	

Regurgitation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 31 (0.00%)	6 / 37 (16.22%)	
occurrences (all)	0	6	
Vomiting			
subjects affected / exposed	3 / 31 (9.68%)	1 / 37 (2.70%)	
occurrences (all)	6	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	2	
Hyperhidrosis			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	2 / 31 (6.45%)	0 / 37 (0.00%)	
occurrences (all)	7	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Renal pain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 31 (12.90%)	5 / 37 (13.51%)	
occurrences (all)	4	6	
Muscle tightness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	

Muscle twitching			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 31 (3.23%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Rhabdomyolysis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	4 / 31 (12.90%)	2 / 37 (5.41%)	
occurrences (all)	7	2	
Laryngitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	8 / 37 (21.62%)	
occurrences (all)	2	10	
Pharyngitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Pulpitis dental			
subjects affected / exposed	0 / 31 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Rhinitis			

subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3	0 / 37 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 0 / 31 (0.00%) 0	 1 / 37 (2.70%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2017	The protocol was amended in response to the request from the Swiss Ethics Committee to exclude patients with controlled hypertension. In addition, this protocol amendment introduced the possibility of performing central and local BE analysis for inclusion, in order to optimize sampling results turnaround time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported