Clinical trial results:
Randomised controlled trial of the short term effects of OROS-methylphenidate on ADHD symptoms and behavioural outcomes in young male prisoners with attention deficit hyperactivity disorder

Summary

EudraCT number	2015-004271-78
Trial protocol	GB
Global end of trial date	06 June 2019

Results information

Result version number	v1
This version publication date	24 September 2020
First version publication date	24 September 2020
Summary attachment (see zip file)	Clinical Study report (Clinical Study Report EudraCT v.1.3 08.08.2020 with stats.docx)

Trial information

Trial identification

Sponsor protocol code	CIAOII

Additional study identifiers

ISRCTN number	ISRCTN16827947
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Prof. Philip Asherson, King's College London, +44 2078480078, philip.asherson@kcl.ac.uk
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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	27 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 June 2019
Global end of trial reached?	Yes
Global end of trial date	06 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an 8-week randomised placebo controlled trial of OROS-MPH, in young adult prisoners meeting diagnostic criteria for ADHD. OROS-MPH is a long acting stimulant medication used to treat ADHD.

The primary objective is to establish the efficacy of OROS-MPH in reducing ADHD symptoms (inattention and hyperactivity-impulsivity) in young male offenders aged 16-25, meeting diagnostic criteria for DSM-5 ADHD.

Protection of trial subjects:

Participants have the right to withdraw from the study at any time for any reason. Healthcare staff has the right to withdraw patients from the trial if they consider the trial is having an adverse effect on the participants. However, where the problem is restricted to taking trial medication we will invite participants to remain in the study to complete trial assessments, thereby minimising loss of data. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Anyone withdrawn from the clinical trial will be reviewed by the prison healthcare team to ensure their safety. All participants will be informed that they have the right to withdraw from the study at any time. If the trial medication is stopped, the participant will remain in the study and will be asked to complete trial assessments. A clinical assessment will be made on a case by case basis as to the safety of restarting the trial medication after 48 hours from the time of stopping the trial medication.

The role of the trial steering committee and data monitoring committee for this trial was to provide independent oversight of ethical and safety aspects of the trial.

Background therapy: -

Evidence for comparator:

It is established that a high proportion of prisoners meet diagnostic criteria for ADHD, with prevalence among prisoners estimated to be between 20 to 30%. It is also established that stimulants such as methylphenidate can reduce the symptoms of ADHD and this is a recommended first line treatment in the UK. However, it is not clear whether prisoners with ADHD will show the same beneficial effects of methylphenidate. Differences may arise because problems with poor attention span, forgetfulness, being overactive and restless or impatient might be better explained by other conditions such as anxiety and depression, personality disorder, post-traumatic stress disorder and drug abuse. This trial follows an open label study investigating the effects of OROS-methylphenidate, an extended release preparation of methylphenidate, showing significant reductions in ADHD symptoms. The trial looks at young male offenders who have undiagnosed or untreated ADHD and investigates the effects of OROS-MPH in this group using a randomised placebo-controlled study design.

Actual start date of recruitment	17 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 200

Worldwide total number of subjects	200
EEA total number of subjects	200

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)	10
Adults (18-64 years)	190
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was between 17Oct16 and 02Apr19. Participants were recruited from HMP YOI Isis (London) and HM YOI Polmont (Falkirk).

Pre-assignment

Screening details:

1183 prisoners consented to be screened. 585 screened negative on the Barkley ADHD self-rating scale and a further 52 excluded. Of the 546 who were then assessed more fully, 153 did not have ADHD , 86 failed to attend, a further 28 were likely to leave the prison during the prison during the course of the trial, and 6 failed eligibility checks.

Pre-assignment period milestones

Number of subjects started	1183[1]
Number of subjects completed	200

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen fail: 983

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The pre-assignment period includes screen fails who were not enrolled into the study.

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:

Over-encapsulated matched placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	OROS-MPH

Arm description:

Concerta XL 18mg (OROS-MPH) prolonged release capsules, taken orally, one to twice daily. Dosing was initiated at 18 mg and increased by 18 mg a week to a maximum dose of 72mg.

Arm type	Experimental
Investigational medicinal product name	Concerta XL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Treatment will start at an initial dose of 18 mg (1 capsule) for 1 week, and be increased weekly in 18 mg increments to a maximum of 72 mg (4 capsules) (i.e. 18 mg (1 capsule), 36 mg (2 capsule), 54 mg (3 capsules) and 72 mg (4 capsules). Medication will be reduced by 18 mg (1 capsule) if there is a limiting adverse event, in which case there will be no further increase in medication for the duration of the trial. Medication may be provided either once or twice daily up to the maximum daily dose.

Arm title	Placebo

Arm description:

Placebo capsules. The titration protocol is followed in the same way for both active medication (IMP) and

placebo.

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

Dosage and administration details:

All trial medication was titrated in the same. Treatment started at an initial dose of 1 capsule of trial medication at the start of week 1. The number of capsules was then increased weekly over the following 4 weeks, in increments of 1 capsule, to a maximum of 4 capsules. This reflected a dose range for the active medication of 18, 36, 54 and 72 mg.

Number of subjects in period 1	OROS-MPH	Placebo
Started	101	99
Completed	90	94
Not completed	11	5
Consent withdrawn by subject	5	2
released, deported or moved	6	3

Baseline characteristics

Reporting groups	
Reporting group title	OROS-MPH
Reporting group description:	
Concerta XL 18mg (OROS-MPH) prolonged release capsules, taken orally, one to twice daily. Dosing was initiated at 18 mg and increased by 18 mg a week to a maximum dose of 72mg.	
Reporting group title	Placebo
Reporting group description:	
Placebo capsules. The titration protocol is followed in the same way for both active medication (IMP) and placebo.	

Reporting group values	OROS-MPH	Placebo	Total
Number of subjects	101	99	200
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	7	3	10
Adults (18-64 years)	94	96	190
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	20.6	20.8	
standard deviation	± 1.9	± 1.9	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	101	99	200
Site Units: Subjects			
ISIS	58	57	115
Polomont	43	42	85
Ethnicity Units: Subjects			
White	64	61	125
Other	19	10	29
Black	18	28	46
Education Units: Subjects			
No qualifications	42	37	79
Any qulaifications	59	62	121
Age of leaving school Units: Subjects			

14 or less	26	25	51
15	32	22	54
16 or more	35	43	78
unknown	8	9	17
Employed (including in education) Units: Subjects			
Unemployed	67	66	133
Employed	34	33	67
Offence category Units: Subjects			
Serious violence or sexual	15	14	29
Assault	25	26	51
Drug related	27	30	57
Burglary or theft	27	20	47
Other	7	9	16
Previous ADHD treatment Units: Subjects			
Yes	27	20	47
No or unknown	74	79	153
Age when ADHD meds last taken Units: Subjects			
13 or less	9	3	12
14 or more	18	12	30
Unknown	74	84	158
Antisocial Personality Disorder (ASPD)			
baseline co-existing disorders and symptoms from the MINI interview assessment			
Units: Subjects			
Antisocial Personality Disorder (ASPD)	72	77	149
No ASPD	29	22	51
Mood disorder (major depression, suicidality, manic, hypomanic)			
baseline co-existing disorders and symptoms from the MINI interview assessment			
Units: Subjects			
Mood disorder	19	19	38
None	82	80	162
Anxiety disorder (panic, agoraphobia, social anxiety, obsessive-compulsive disorder, PTSD)			
baseline co-existing disorders and symptoms from the MINI interview assessment			
Units: Subjects			
Anxiety disorder	19	19	38
None	82	80	162
Potential problematic alcohol use			
Baseline co-existing disorders and symptoms from the MINI interview assessment. Alcohol use is defined using the AUDIT-C definition of problematic alcohol use, i.e. a score of 5 or more.			
Units: Subjects			
None	23	28	51
Potential problematic alcohol use	78	71	149
Illicit drug use			
Baseline co-existing disorders and symptoms from the MINI interview assessment. Illicit drug use is defined as any reported use (problematic or not) within the year prior to incarceration of cannabis, cocaine, methamphetamine, inhalants, sedatives, sleeping pills, hallucinogens, street or			

prescription opioids, spice or other misuse.			
Units: Subjects			
Illicit drug use	99	95	194
None	2	4	6
WASI-II (IQ)			
Units: Score			
arithmetic mean	89.9	88.9	
standard deviation	± 13.5	± 12.4	-
Height			
Units: cm			
arithmetic mean	176.4	177.2	
standard deviation	± 7.2	± 6.6	-
Body mass index			
Units: kg/m2			
arithmetic mean	23.7	23.7	
standard deviation	± 3.4	± 3.7	-
CAARS-O [range 0-54]			
CAARS-O reported for 100 cases in OROS-MPH arm because there were more than 20% missing items (2 out of 9) in the hyperactivity subscale for one individual			
Units: Score			
arithmetic mean	36.4	37.2	
standard deviation	± 9.8	± 8.7	-
CAARS-O Inattention [range 0-27]			
Units: Score			
arithmetic mean	17.9	18.5	
standard deviation	± 5.1	± 4.7	-
CAARS-O Hyperactivity [range 0-27]			
CAARS-O reported for 100 cases in OROS-MPH arm because there were more than 20% missing items (2 out of 9) in the hyperactivity subscale for one individual			
Units: Score			
arithmetic mean	18.6	18.7	
standard deviation	± 5.7	± 5.1	-
WRAADDS [range 0-30]			
Units: Score			
arithmetic mean	17.5	18.1	
standard deviation	± 5.7	± 5.6	-
WRAADDS - Temper subscale [range 0-9]			
Units: Score			
arithmetic mean	4.7	5.2	
standard deviation	± 2.5	± 2.3	-
WRAADDS - Lability subscale [range 0-12]			
Units: Score			
arithmetic mean	8.0	8.1	
standard deviation	± 2.3	± 2.2	-
WRAADDS - Over-reactivity subscale [range 0-9]			
Units: Score			
arithmetic mean	4.8	4.8	
standard deviation	± 2.2	± 2.3	-
ARI-S [range 0-14]			
Units: Score			

arithmetic mean	9.3	9.3	
standard deviation	± 3.5	± 3.7	-
MEWS [range 0-36]			
Units: Score			
arithmetic mean	25.7	26.8	
standard deviation	± 6.7	± 6.2	-
CGI-severity score [range 1-7]			
Units: Score			
arithmetic mean	4.0	3.9	
standard deviation	± 1.0	± 1.1	-
CORE-M [range 0-136]			
Units: Score			
arithmetic mean	43.5	44.8	
standard deviation	± 13.9	± 15.3	-
MVQ [range 0-75]			
MVQ subscale scores were not included in the statistical analysis plan			
Units: Score			
arithmetic mean	33.2	34.6	
standard deviation	± 9.4	± 9.9	-
Weiss CD [range 0-45]			
Units: Score			
arithmetic mean	17.9	18.7	
standard deviation	± 7.7	± 7.8	-
Blood pressure systolic			
Units: mmHg			
arithmetic mean	123.6	124.1	
standard deviation	± 11.2	± 11.9	-
Blood pressure diastolic			
Units: mmHg			
arithmetic mean	68.2	68.1	
standard deviation	± 9.9	± 9.5	-
Heart rate			
Units: beats per minute			
arithmetic mean	70.9	70.0	
standard deviation	± 10.7	± 11.8	-
RPAQ_P [range 0-24]			
RPAQ reported for 57 cases in the placebo arm but there were more than 20% missing items for one participant			
Units: Score			
arithmetic mean	6.8	7.6	
standard deviation	± 5.2	± 5.6	-
RPAQ_R [range 0-22]			
RPAQ reported for 57 cases in the placebo arm but there were more than 20% missing items for one participant			
Units: Score			
arithmetic mean	14.1	14.6	
standard deviation	± 4.8	± 5.0	-
RPAQ total [range 0-46]			
RPAQ reported for 57 cases in the placebo arm but there were more than 20% missing items for one participant			
Units: Score			
arithmetic mean	20.9	22.2	
standard deviation	± 9.2	± 9.7	-

CTQ [range 28-140]			
CTQ subscale scores not included in the statistical analysis plan			
Units: Score			
arithmetic mean	54.4	54.0	
standard deviation	± 16.9	± 18.1	-
ZAN-BPD [range 0-36]			
Units: Score			
arithmetic mean	6.9	6.3	
standard deviation	± 5.1	± 4.2	-
BSI [range 0-212]			
Units: Score			
arithmetic mean	52.5	52.9	
standard deviation	± 32.5	± 35.9	-
Depression			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Scores			
median	1	1	
full range (min-max)	0 to 7	0 to 8	-
Anger			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	4	5	
full range (min-max)	0 to 9	0 to 9	-
Mania			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	0	0	
full range (min-max)	0 to 6	0 to 3	-
Anxiety			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	1	1	
full range (min-max)	0 to 8	0 to 8	-
Physical symptoms			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	0	0	
full range (min-max)	0 to 6	0 to 5	-
Suicidal thoughts			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	0	0	
full range (min-max)	0 to 3	0 to 3	-
Psychosis			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	0	0	
full range (min-max)	0 to 1	0 to 3	-
Sleep problems			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	4	4	

full range (min-max)	0 to 9	0 to 10	-
Memory problems			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	3	3	
full range (min-max)	0 to 7	0 to 7	-
Repetitive thoughts/behaviours			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	0	0	
full range (min-max)	0 to 7	0 to 7	-
Dissociation			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	0	0	
full range (min-max)	0 to 0	0 to 5	-
Personality function			
MINI checklist symptom scores [range 0-10 for each item]			
Units: Score			
median	2	2	
full range (min-max)	0 to 9	0 to 8	-

End points

End points reporting groups

Reporting group title	OROS-MPH
Reporting group description:	
Concerta XL 18mg (OROS-MPH) prolonged release capsules, taken orally, one to twice daily. Dosing was initiated at 18 mg and increased by 18 mg a week to a maximum dose of 72mg.	
Reporting group title	Placebo
Reporting group description:	
Placebo capsules. The titration protocol is followed in the same way for both active medication (IMP) and placebo.	

Primary: Reduction in CAARS-O

End point title	Reduction in CAARS-O
End point description:	
The primary outcome measure is the level of ADHD symptoms measured at 8 weeks on the investigator rated Connors Adult ADHD rating scale (CAARS-O). This addressed the question of efficacy of OROS-MPH on ADHD symptoms in young prisoners meeting DSM-5 diagnostic criteria for ADHD.	
End point type	Primary
End point timeframe:	
Score difference between baseline and 8 weeks	

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	94		
Units: Percentage				
arithmetic mean (standard deviation)				
CAARS-O: total scale	21.24 (± 33.8)	20.12 (± 29.7)		
CAARS-O: inattention subscale	26.40 (± 36.9)	22.12 (± 35.6)		
CAARS-O: hyperactivity/ impulsivity subscale	11.67 (± 59.3)	16.33 (± 36.4)		

Statistical analyses

Statistical analysis title	CAARS-O estimated trial arm differences
Statistical analysis description:	
CAARS-O Estimated trial arm differences for the continuous primary and secondary outcomes at week-8 (positive differences indicate an improvement in the OROS-MPH compared to placebo arm)	
Comparison groups	OROS-MPH v Placebo

Number of subjects included in analysis	183
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	3.56
Variability estimate	Standard deviation

Secondary: The mind excessively wandering scale (MEWS)

End point title	The mind excessively wandering scale (MEWS)
End point description:	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	94		
Units: Score				
arithmetic mean (standard deviation)	19.8 (± 10.0)	21.9 (± 9.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cormorbid Symptoms (BSI)

End point title	Cormorbid Symptoms (BSI)
End point description:	
Brief symptom inventory (BSI) - self-rating scale for comorbid symptoms (baseline and outcome rating scale)	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	93		
Units: Scale				
arithmetic mean (standard deviation)	35.0 (± 25.1)	39.0 (± 34.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: WRAADDS emotional dysregulation

End point title	WRAADDS emotional dysregulation

End point description:

End point type	Secondary

End point timeframe:

Week 8

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	94		
Units: score				
arithmetic mean (standard deviation)	13.4 (± 6.1)	14.5 (± 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: ARI-S

End point title	ARI-S

End point description:

Symptoms of Emotional Dysregulation (ARI)

End point type	Secondary

End point timeframe:

8 weeks

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	94		
Units: score				
arithmetic mean (standard deviation)	8.2 (± 4.1)	8.0 (± 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Core-M

End point title	Core-M

End point description:

CORE Outcome Measure (CORE-M), a self-rated scale of subjective well-being, problems/symptoms, life functioning and risk/harm, designed to measure psychological distress before and after treatment.

End point type	Secondary

End point timeframe:

8 weeks

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	94		
Units: Score				
arithmetic mean (standard deviation)	38.0 (± 12.3)	39.0 (± 13.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: CGI severity of illness

End point title	CGI severity of illness

End point description:

clinical global impression

End point type	Secondary

End point timeframe:

8 weeks

End point values	OROS-MPH	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	94		
Units: Score				
arithmetic mean (standard deviation)	3.5 (± 1.1)	3.6 (± 1.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to 8 weeks after start of medication

Adverse event reporting additional description:

Patients are monitored daily. Safety checks will be conducted in line with NICE Guidelines (2009). Other safety checks will include monitoring of AEs during assessments. In addition, participants will be monitored daily by prison staff and any potential adverse events will be reported to the prison healthcare team.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	OROS-MPH
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	OROS-MPH	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 101 (0.00%)	0 / 99 (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	OROS-MPH	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 101 (81.19%)	78 / 99 (78.79%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	1 / 101 (0.99%)	2 / 99 (2.02%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
General disorders NOS			
subjects affected / exposed	12 / 101 (11.88%)	7 / 99 (7.07%)	
occurrences (all)	13	7	

Immune system disorders			
Hayfever			
subjects affected / exposed	5 / 101 (4.95%)	9 / 99 (9.09%)	
occurrences (all)	5	13	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Drug abuse			
subjects affected / exposed	4 / 101 (3.96%)	9 / 99 (9.09%)	
occurrences (all)	7	13	
Depressed mood			
subjects affected / exposed	12 / 101 (11.88%)	4 / 99 (4.04%)	
occurrences (all)	13	6	
Psychiatric symptom			
subjects affected / exposed	5 / 101 (4.95%)	5 / 99 (5.05%)	
occurrences (all)	5	5	
Sleep disorder			
subjects affected / exposed	11 / 101 (10.89%)	7 / 99 (7.07%)	
occurrences (all)	11	7	
Somatic symptom disorder			
subjects affected / exposed	3 / 101 (2.97%)	0 / 99 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
bone and joint injures			
subjects affected / exposed	1 / 101 (0.99%)	5 / 99 (5.05%)	
occurrences (all)	1	9	
Soft tissue injury			
subjects affected / exposed	11 / 101 (10.89%)	8 / 99 (8.08%)	
occurrences (all)	14	8	
Cardiac disorders			
Palpitations			
subjects affected / exposed	4 / 101 (3.96%)	1 / 99 (1.01%)	
occurrences (all)	4	1	
Nervous system disorders			

dizziness			
subjects affected / exposed	6 / 101 (5.94%)	0 / 99 (0.00%)	
occurrences (all)	6	0	
headache			
subjects affected / exposed	17 / 101 (16.83%)	14 / 99 (14.14%)	
occurrences (all)	27	26	
Seizure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
abnormal PLT and Hb			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
external ear disorder			
subjects affected / exposed	3 / 101 (2.97%)	0 / 99 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
eye disorders NOS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
ocular infection, infestations, irritations and inflammation			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
dental and gum disorders			
subjects affected / exposed	22 / 101 (21.78%)	15 / 99 (15.15%)	
occurrences (all)	35	37	
Gastrointestinal motility disorder			
subjects affected / exposed	11 / 101 (10.89%)	11 / 99 (11.11%)	
occurrences (all)	11	12	
gastrointestinal NOS			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			

epidermal and dermal conditions			
subjects affected / exposed	16 / 101 (15.84%)	22 / 99 (22.22%)	
occurrences (all)	20	26	
Renal and urinary disorders			
urinary problem NOS			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	15 / 101 (14.85%)	13 / 99 (13.13%)	
occurrences (all)	17	16	
Infections and infestations			
cold			
subjects affected / exposed	2 / 101 (1.98%)	9 / 99 (9.09%)	
occurrences (all)	2	9	
Balanitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 99 (1.01%)	
occurrences (all)	0	1	
chest infection			
subjects affected / exposed	0 / 101 (0.00%)	2 / 99 (2.02%)	
occurrences (all)	0	2	
Chlamydia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Trichomoniasis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
urethritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 99 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			

subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	13 / 101 (12.87%)	2 / 99 (2.02%)	
occurrences (all)	14	2	
vitamin related disorders			
subjects affected / exposed	1 / 101 (0.99%)	1 / 99 (1.01%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2018	Protocol v2.0: Update to secondary endpoints Update to secondary efficacy parameters Eligibility criteria updates Other protocol changes and clarifications

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/31791384