Clinical trial results:
A PHASE II, RANDOMISED, SINGLE CENTRE, OPEN-LABEL, TWO-ARM STUDY TO DETERMINE THE SAFETY AND EFFICACY OF BUPRENORPHINE ORAL LYOPHILISATE (XPRENOR ®) IN COMPARISON WITH BUPRENORPHINE SUBLINGUAL TABLETS (SUBUTEX®)IN OPIOID-DEPENDENT PATIENTS

Summary

EudraCT number	2012-003560-49
Trial protocol	GB
Global end of trial date	22 December 2013

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022
Summary attachment (see zip file)	Espranor result summary (ETH_REG_StudyResults_ESPRANOR_2022-02-28.pdf) Clinical Study Summary: MD2012/01XP (Espranor Study Results for EUDRACT 29.01.21.docx)

Trial information

Trial identification

Sponsor protocol code	MD2012/01XP

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Macarthys Laboratories Limited (trading as Martindale Pharma)
Sponsor organisation address	Building A2, Glory Park, Wooburn Green, High Wycombe, United Kingdom, hp100df
Public contact	Ethypharm global headquarters, ETHYPHARM, +33 (0) 141121720, information@ethypharm.com
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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	09 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2013
Global end of trial reached?	Yes
Global end of trial date	22 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective
The primary objective of this study was to establish the safety profile of Xprenor compared to Subutex.
Secondary objectives
The secondary objectives of this study were to:
1. Establish the pharmacokinetic (PK) profile in terms of time to maximum concentration (Tmax) and maximum concentration (Cmax) for Xprenor and Subutex
2. Measure the disintegration and disappearance of Xprenor and Subutex from the mouth under normal administration conditions
3. Establish the suitability of the recommended initiation dose (2 to 4 mg) and maintenance doses (up to 24 mg) of Xprenor in opioid-dependent subjects.
Exploratory objective
The exploratory objective was to compare the dose requirements of Subutex vs. Xprenor.

Protection of trial subjects:

The handling of data, including data quality control, were to comply with regulatory guidelines and local regulations where applicable, and the relevant Martindale Pharma's SOPs and Working Instructions. All data were to be stored in an anonymous form in accordance with the data-protection regulations.

Background therapy:

Xprenor: Starting dose of 2 to 4 mg/day, increasing in 2 to 6 mg steps up to 24 mg/day.

Evidence for comparator:

Subutex: Starting dose of 2 to 4 mg/day, increasing in 2 to 8 mg steps up to 32 mg/day.

Actual start date of recruitment	14 February 2013
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	United Kingdom: 55
Worldwide total number of subjects	55
EEA total number of subjects	0

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)	55
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

55 subjects have been recruited by two centers.

Pre-assignment

Screening details:

A total of 55 subjects were screened, of these 17 subjects (30.9%) did not meet the inclusion/exclusion criteria and were Screen failures.
There were 2 subjects that were randomised but did not receive study treatment: 1 subject was lost to follow-up and the other subject withdrew his consent.

Pre-assignment period milestones

Number of subjects started	55
Intermediate milestone: Number of subjects	Patients randomised: 38
Intermediate milestone: Number of subjects	Patients who received medication: 36
Number of subjects completed	36

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 17
Reason: Number of subjects	Not treated: 2

Period 1

Period 1 title	Titration/Maintenance/Extension periods (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-labelled study and no blinding was performed.

Arms

Are arms mutually exclusive?	Yes
Arm title	Xprenor

Arm description:

Eligible patients randomised to receive Xprenor

Arm type	Experimental
Investigational medicinal product name	Xprenor
Investigational medicinal product code	ND
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oromucosal use

Dosage and administration details:

Started with an initial dose of 2 to 4 mg/day, with and then increased by 2 to 6 mg up to a maximum dose of 24 mg/day.

Arm title	Subutex

Arm description:

Eligible patients radomised to receive Subutex

Arm type	Active comparator

Investigational medicinal product name	Subutex
Investigational medicinal product code	ND
Other name	Buprenorphine
Pharmaceutical forms	Sublingual tablet
Routes of administration	Sublingual use

Dosage and administration details:

Started with an initial dose of 2 to 4 mg/day, with additional doses up to an additional maximum of 4 mg on the first day if required up to a maximum dose of 32 mg/day.

Number of subjects in period 1[1]	Xprenor	Subutex
Started	23	13
Completed	20	10
Not completed	3	3
Consent withdrawn by subject	2	2
Inadequate contraception	-	1
Lost to follow-up	1	-

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: A total of 55 subjects were screened, of these 17 subjects (30.9%) did not meet the inclusion/exclusion criteria and were Screen failures.
There were 2 subjects that were randomised but did not receive study treatment: 1 subject was lost to follow-up and the other subject withdrew his consent.

Baseline characteristics

Reporting groups	
Reporting group title	Xprenor
Reporting group description:	
Eligible patients randomised to receive Xprenor	
Reporting group title	Subutex
Reporting group description:	
Eligible patients radomised to receive Subutex	

Reporting group values	Xprenor	Subutex	Total
Number of subjects	23	13	36
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)	0	0	0
Adults (18-64 years)	23	13	36
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	43.0	45.0	
full range (min-max)	26.0 to 58.0	23.0 to 53.0	-
Gender categorical Units: Subjects			
Female	3	2	5
Male	20	11	31
Race Units: Subjects			
Asian	0	1	1
Caucasian	15	9	24
Other	8	3	11
Opioid dependance history Units: Subjects			
> 6-12 months	1	0	1
> 24 months	22	13	35
Type of opioid abused Units: Subjects			
Opioid painkiller addiction	1	0	1
Heroin addiction	21	12	33
Other	1	1	2

Height Units: cm median full range (min-max)	 176.0 154.0 to 192.0	 168.5 153.0 to 199.0	 -
Weight Units: kg median full range (min-max)	 73.4 49.4 to 102.8	 64.1 44.5 to 89.0	 -
BMI Units: KG/m2 median full range (min-max)	 23.5 18.4 to 29.9	 21.6 18.8 to 29.9	 -

Subject analysis sets

Subject analysis set title	Safety and Efficacy population
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received at least one dose of the study medications.	
Subject analysis set title	PK Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: PK Population : 50% of all randomised subjects	
Subject analysis set title	PK data after administration of both Xprenor and Subutex.
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects for which PK data were available following administration of both Xprenor and Subutex.	

Reporting group values	Safety and Efficacy population	PK Population	PK data after administration of both Xprenor and Subutex.
Number of subjects	36	11	5
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)	36		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female	5		

Male	31		

Race Units: Subjects			
Asian	1		
Caucasian	24		
Other	11		
Opioid dependance history Units: Subjects			
> 6-12 months	1		
> 24 months	35		
Type of opioid abused Units: Subjects			
Opioid painkiller addiction	1		
Heroin addiction	33		
Other	2		
Height Units: cm			
median	175.5		
full range (min-max)	153.0 to 199.0		
Weight Units: kg			
median	71.4		
full range (min-max)	44.5 to 102.8		
BMI Units: KG/m2			
median	23.4		
full range (min-max)	18.4 to 29.9		

End points

End points reporting groups

Reporting group title	Xprenor
Reporting group description: Eligible patients randomised to receive Xprenor	
Reporting group title	Subutex
Reporting group description: Eligible patients radomised to receive Subutex	
Subject analysis set title	Safety and Efficacy population
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received at least one dose of the study medications.	
Subject analysis set title	PK Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: PK Population : 50% of all randomised subjects	
Subject analysis set title	PK data after administration of both Xprenor and Subutex.
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects for which PK data were available following administration of both Xprenor and Subutex.	

Primary: Safety end points (AE)

End point title	Safety end points (AE)[1]
End point description: To compare the incidence of AEs reported in Subutex and Xprenor arms compared to Subutex.	
End point type	Primary
End point timeframe: All over the study	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Other method name: (specify) : Listing of events without statistical analysis (Medical Dictionary for Regulatory Activities (MedDRA, Version 15))

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	13		
Units: Adverse events				
At least one AE	17	4		
AE severity Mild	13	1		
AE severity Moderate	4	3		
At least one Treatment-related TEAE	16	2		

Statistical analyses

No statistical analyses for this end point

Primary: Safety end points (Oxygen desaturation)

End point title	Safety end points (Oxygen desaturation)

End point description:

To examine potential oxygen desaturation (SpO2) up to 3 hours post-dose as measured by pulse oximetry continuously and at a series of time-points in each visit.
PDPT : Post-Dose Period on Titration - PDPM : Post-Dose Period on Maintenance

End point type	Primary

End point timeframe:

Continuous pulse oximetry :3 hours post-dose during active titration + Days 2 and 7 of Maintenance Period (D9-D14). Manual pulse oximetry : 0, 15, 30, 60 min post-study treatment during active titration + Days 2 and 7 of Maintenance Period (D9-D14).

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	13		
Units: Seconds				
arithmetic mean (standard deviation)				
Dur. SpO2<90% 0 to 30 min PDPT Day 1	8.1 (± 16.69)	158.3 (± 510.09)		
Dur. SpO2<90% 0 to 30 min PDPT Day 2	6.2 (± 10.39)	23.6 (± 29.96)		
Dur. SpO2<90% 0 to 30 min PDPT Day 3	5.0 (± 10.35)	21.7 (± 29.3)		
Dur. SpO2<90% 0 to 30 min PDPT Day 5	3.3 (± 5.77)	10.0 (± 14.14)		
Dur. SpO2<90% 0 to 30 min PDPM Day 2	6.1 (± 11.95)	177.0 (± 544.0)		
Dur. SpO2<90% 0 to 30 min PDPM Day 7	7.1 (± 13.47)	14.0 (± 31.25)		
Dur. SpO2<90% 0 to 120 min PDPT Day 1	0.0 (± 0.0)	0.5 (± 0.71)		
Dur. SpO2<90% 0 to 120 min PDPT Day 2	0.1 (± 0.28)	0.4 (± 0.79)		
Dur. SpO2<90% 0 to 120 min PDPT Day 3	0.6 (± 0.89)	0.0 (± 0.0)		
Dur. SpO2<90% 0 to 120 min PDPT Day 5	105.0 (± 0.00)	122.5 (± 137.89)		
Dur. SpO2<90% 0 to 120 min PDPM Day 2	68.0 (± 92.37)	499.3 (± 959.26)		
Dur. SpO2<90% 0 to 120 min PDPM Day 7	61.1 (± 88.94)	226.0 (± 281.46)		

Statistical analyses

Statistical analysis title	Pulse oximetry (SpO2 < 90% (0 to 30 min PDPT))

Statistical analysis description:

Continuous oximetry saturation data (SpO2) records for all subjects by time post-dose, for each period of assessment.PDPT= Post Dose Period on Titration

Comparison groups	Xprenor v Subutex

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.6683
Method	ANOVA

Notes:

[2] - Mean difference compared to ANOVA

Statistical analysis title	Pulse oximetry (SpO2 < 90% (0 to 120 min PDPT))

Statistical analysis description:

Continuous oximetry saturation data (SpO2) records for all subjects by time post-dose, for each period of assessment. PDPT: Post Dose Period on Titration

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.3966
Method	ANOVA

Notes:

[3] - Mean difference compared to ANOVA

Statistical analysis title	Pulse oximetry (SpO2 < 90% (0 to 30 min PDPM))

Statistical analysis description:

Continuous oximetry saturation data (SpO2) records for all subjects by time post-dose, for each period of assessment. PDPM: Post Dose Period on Maintenance

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0734
Method	ANOVA

Notes:

[4] - Mean difference compared to ANOVA

Statistical analysis title	Pulse oximetry (SpO2 < 90% (0 to 120 min PDPM))

Statistical analysis description:

Continuous oximetry saturation data (SpO2) records for all subjects by time post-dose, for each period of assessment. PDPM: Post Dose Period on Maintenance

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.5603
Method	ANOVA

Notes:

[5] - Mean difference compared to ANOVA

Primary: Safety end points (Respiration Rate)

End point title	Safety end points (Respiration Rate)

End point description:

To monitor respiration rate (RR)

End point type	Primary

End point timeframe:

0, 15, 30, and 60 minutes post-dosing at the first visit of the Titration Period, all other visits in the Titration Period when the buprenorphine dose was increased, and on Days 2 and 7 of the Maintenance Period.

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	13		
Units: Breaths/min				
arithmetic mean (standard deviation)				
RR - Titration D1 - 0 min	15.3 (± 2.03)	15.6 (± 2.97)		
RR - Titration D1 - 15 min	14.8 (± 2.28)	15.1 (± 2.47)		
RR - Titration D1 - 30 min	14.7 (± 2.20)	14.7 (± 2.10)		
RR - Titration D1 - 60 min	14.0 (± 2.07)	14.3 (± 2.14)		
RR - Titration D7 - 0 min	16.0 (± 0.00)	17.0 (± 1.41)		
RR - Titration D7 - 15 min	16.3 (± 1.15)	16.0 (± 2.83)		
RR - Titration D7 - 30 min	15.3 (± 0.58)	15.0 (± 1.41)		
RR - Titration D7 - 60 min	15.0 (± 1.41)	16.0 (± 2.83)		
RR - Maintenance D2 - 0 min	15.1 (± 1.98)	15.0 (± 1.84)		
RR - Maintenance D2 - 15 min	14.9 (± 2.02)	15.0 (± 1.84)		
RR - Maintenance D2 - 30 min	14.6 (± 1.77)	14.2 (± 2.09)		
RR - Maintenance D2 - 60 min	14.7 (± 1.73)	14.5 (± 2.34)		
RR - Maintenance D7 - 0 min	15.3 (± 2.74)	15.5 (± 2.59)		
RR - Maintenance D7 - 15 min	14.9 (± 2.20)	15.3 (± 2.26)		
RR - Maintenance D7 - 30 min	15.0 (± 1.67)	14.9 (± 2.56)		
RR - Maintenance D7 - 60 min	14.9 (± 1.67)	15.0 (± 2.56)		

Statistical analyses

Statistical analysis title	Respiration rate (RR) - 0 min

Statistical analysis description:

The absolute respiration rate was to be statistically compared between Xprenor and Subutex groups on Maintenance Days 2 and 7 pre-dose, and at 15, 30, and 60 minutes post-dose treatment by analysis of variance (ANOVA).

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.8734 [7]
Method	ANOVA
Variability estimate	Standard deviation

Notes:

[6] - ANOVA

[7] - P-value Comparison of Xprenor and Subutex at corresponding times for Maintenance Day 7

Statistical analysis title	Respiration rate (RR) - 15 min

Statistical analysis description:

The absolute respiration rate was to be statistically compared between Xprenor and Subutex groups on Maintenance Days 2 and 7 pre-dose, and at 15, 30, and 60 minutes post-dose treatment by analysis of variance (ANOVA).

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.6072 [9]
Method	ANOVA
Variability estimate	Standard deviation

Notes:

[8] - ANOVA

[9] - P-value Comparison of Xprenor and Subutex at corresponding times for Maintenance Day 7

Statistical analysis title	Respiration rate (RR) - 30 min

Statistical analysis description:

The absolute respiration rate was to be statistically compared between Xprenor and Subutex groups on Maintenance Days 2 and 7 pre-dose, and at 15, 30, and 60 minutes post-dose treatment by analysis of variance (ANOVA).

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.8969 [11]
Method	ANOVA
Variability estimate	Standard deviation

Notes:

[10] - ANOVA

[11] - P-value Comparison of Xprenor and Subutex at corresponding times for Maintenance Day 7

Statistical analysis title	Respiration rate (RR) - 60 min

Statistical analysis description:

The absolute respiration rate was to be statistically compared between Xprenor and Subutex groups on Maintenance Days 2 and 7 pre-dose, and at 15, 30, and 60 minutes post-dose treatment by analysis of variance (ANOVA).

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.8986 [13]
Method	ANOVA
Variability estimate	Standard deviation

Notes:

[12] - ANOVA

[13] - P-value Comparison of Xprenor and Subutex at corresponding times for Maintenance Day 7

Secondary: Pharmacokinetic end points (Tmax)

End point title	Pharmacokinetic end points (Tmax)

End point description:

To evaluate and compare the pharmacokinetics between Subutex and Xprenor in terms of the maximum concentration (Cmax) and time to reach maximum concentration (Tmax) in opioid dependent patients.

End point type	Secondary

End point timeframe:

Samples collected at 0, 5, 10, 15, 30, 60, 120, and 180 min on Day 1 of Titration Period and at 0, 5, 10, 15, 30, 60, 120, and 180 min post-study dosing on Days 2 and 7 of Maintenance Period and the last day of Extension Period (Days 27 to 29).

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Minutes				
median (full range (min-max))				
Buprenorphine Norbuprenorphine	60 (60 to 60) 60 (60 to 60)	60 (60 to 60) 120 (60 to 120)		

Statistical analyses

Statistical analysis title	Pharmacokinetics
Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [14]
Method	NA

Notes:

[14] - Single dose pharmacokinetic parameters of Cmax, Tmax, and as data allows; AUC0-3, Kel, and t1/2 summarized using descriptive statistics (mean, SD, minimum, median, maximum geometric mean and CV%). Incurrent sample reanalysis (ISR) performed.

Secondary: Pharmacokinetic end points (Cmax)

End point title	Pharmacokinetic end points (Cmax)

End point description:

To evaluate and compare the pharmacokinetics between Subutex and Xprenor in terms of the maximum concentration (Cmax) and time to reach maximum concentration (Tmax) in opioid dependent patients.

End point type	Secondary

End point timeframe:

Samples collected at 0, 5, 10, 15, 30, 60, 120, and 180 min on Day 1 of Titration Period and at 0, 5, 10, 15, 30, 60, 120, and 180 min post-study dosing on Days 2 and 7 of Maintenance Period and the last day of Extension Period (Days 27 to 29).

End point values	PK data after administration of both Xprenor and Subutex.			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: ng/ml				
median (standard deviation)				
Buprenorphine Norbuprenorphine	146.0 (± 88.2) 109.09 (± 42.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic end points (AUC 0 to 3 h post-dose)

End point title	Pharmacokinetic end points (AUC 0 to 3 h post-dose)

End point description:

AUC0-3hr calculated using the linear trapezoidal rule from pre-dose to 3 hr post-dose or the time of the last quantifiable plasma concentration, respectively. For the purpose of calculating AUC0-3hr, when two consecutive plasma concentrations below the lower limit of quantification (LOQ) are encountered after Tmax all subsequent values are excluded from the analysis. Missing values are excluded from the analysis. All values <LOQ prior to Tmax will be set to zero. Cmax and AUC0-3hr data are summarised by treatment group and dose at each of the four sampling periods using standard dispersion parameters. Tmax Data will be summarised by treatment group and dose at each of the four sampling periods using median and ranges. A statistical comparison of median Tmax between these two treatments are undertaken using the Wilcoxon matched pairs signed rank test. An estimate of the median difference between pairs along with the 90% CIs obtained based on the Hodges Lehman estimator.

End point type	Secondary

End point timeframe:

Samples collected at 0, 5, 10, 15, 30, 60, 120, and 180 min on Day 1 of Titration Period and at 0, 5, 10, 15, 30, 60, 120, and 180 min post-study dosing on Days 2 and 7 of Maintenance Period and the last day of Extension Period (Days 27 to 29).

End point values	PK data after administration of both Xprenor and Subutex.			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: min*ng/ml				
median (standard deviation)				
Buprenorphine Norbuprenorphine	156.0 (± 62.0) 96.0 (± 39.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy end points (Likert scale)

End point title	Efficacy end points (Likert scale)

End point description:

To evaluate and compare opioid withdrawal symptoms and satisfaction of treatment using medication hold and dose adequacy (Likert) scales between Subutex and Xprenor including; the examination of changes from Baseline and absolute scores between Maintenance Day 7 and the last day of the Extension Period for each treatment group.
The subjects were to be asked to score the adequacy of 'hold' from their prescribed dose of study medication. There were 3 questions:
1. To assess adequacy of 'hold' on current dose of buprenorphine
2. To assess intensity of withdrawal symptoms on current dose of buprenorphine
3. To assess intensity of craving for heroin on current dose of buprenorphine
Likert Scale: 4 = worst adequacy of hold/highest intensity of withdrawal/craving, 1 = best adequacy of hold/lowest intensity of withdrawal/craving

End point type	Secondary

End point timeframe:

From baseline to the end of the study - TP=Titration Period - MP=Mainenance Period - EP=Extension Period

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: Score Likert scale				
median (full range (min-max))				
Adequacy of Hold - TP Day 2	3.0 (1 to 4)	2.0 (1 to 4)		
Adequacy of Hold - TP Day 3	2.0 (1 to 4)	1.0 (1 to 4)		
Adequacy of Hold - TP Day 4	1.5 (1 to 3)	1.0 (1 to 3)		
Adequacy of Hold - TP Day 5	2.0 (1 to 3)	1.0 (1 to 3)		
Adequacy of Hold - TP Day 6	2.0 (1 to 3)	1.0 (1 to 3)		
Adequacy of Hold - TP Day 7	1.0 (1 to 3)	1.0 (1 to 3)		
Intensity of Withdrawal - TP Day 2	2.0 (1 to 4)	1.0 (1 to 3)		
Intensity of Withdrawal - TP Day 3	2.0 (1 to 4)	1.0 (1 to 4)		
Intensity of Withdrawal - TP Day 4	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Withdrawal - TP Day 5	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Withdrawal - TP Day 6	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Withdrawal - TP Day 7	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Craving - TP Day 2	1.0 (1 to 4)	1.0 (1 to 3)		
Intensity of Craving - TP Day 3	1.0 (1 to 4)	2.0 (1 to 4)		
Intensity of Craving - TP Day 4	1.0 (1 to 3)	1.0 (1 to 2)		
Intensity of Craving - TP Day 5	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Craving - TP Day 6	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Craving - TP Day 7	1.0 (1 to 3)	1.0 (1 to 2)		
Adequacy of Hold - MP Day 2	1.0 (1 to 3)	1.0 (1 to 3)		
Adequacy of Hold - MP Day 7	1.0 (1 to 3)	1.0 (1 to 3)		
Intensity of Withdrawal - MP Day 2	1.0 (1 to 2)	1.0 (1 to 2)		
Intensity of Withdrawal - MP Day 7	1.0 (1 to 4)	1.0 (1 to 2)		
Intensity of Craving - MP Day 2	1.0 (1 to 2)	1.0 (1 to 2)		

Intensity of Craving - MP Day 7	1.0 (1 to 4)	1.0 (1 to 2)		
Adequacy of Hold - EP Day 2	1.0 (1 to 3)	1.5 (1 to 3)		
Adequacy of Hold - EP Day 3	1.0 (1 to 3)	1.0 (1 to 2)		
Adequacy of Hold - EP Day 4	1.0 (1 to 3)	1.0 (1 to 2)		
Intensity of Withdrawal - EP Day 2	1.0 (1 to 2)	1.5 (1 to 2)		
Intensity of Withdrawal - EP Day 3	1.0 (1 to 3)	1.0 (1 to 1)		
Intensity of Withdrawal - EP Day 4	1.0 (1 to 2)	1.0 (1 to 1)		
Intensity of Craving - EP Day 2	1.0 (1 to 2)	1.5 (1 to 2)		
Intensity of Craving - EP Day 3	1.0 (1 to 2)	1.0 (1 to 1)		
Intensity of Craving - EP Day 4	1.0 (1 to 1)	1.0 (1 to 1)		

Statistical analyses

Statistical analysis title	Likert Scale (Adequacy of Hold)

Statistical analysis description:

The subjective 4 point assessments of hold, craving, and withdrawal symptoms were to be summarised by percentage. Also, for each of the 3 categories, the data were to be scored according to the four tick boxes (1 to 4) [‘Hold’, worst held 4; ‘Withdrawal’, severe symptoms 4; ‘Craving’, severe craving 4] and the scored data presented using standard descriptive statistics across each study period day, by treatment group
Likert Scale: 4 = worst adequacy of hold/highest intensity of withdrawal/crav

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.603
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Statistical analysis title	Likert Scale (Intensity of Withdrawal)

Statistical analysis description:

The subjective 4 point assessments of hold, craving, and withdrawal symptoms were to be summarised by percentage. Also, for each of the 3 categories, the data were to be scored according to the four tick boxes (1 to 4) [‘Hold’, worst held 4; ‘Withdrawal’, severe symptoms 4; ‘Craving’, severe craving 4] and the scored data presented using standard descriptive statistics across each study period day, by treatment group
Likert Scale: 4 = worst adequacy of hold/highest intensity of withdrawal/crav

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.062
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Statistical analysis title	Likert Scale (Intensity of Craving)

Statistical analysis description:

The subjective 4 point assessments of hold, craving, and withdrawal symptoms were to be summarised by percentage. Also, for each of the 3 categories, the data were to be scored according to the four tick boxes (1 to 4) [‘Hold’, worst held 4; ‘Withdrawal’, severe symptoms 4; ‘Craving’, severe craving 4] and the scored data presented using standard descriptive statistics across each study period day, by treatment group
Likert Scale: 4 = worst adequacy of hold/highest intensity of withdrawal/crav

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.269
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Secondary: Efficacy end points (OOWS and SOWS)

End point title	Efficacy end points (OOWS and SOWS)

End point description:

Evaluate and compare the scores on the OOWS and SOWS from baseline to end of study between Subutex and Xprenor, including examination of changes from Baseline.
Subjective and Objective Opioid Withdrawal Scales (SOWS and OOWS scores) :
- SOWS scale: 5 point scale (from 0 to 4) on 16 parameters assessing withdrawal (Section 9.5.1.1). For each parameter: 0 = not at all, 1 = a little, 2 = moderate, 3 = quite a bit, and 4 = extremely, so the lower the overall SOWS score, the fewer the withdrawal symptoms the subject felt they were experiencing
- OOWS scale: 13 parameters with 1 of 2 ratings (either 0 or 1) ascribed to each. In each case, the ‘0' corresponded to either the absence of the withdrawal sign, or, in the case of rhinorrhea, < 3 sniffs, so the lower the mean OOWS score, the fewer opioid withdrawal signs were observed by the PI (or her/his designee).
Parameter: 0 = not at all, 1 = a little, 2 = moderate, 3 = quite a bit, and 4 = extremely.

End point type	Secondary

End point timeframe:

From baseline to end of study.

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	11		
Units: Score				
median (full range (min-max))				
SOWS Titration Day 2	4.0 (0 to 25)	4.0 (0 to 13)		
SOWS Titration Day 3	4.0 (0 to 23)	2.0 (0 to 33)		
SOWS Titration Day 4	0.0 (0 to 14)	0.0 (0 to 3)		
SOWS Titration Day 5	1.0 (0 to 12)	0.0 (0 to 2)		
SOWS Titration Day 6	1.0 (0 to 7)	0.0 (0 to 4)		
SOWS Titration Day 7	0.0 (0 to 4)	1.0 (0 to 3)		
SOWS Maintenance Day 2	0.0 (0 to 6)	1.0 (0 to 6)		
SOWS Maintenance Day 7	0.0 (0 to 1)	0.0 (0 to 3)		

OOWS Titration Day 2	1.0 (0 to 9)	0.0 (0 to 4)		
OOWS Titration Day 3	0.0 (0 to 5)	1.0 (0 to 4)		
OOWS Titration Day 4	0.0 (0 to 7)	0.0 (0 to 1)		
OOWS Titration Day 5	0.0 (0 to 5)	0.0 (0 to 2)		
OOWS Titration Day 6	0.0 (0 to 2)	0.0 (0 to 1)		
OOWS Titration Day 7	0.0 (0 to 1)	0.0 (0 to 1)		
OOWS Maintenance Day 2	0.0 (0 to 1)	0.0 (0 to 1)		
OOWS Maintenance Day 7	0.0 (0 to 1)	0.0 (0 to 1)		

Statistical analyses

Statistical analysis title	SOWS Maintenance D2
Statistical analysis description: Subjective and Objective Opioid Withdrawal Scales	
Comparison groups	Subutex v Xprenor
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8336
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Statistical analysis title	SOWS Maintenance D7
Statistical analysis description: Subjective and Objective Opioid Withdrawal Scales	
Comparison groups	Subutex v Xprenor
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8963
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Statistical analysis title	OOWS Maintenance D2
Statistical analysis description: Subjective and Objective Opioid Withdrawal Scales	
Comparison groups	Subutex v Xprenor

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 1
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Statistical analysis title	OOWS Maintenance D7

Statistical analysis description:

Subjective and Objective Opioid Withdrawal Scales

Comparison groups	Subutex v Xprenor
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7609
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Secondary: Efficacy end points (Study drug oral disintegration time)

End point title	Efficacy end points (Study drug oral disintegration time)

End point description:

Study Drug Oral Disintegration Time :
To establish the time required for (a) disintegration (partial) of the test medications Subutex and Xprenor, and (b) complete disappearance, when placed in the therapeutic area of administration (Subutex, sublingually i.e. under the tongue; Xprenor, oro-mucosally, i.e. on the tongue).
The oral disintegration speed of Xprenor and Subutex was to be assessed visually at the following time points using a stop watch: 0, 15 and 30 seconds, 1, 2, 3, 5, 10, and 15 minutes on Days 1, 7, 9, and 14. The same person was to assess the complete course of 1 tablet disintegration. Separate measurements were taken for the time to partial disintegration (no longer able to remove from the mouth) and time to completely disintegrate.

End point type	Secondary

End point timeframe:

From baseline to end of study, on Days 1, 7, 9, and 14

End point values	Xprenor	Subutex		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	13		
Units: Minutes				
median (full range (min-max))				
Partial disintegration at Titration D1	0.3 (0.25 to 0.50)	0.3 (0.25 to 1.00)		
Complete disintegration at Titration D1	2.0 (1.00 to 15.00)	5.0 (2.00 to 15.00)		

Partial disintegration at Titration D7	0.3 (0.25 to 0.50)	0.3 (0.25 to 0.50)		
Complete disintegration at Titration D7	2.0 (1.00 to 10.00)	10.0 (3.00 to 10.00)		
Partial disintegration at Maintenance D2	0.25 (0.25 to 0.25)	0.3 (0.25 to 0.50)		
Complete disintegration at Maintenance D2	2.0 (1.00 to 10.00)	10.0 (3.00 to 15.00)		
Partial disintegration at Maintenance D7	0.3 (0.25 to 0.50)	0.3 (0.25 to 2.00)		
Complete disintegration at Maintenance D7	2.0 (1.00 to 10.00)	7.5 (3.00 to 15.00)		
Partial disintegration All periods	0.3 (0.25 to 0.50)	0.3 (0.25 to 2.00)		
Complete disintegration All periods	2.0 (1.00 to 15.00)	10.0 (2.00 to 15.00)		

Statistical analyses

Statistical analysis title	Drug Disintegration Status Post-dose

Statistical analysis description:

Times of both partial and complete oral disintegration for each study drug summarised separately. Proportion of all treatments at each time point with whole disintegration determined separately for Xprenor and Subutex (phase and dose). Disintegration time records inadvertently recorded after a second dose on Titration Day 1 not included. Mean and median time to whole, partial, complete disintegration determined separately for Xprenor and Subutex and compared using Cox model for multiple events.

Comparison groups	Xprenor v Subutex
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	Cox
Parameter estimate	Cox proportional hazard
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were to be monitored throughout the study from the time the subject signed the ICF.

Adverse event reporting additional description:

AEs and SAEs were reported until the end of the Extension Period. All AE's were to be recorded within 24 h of when the site became aware of it. Life-threatening or fatal AEs were to be reported to Aptiv Solutions within 2 hours of knowledge of the event if this occurred before recognised recurrence of the disease.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Subutex

Reporting group description:

Subjects who had received Subutex

Reporting group title	Xprenor

Reporting group description:

Subjects who had received Xprenor

Reporting group title	Extension

Reporting group description:

Subjects entered until Extension period (during which all Xprenor randomized subjects were to be transferred to Subutex)

Serious adverse events	Subutex	Xprenor	Extension
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events		0	0

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

Non-serious adverse events	Subutex	Xprenor	Extension
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 13 (30.77%)	17 / 23 (73.91%)	13 / 32 (40.63%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Hypotension			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Chest discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 32 (3.13%)
occurrences (all)	0	2	2
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	2 / 32 (6.25%)
occurrences (all)	0	4	4
Feeling hot			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Vessel puncture site reaction			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	2 / 32 (6.25%)
occurrences (all)	0	3	3
Nasal congestion			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	0 / 32 (0.00%)
occurrences (all)	0	2	0

Oropharyngeal pain			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 13 (0.00%)	3 / 23 (13.04%)	1 / 32 (3.13%)
occurrences (all)	0	4	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	2
Depressed mood			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Restlessness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	2 / 32 (6.25%)
occurrences (all)	3	0	3
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Blood pressure diastolic decreased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 23 (4.35%)	1 / 32 (3.13%)
occurrences (all)	3	3	3
Blood pressure increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 32 (3.13%)
occurrences (all)	0	2	2
Electrocardiogram abnormal			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Heart rate decreased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Mean cell volume abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Platelet count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Laceration			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	1 / 13 (7.69%)	4 / 23 (17.39%)	1 / 32 (3.13%)
occurrences (all)	6	6	6
Hyperaesthesia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Migraine			

subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Foreign body sensation in eyes			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	1 / 32 (3.13%)
occurrences (all)	0	3	3
Hypoaesthesia oral			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	0 / 32 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	2	0	2
Toothache			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 32 (3.13%)
occurrences (all)	0	2	2
Vomiting			

subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	2 / 32 (6.25%)
occurrences (all)	3	0	3
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 23 (8.70%)	1 / 32 (3.13%)
occurrences (all)	0	3	3
Pruritus			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	3 / 23 (13.04%)	1 / 32 (3.13%)
occurrences (all)	0	4	4
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Muscle twitching			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			

subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	1 / 32 (3.13%)
occurrences (all)	0	2	2
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 23 (0.00%)	1 / 32 (3.13%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 13 (0.00%)	1 / 23 (4.35%)	0 / 32 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 13 (7.69%)	0 / 23 (0.00%)	0 / 32 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2012	Amendment 1 (Protocol version12)
28 November 2012	Amendment 2 (Protocol version 13)
04 April 2013	Amendment 3 (Protocol version 15)
01 August 2013	Amendment 4 (Protocol version 16)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported