Title of trial

Full Title of the trial	**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.**

Trial Identifiers

EudraCT Number	2012-003560-49		**Sponsor Protocol Code**		MD2012/01XP	
Other Trial Identifiers						
Other Identifier name	ISRCTN Number	NCT Number	WHO Universal Trial Reference Number (UTRN)			
Other Identifier						

Sponsor

Organisation Name	Martindale Pharma®		
Street Address	Building A2, Glory Park, Glory Park Avenue, Wooburn Green	**Town/City**	Buckinghamshire
Post code	HP10 0DF	**Country**	United Kingdom

Contact Points - **Scientific Contact Point**

Functional name of contact point	Dr Mehemed OUZID	**Name of organisation**	ETHYPHARM
Telephone number	+33 (0)1 41 12 17 20		
Email address	ouzid.mehemed@ethypharm.com		

Contact Points - **Public contact point** ②

Functional name of contact point	Ethypharm global headquarters	**Name of organisation**	**ETHYPHARM**
Telephone number	+33 (0)1 41 12 17 20		
Email address	information@ethypharm.com		

Paediatric regulatory details

Is trial part of a Paediatric Investigation Plan?	***[Circle one]*** Yes/No					
EMA Paediatric Investigation Plans	NA					
Does article 45 REGULATION (EC) No 1901/2006 apply to this trial?	***[Circle one]*** Yes/No		**Does article 46 REGULATION (EC) No 1901/2006 apply to this trial?**		***[Circle one]*** Yes/No	

Result analysis stage

Primary completion date reached?	***[Circle one]*** Yes/No	**Primary completion date**	22 December 2013
Analysis stage	***[Circle one]*** Interim; Final	**Date of interim/final analysis**	09 April 2014
Global end of trial reached?	***[Circle one]*** Yes/No	**Date of global end of trial**	22 December 2013

Main objective of the trial	To establish the safety profile of Xprenor compared to Subutex.		
Actual date of start of recruitment to the protocol (in any country)	14 February 2013		
Long term follow up planned	***[Circle one]*** Yes/No	**Follow up planning rationale**	
Long term follow up duration	Value: _____ Unit: *[Select one]* Months; Years		

Independent Data-Monitoring Committee (IDMC) involvement	***[Circle one]*** Yes/No
Protection of subjects ③	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 ④	Xprenor: Starting dose of 2 to 4 mg/day, increasing in 2 to 6 mg steps up to 24 mg/day.
Evidence for comparator(s)	Subutex: Starting dose of 2 to 4 mg/day, increasing in 2 to 8 mg steps up to 32 mg/day.

Actual number of subjects included in the trial

Actual number of subjects included in each Country concerned

Country	UK									
Number of subjects	55									

For multinational trials

Actual number of subjects included in the EEA	[Derived from table above]
Actual number of subjects included worldwide	[Derived from table above]

Age Group Breakdown for the whole trial

Age of subjects	**Number of Subjects**
In Utero	0
Preterm newborn- gestational age < 37 wk	0
Newborns (0-27days)	0
Infants and toddlers (28days – 23months)	0
Children (2-11 years)	0
Adolescents (12-17 year)	0
Between 18 and 65 years	55
From 65 years to 84 years	0

85 years and over	0

The EudraCT number cannot be amended

② The public contact and scientific contact points may be the same as each other.

③ A description of the actual measures taken to protect subjects.

④ Details such as the dosage and frequency plus any other relevant information should be captured here.

Subject disposition form *EMA*

Recruitment Details ①	55 subjects have been recruited by two centers.
Screening Details ②	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 their consent.

Pre-Assignment Period **Title: Pre-Assignment Period**

		Number of Subjects
STARTED		55
Milestone Title ③	Patients randomised	38
Milestone Title ③	Patients randomised who Received Study Medication	36
COMPLETED		30
Reason Not Completed		
Adverse event, not serious		0
Adverse event, serious fatal		0
Adverse event, serious non-fatal		0
Consent withdrawn by subject		4

Physician decision		0
Pregnancy		0
Protocol Violation		0
Other Reason ④	Lost to follow-up	1
Other Reason ④	Inadequate contraception	1

① Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and types of location (e.g. medical clinic), to provide context.

② Screening details are required if the results will not contain a pre-assignment period.

③ Add as many Milestone Title. A descriptive title for each row is required.

④ Add as many other reason not completed rows as needed. A descriptive title for each row is required.

Period ① **Title: Title Name:** Titration/Maintenance/Extension Periods **Baseline Period: Yes/No** [Circle one]

Blinding	***[Circle one]*** Double blind; Single blind ; Not applicable	**Roles blinded ②**	***[Circle any]*** Subject; Investigator; Monitor; Data analyst; Carer ; Assessor
Blinding implementation details	This was an open-labelled study and no blinding was performed.		
Allocation Method	***[Circle one]*** Randomised – controlled; Non-randomised – controlled; Not applicable		

Arm Title ③		**Xprenor group**	**Subutex group**	**TOTAL**
Arm Description ④		Eligible patients randomised to receive Xprenor	Eligible patients randomised to receive Subutex	
		Number of Subjects	**Number of Subjects**	**Number of Subjects**
STARTED		23	13	36
Milestone Title ⑤	Titration Period 7 days	23	13	36
Milestone Title ⑤	Maintenance Period 7 days	ND	ND	33
Extension Period 13 to 15 days	To switch xprenor patients to subutex	21	11	32
COMPLETED		20	10	30
Reason Not Completed ⑥				
Adverse event, not serious		0	0	0
Adverse event, serious fatal		0	0	0
Adverse event, serious non-fatal		0	0	0

Consent withdrawn by subject		2	2	4
Lack of Efficacy		0	0	0
Lost to follow-up		1	0	1
Physician decision		0	0	0
Pregnancy		0	0	0
Protocol Violation		0	0	0
Transferred to other arm/group		0	0	0
Other Reason ⑦	Inadequate contraception	0	1	1
Reasons for joining		NA	NA	NA
Transferred in from other arm/group		NA	NA	NA
Late recruitment		NA	NA	NA
Other reason ⑧		NA	NA	NA
Other reason ⑧		NA	NA	NA

① Complete a period table for each period you wish to report. Provide a descriptive title for each reported period.

② If blining is single or double, then the roles blinded must be specified.

③ Arms are created on the next form. Only the Arm title and description will be displayed on the Subject disposition form

④ Arm Description provides more details about the Arm.

⑤ Add as many Milestone Titles as necessary. A descriptive title for each row is required.

⑥ Use only the most appropriate reason for not completing in each case and do not double count.

⑦ Add as many other reason not completed rows as needed. A descriptive title for each row is required.

⑧ Add as many other reasons for joining the Arm as needed. A descriptive title for each row is required.

Subject disposition arm form *EMA*

Arm Title	Xprenor® treatment group
Arm Description ②	Eligible subjects randomised to receive Xprenor for the first 14 days
Arm Type	***[Circle one]*** Experimental; Active Comparator; Placebo Comparator; No IMP; Other (specify):_____

IMP Name	Xprenor
IMP Code	NA
Other names **(separated by commas)**	Buprenorphine
Route of Administration ④	oro-mucosal (on the tongue)
Pharmaceutical Form ⑤	Oral tablets.
Dosage and Administration Details ⑥	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® treatment group
Arm Description ②	Eligible subjects randomised to receive Subutex for the first 14 days
Arm Type	***[Circle one]*** Experimental; Active Comparator; Placebo Comparator; No IMP; Other (specify):_____

IMP Name	Subutex
IMP Code	NA
Other names **(separated by commas)**	Buprenorphine
Route of Administration ④	Sublingual
Pharmaceutical Form ⑤	Sublingual tablets.
Dosage and Administration Details ⑥	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.

① This form is used to create the Arms used as reference information in the Subject disposition details (see previous)

② Arm Description describes details about the arms evaluated.

③ Details of the products used. There may be multiple products created.

④ A product may have any number of Routes of Administration

⑤ A product may have any number of Pharmaceutical Forms

⑥ Provide any or all of the following details: the dosage and frequency of administration.

Subject analysis sets form *EMA*

Subject analysis set ①

Subject analysis set title	The safety population
Subject analysis set type	***[Circle one]*** Intent to treat; Per protocol; Full analysis set; Safety population; Sub-group analysis set
Subject analysis set description②	All subjects who received at least one dose of the study medications.
Number of subjects③	36

Complete a subject analysis set table for additional groups of subjects you wish to report on.

Subject analysis set description that defines the population type.

Provide the number of subjects that constitute this subject analysis set.

Baseline characteristics form Age *EMA*

Reporting Group Title	Xprenor	Subutex	TOTAL
Reporting Group Description ①	Subjects from the Evaluable Population treated with Xprenor	Subjects from the Evaluable Population treated with Subutex	
Overall number of baseline subjects	23	13	[Derived: total]
Age, Categorical ②	Number of subjects	Number of subjects	Number of subjects
Unit of measure: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 year)	0	0	0
From 18 - 64 years	23	13	36
From 65 – 84 years	0	0	0
Over 85 years	0	0	0

Age, Continuous		**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**	
		[Circle One] arithmetic mean, geometric mean, least squares mean, log mean, median.	***[Circle One]*** standard deviation, interquartile range, range, sample min/max.	***[Circle One]*** arithmetic mean, geometric mean, least squares mean, log mean, median.	***[Circle One]*** standard deviation, interquartile range, range, sample min/max.	
Unit of measure	Years	43.0	26.0 - 58.0	45.0	23.0 - 53.0	

① Reporting group description contains details about the group of subjects receiving treatment.

②The age categories above are the default categories that match the protocol details in the clinical trial application. However, any age categorisation can be used.

Baseline characteristics form Gender *EMA*

Reporting group title	Xprenor	Subutex	TOTAL
Reporting group description ①	Subjects from the Evaluable Population treated with Xprenor	Subjects from the Evaluable Population treated with Subutex	
Overall number of baseline subjects	23	13	36
Gender, female, male ②	Number of subjects	Number of subjects	Number of subjects
Unit of measure: Number of Subjects			
Female	3	2	5
Male	20	11	31

① Reporting group description contains details about the group of subjects receiving treatment.

② At least one Gender baseline measure (female, male or Customised) is required

Baseline characteristics form *Study Specific Measure* *EMA*

Study specific characteristic title	Demographic and Other Baseline Characteristics
Baseline measure description	Data on subject demographics (gender, age, height, weight, BMI, race [5 categories]), opioid dependence, and laboratory data were to be summarised using standard descriptive statistics (mean, standard deviation [SD], median, range).

Reporting group title		**Xprenor**		**Subutex**		**TOTAL ④**	
Reporting group description ①		Subjects from the Evaluable Population treated with Xprenor		Subjects from the Evaluable Population treated with Subutex			
Overall number of baseline subjects		23		13		**36**	
Unit of Measure		**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**	**Measure type**	**Dispersion type**
		[Circle One] arithmetic mean, geometric mean, least squares mean, log mean, median.	*[Circle One]* ② standard deviation, interquartile range, range, sample min/max.	*[Circle One]* arithmetic mean, geometric mean, least squares mean, log mean, median,	*[Circle One]* ② standard deviation, interquartile range, range, sample min/max.		
		Number of subjects		**Number of subjects**		**Number of subjects**	

Height	cm	176.0	154.0 – 192.0	168.5	153.0 – 199.0	**175,5**
Weight	kg	73.4	49.4 - 102.8	64.1	44.5 - 89.0	71,4
BMI	Kg/m²	23.5	18.4 - 29.9	21.6	18.8 - 29.9	23,4
Race : Asian	Number	0		1		NA
Race : Caucasian	Number	15		9		NA
Race : Other	Number	8		3		NA
Opioid dependence history >6-12 months	Number	1		0		NA
Opioid dependence history >24 months	Number	22		13		NA
Type of opioid abused Opioid painkiller addiction	Number	1		0		NA
Type of opioid abused Heroin addiction	Number	21		12		NA
Type of opioid abused Other	Number	1		1		NA

① Reporting group description contains details about the group of subjects receiving treatment.

② A single number should be entered for all dispersion types in this table.

③ Add as many Categories as needed if the data can be categorised.

④ The total group is only relevant to categorical data.

End points form *EMA*

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Safety end-points
End Point Description **[Max. 999 characters]**	To compare the incidence of AEs reported in Subutex and Xprenor arms compared to Subutex.
End Point Time Frame **[Max 255 characters]**	All over the study
Arm(s)/Subjects analysis sets	Xprenor group + Subutex group

Reporting Group Title	**Xprenor group**			**Subutex group**		
Reporting Group Description ①	Subjects of the study who received at least one dose of Xprenor during the study			Subjects of the study who received at least one dose of Subutex during the study		
Overall Number of Baseline Subjects	23	**Comment②**		13	**Comment②**	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

		[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure					
Category Title ⑤	At least one AE (number of subjects)	17	NA	4	NA
Category Title ⑤	AE Severity Mild (number of subjects)	13	NA	1	NA
Category Title ⑤	AE Severity Moderate (number of subjects)	4	NA	3	NA
Category Title ⑤	At least one Treatment-related TEAE (number of subjects)	16	NA	2	NA

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Safety end-points
End Point Description **[Max. 999 characters]**	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.
End Point Time Frame **[Max 255 characters]**	Continuous pulse oximetry was assessed for 3 hours post-dose during active titration and on Days 2 and 7 of the Maintenance Period (Study Days 9 and 14). Manual pulse oximetry was assessed at 0, 15, 30, and 60 minutes post-study treatment during active titration and on Days 2 and 7 of the Maintenance Period (Study Days 9 and 14).
Arm(s)/Subjects analysis sets	Evaluable population

Reporting Group Title	**Xprenor group**			**Subutex group**		
Reporting Group Description ①	Subjects of the study who received at least one dose of Xprenor during the study			Subjects of the study who received at least one dose of Subutex during the study		
Overall Number of Baseline Subjects	23	**Comment②**		13	**Comment②**	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

		[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure	Seconds				
Category Title	Durations of SpO2 < 90% in the 0 to 30 minutes post-dose period on Titration Day 1	8.1	16.69	158.3	510.09
Category Title	Durations of SpO2 < 90% in the 0 to 30 minutes post-dose period on Titration Day 2	6.2	10.39	23.6	29.96
Category Title	Durations of SpO2 < 90% in the 0 to 30 minutes post-dose period on Titration Day 3	5.0	10.35	21.7	29.30
Category Title	Durations of SpO2 < 90% in the 0 to 30 minutes post-dose period on Titration Day 5	3.3	5.77	10.0	14.14
Category Title	Durations of SpO2 < 90% in the 0 to 30 minutes post-dose period on Maintenance Days 2	6.1	11.95	177.0	544.00
Category Title	Durations of SpO2 < 90% in the 0 to 30 minutes post-dose period on Maintenance Days 7	7.1	13.47	14.0	31.25
Category Title	Durations of SpO2 < 90% in the 0 to 120 minutes post-dose period on Titration Day 1	0.0	0.0	0.5	0.71
Category Title	Durations of SpO2 < 90% in the 0 to 120 minutes post-dose period on Titration Day 2	0.1	0.28	0.4	0.79
Category Title	Durations of SpO2 < 90% in the 0 to 120 minutes post-dose period on Titration Day 3	0.6	0.89	0.0	0.0
Category Title	Durations of SpO2 < 90% in the 0 to 120 minutes post-dose period on Titration Day 5	105.0	ND	122.5	137.89
Category Title	Durations of SpO2 < 90% in the 0 to 120 minutes post-dose period on Maintenance Days 2	68.0	92.37	499.3	959.26

Category Title	Durations of SpO2 < 90% in the 0 to 120 minutes post-dose period on Maintenance Days 7	61.1	88.94	226.0	281.46

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Safety end-points
End Point Description **[Max. 999 characters]**	To monitor respiration rate (RR)
End Point Time Frame **[Max 255 characters]**	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.
Arm(s)/Subjects analysis sets	Evaluable population

Reporting Group Title	**Xprenor group**			**Subutex group**		
Reporting Group Description ①	Subjects of the study who received at least on doses of Xprenor during the study			Subjects of the study who received at least on doses of Subutex during the study		
Overall Number of Baseline Subjects	23	**Comment②**		13	**Comment②**	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

		[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	[Circle One] ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	[Circle One] ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure	breaths/min				
Category Title	RR - TitrationD1 – 0 min	15.3	2.03	15.6	2.97
Category Title	RR - TitrationD1 – 15 min	14.8	2.28	15.1	2.47
Category Title	RR - TitrationD1 – 30 min	14.7	2.20	14.7	2.10
Category Title	RR - TitrationD1 – 60 min	14.0	2.07	14.3	2.14
Category Title	RR – TitrationD7 – 0 min	16.0	0.00	17.0	1.41
Category Title	RR – TitrationD7 – 15 min	16.3	1.15	16.0	2.83
Category Title	RR – TitrationD7 – 30 min	15.3	0.58	15.0	1.41
Category Title	RR – TitrationD7 – 60 min	15.0	1.41	16.0	2.83
Category Title	RR - MaintenanceD2 – 0 min	15.1	1.98	15.0	1.84
Category Title	RR - MaintenanceD2 – 15 min	14.9	2.02	15.0	1.84
Category Title	RR - MaintenanceD2 – 30 min	14.6	1.77	14.2	2.09
Category Title	RR - MaintenanceD2 – 60 min	14.7	1.73	14.5	2.34
Category Title	RR – MaintenanceD7 – 0 min	15.3	2.74	15.5	2.59
Category Title	RR – MaintenanceD7 – 15 min	14.9	2.20	15.3	2.26
Category Title	RR – MaintenanceD7 – 30 min	15.0	1.67	14.9	2.56
Category Title	RR – MaintenanceD7 – 60 min	14.9	1.67	15.0	2.56

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Adverse events	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	
Statistical analysis description	The number and percentage of subjects in each dose group experiencing TEAEs, treatment-related TEAEs, SAEs, AEs resulting in withdrawal from the study, and deaths were to be presented. The number and percentage of subjects experiencing a TEAE were also to be presented by body system across treatment groups in decreasing order of frequency and by maximum intensity.		
Comparison group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets	**Selection of Reporting groups:**_____ ②	
Number of subjects	36		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		
Statistical hypothesis test			
P-value	***[Circle one]*** = < ≤ > ≥ ③ NA	Value: NA	**Comment ④**
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify) : Medical Dictionary for Regulatory Activities (MedDRA, Version 15)		
Parameter Estimate			
Point estimate	Adverse events : Numbers and %		

Confidence interval	**Level**	**95%; 90%; Other:_____% NA**	**Sides**	***[Circle one]*** 1 2	**Lower limit**		**Upper limit**
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_____						
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean		**Dispersion Value**				

Statistical analysis title	Pulse oximetry (SpO2)	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	Mean difference compared to ANOVA
Statistical analysis description	Continuous oximetry saturation data (SpO2) records for all subjects by time post-dose, for each period of assessment.		
Comparison group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets	**Selection of Reporting groups:**_____ ②	
Number of subjects	36		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		

Statistical hypothesis test

P-value	***[Circle one]*** = < ≤ > ≥ ③	Value:NA	**Comment** ④	Maintenance D2: SpO2 < 90% (0 to 30 min PDP) : p-value = 0.6683 / SpO2 < 90% (0 to 120 min PDP: p-value = 0.3966 Maintenance D7: SpO2 < 90% (0 to 30 min PDP) : p-value = 0.0734 / SpO2 < 90% (0 to 120 min PDP) : p-value = 0.5603
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify)_____			
Point estimate	Pulse oximetry (SpO2)			

Parameter Estimate

Confidence interval	**Level**	95%; 90%; Other:_____% NA	**Sides**	***[Circle one]*** 1 2	**Lower limit**	**Upper limit**	
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_____						
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean NA		**Dispersion Value**				

Statistical analysis title	Respiration rate (RR)	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	ANOVA
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 group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets	**Selection of Reporting groups:**_____ ②	
Number of subjects	36		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		

Statistical hypothesis test

P-value	***[Circle one]*** = < ≤ > ≥ ③	Value:_____	**Comment** ④	Maintenance Day 7: - RR 0 min : p-value = 0.8734 / - RR 15 min : p-value = 0.6072 / - RR 30 min : p-value = 0.8969 / RR 60 min : p-value = 0.8986
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify)_____			

Point estimate	Respiration rate (RR)	**Parameter Estimate**						
Confidence interval	**Level**	**95%; 90%; Other:_____% NA**	**Sides**	***[Circle one]*** 1 2	**Lower limit**		**Upper limit**	
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_____							
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean NA			**Dispersion Value**				

End points form

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Pharmacokinetic Endpoints
End Point Description **[Max. 999 characters]**	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 Time Frame **[Max 255 characters]**	Samples were to be collected at 0, 5, 10, 15, 30, 60, 120, and 180 minutes on Day 1 of the Titration Period and at 0, 5, 10, 15, 30, 60, 120, and 180 minutes post-study dosing on Days 2 and 7 of the Maintenance Period and the last day of the Extension Period (Days 27 to 29).
Arm(s)/Subjects analysis sets	PK Population : 50% of all randomised subjects

Reporting Group Title	**Xprenor group**			**Subutex group**			**Relative**		
Reporting Group Description ①	Subjects of the study who received at least one dose of Xprenor during the study			Subjects of the study who received at least one dose of Subutex during the study			Subjects for which PK data were available following administration of both Xprenor and Subutex.		
Overall Number of Baseline Subjects	12	**Comment**②		6	**Comment**②		5	**Comment**②	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

		[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure	Minutes						
Category Title ⑤	Tmax Buprenorphine	60	[60 – 60]	60	[60 – 60]	NA	NA
Category Title ⑤	Tmax Norbuprenorphine	60	[60 – 60]	120	[60 – 120]	NA	NA
		[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure	ng/ml = Cmax min*ng/ml = AUC						
Category Title ⑤	Cmax Buprenorphine	NC	NA	NC	NA	146.0	88.2
Category Title ⑤	AUC (0 to 3h post-dose) Buprenorphine	NC	NA	NC	NA	156.0	62.0
Category Title ⑤	Cmax Norbuprenorphine	NC	NA	NC	NA	109.09	42.2
Category Title ⑤	AUC (0 to 3h post-dose) Norbuprenorphine	NC	NA	NC	NA	96.0	39.4

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Pharmacokinetics	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	
Statistical analysis description	AUC0-3hr will be 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 will be excluded from the analysis. When embedded missing values occur, they will be excluded from the analysis. All values <LOQ prior to Tmax will be set to zero. Cmax and AUC0-3hr Data will be 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 will be undertaken using the Wilcoxon matched pairs signed rank test. An estimate of the median difference between pairs along with the 90% CIs will be obtained based on the Hodges Lehman estimator.		
Comparison group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets		**Selection of Reporting groups:**_____ ②
Number of subjects	18		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		
Statistical hypothesis test			
P-value	***[Circle one]*** = < ≤ > ≥ ③ NA	Value:_____	**Comment** ④ Single dose pharmacokinetic parameters of Cmax, Tmax, and as data allows; AUC0-3, Kel, and t1/2 will be summarized using descriptive statistics (mean, SD, minimum, median, maximum geometric mean and CV%). Incurrent sample reanalysis (ISR) will be performed.
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify) : NA		
Parameter Estimate			

Point estimate	$AUC_{0\text{-}3hr}$; Cmax ; Tmax ; T1/2							
Confidence interval	**Level**	**95%; 90%; Other:_____%**	**Sides**	***[Circle one]*** **1 2**	**Lower limit**		**Upper limit**	
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_ : NA							
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean			**Dispersion Value**	NA			

End points form

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Efficacy Endpoints : Likert scale
End Point Description **[Max. 999 characters]**	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 Time Frame **[Max 255 characters]**	From baseline to the end of the study
Arm(s)/Subjects analysis sets	**Evaluable population**

Reporting Group Title	**Xprenor group**			**Subutex group**		
Reporting Group Description ①	Subjects of the study who received at least on doses of Xprenor during the study			Subjects of the study who received at least on doses of Subutex during the study		
Overall Number of Baseline Subjects	22	**Comment**②		11	**Comment**②	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

		[Circle One] number, arithmetic mean, least squares mean, geometric mean, log mean, median.	***[Circle One]*** ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	***[Circle One]*** number, arithmetic mean, least squares mean, geometric mean, log mean, median.	***[Circle One]*** ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure	Score on the Likert Scale				

Cf captures d'écran ci-dessous

Titration period

	Titration Day 2 Xpr N=22	Titration Day 2 Sub N=11	Titration Day 3 Xpr N=22	Titration Day 3 Sub N=11	Titration Day 4 Xpr N=22	Titration Day 4 Sub N=11	Titration Day 5 Xpr N=22	Titration Day 5 Sub N=11	Titration Day 6 Xpr N=21	Titration Day 6 Sub N=10	Titration Day 7 Xpr N=21	Titration Day 7 Sub N=11
Adequacy of Hold												
n	22	11	22	11	22	11	22	11	21	10	21	11
Mean	2.7	1.8	2.0	1.8	1.7	1.5	1.7	1.4	1.7	1.4	1.5	1.5
SD	1.09	0.98	0.93	1.08	0.83	0.69	0.77	0.67	0.73	0.70	0.60	0.69
Median	3.0	2.0	2.0	1.0	1.5	1.0	2.0	1.0	2.0	1.0	1.0	1.0
Range	1-4	1-4	1-4	1-4	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-3
Intensity of Withdrawal												
n	22	11	22	11	22	11	22	11	21	10	21	11
Mean	2.0	1.6	1.8	1.7	1.2	1.1	1.2	1.1	1.2	1.2	1.2	1.2
SD	0.90	0.81	0.87	1.01	0.39	0.30	0.43	0.30	0.44	0.42	0.40	0.40
Median	2.0	1.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range	1-4	1-3	1-4	1-4	1-2	1-2	1-2	1-2	1-2	1-2	1-2	1-2
Intensity of Craving												
n	22	11	22	11	22	11	21	11	21	10	21	11
Mean	1.8	1.4	1.5	1.8	1.2	1.3	1.1	1.2	1.2	1.2	1.2	1.1
SD	1.05	0.67	1.01	0.98	0.61	0.47	0.36	0.40	0.40	0.42	0.54	0.30
Median	1.0	1.0	1.0	2.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Range	1-4	1-3	1-4	1-4	1-3	1-2	1-2	1-2	1-2	1-2	1-3	1-2

Evaluable Population - Maintenance and Extension Periods

maintenance period | extension period

	Maintenance Day 2		Maintenance Day 7		Extension Day 2		Extension Day 3		Extension Day 4	
	Xpr N=22	Sub N=11	Xpr N=21	Sub N=9	Xpr[1] N=21	Sub N=4	Xpr[1] N=18	Sub N=3	Xpr[1] N=14	Sub N=3
Adequacy of Hold										
n	22	11	21	9	21	4	18	3	14	3
Mean	1.4	1.5	1.3	1.4	1.3	1.8	1.3	1.3	1.4	1.3
SD	0.59	0.69	0.58	0.73	0.58	0.96	0.59	0.58	0.63	0.58
Median	1.0	1.0	1.0	1.0	1.0	1.5	1.0	1.0	1.0	1.0
Range	1-3	1-3	1-3	1-3	1-3	1-3	1-3	1-2	1-3	1-2
P-value [3]										
Intensity of Withdrawal										
n	22	11	21	9	21	4	18	3	14	3
Mean	1.1	1.1	1.4	1.2	1.2	1.5	1.2	1.0	1.2	1.0
SD	0.35	0.30	0.80	0.44	0.40	0.58	0.55	0.00	0.43	0.00
Median	1.0	1.0	1.0	1.0	1.0	1.5	1.0	1.0	1.0	1.0
Range	1-2	1-2	1-4	1-2	1-2	1-2	1-3	1-1	1-2	1-1
P-value [3]										
Intensity of Craving										
n	22	11	21	9	21	4	18	3	14	3
Mean	1.1	1.2	1.2	1.2	1.1	1.5	1.1	1.0	1.0	1.0
SD	0.29	0.40	0.70	0.44	0.30	0.58	0.32	0.00	0.00	0.00
Median	1.0	1.0	1.0	1.0	1.0	1.5	1.0	1.0	1.0	1.0
Range	1-2	1-2	1-4	1-2	1-2	1-2	1-2	1-1	1-1	1-1
P-value [3]										

e: Likert scales assessed 24hr AFTER dosing with Xpr (Xprenor) or Sub (Subutex)

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	LIKERT SCALE	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	
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/craving, 1 = best adequacy of hold/lowest intensity of withdrawal/craving		
Comparison group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets		**Selection of Reporting groups:**_____ ②
Number of subjects	**33**		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		
Statistical hypothesis test			
P-value	***[Circle one]*** = < ≤ > ≥ ③	Value:_____	**Comment** ④ Adequacy of Hold : p= 0.603 Intensity of Withdrawal : p= 0.062 Intensity of Craving : p= 0.269
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify)_____		
Parameter Estimate			

Point estimate	Adequacy of 'hold' + withdrawal symptoms + intensity of craving for heroin							
Confidence interval	**Level**	**95%; 90%; Other:_____% NA**	**Sides**	***[Circle one]*** **1 2**	**Lower limit**		**Upper limit**	
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_____							
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean			**Dispersion Value**	NA			

End points form

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Efficacy Endpoints : OOWS and SOWS
End Point Description **[Max. 999 characters]**	To evaluate and compare the scores on the OOWS and SOWS from baseline to end of study between Subutex and Xprenor, including the examination of changes from Baseline. Subjective and Objective Opioid Withdrawal Scales (SOWS and OOWS scores) : - The SOWS scale was self-administered by the subject on a 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 - The OOWS scale consisted of 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 rhinorrhoea, < 3 sniffs, so the lower the mean OOWS score, the fewer opioid withdrawal signs were observed by the PI (or her/his designee). For each parameter: 0 = not at all, 1 = a little, 2 = moderate, 3 = quite a bit, and 4 = extremely.
End Point Time Frame **[Max 255 characters]**	From baseline to end of study.
Arm(s)/Subjects analysis sets	Evaluable population

Reporting Group Title	**Xprenor group**			**Subutex group**		
Reporting Group Description ①	Subjects of the study who received at least on doses of Xprenor during the study			Subjects of the study who received at least on doses of Subutex during the study		
Overall Number of Baseline Subjects	22	**Comment②**		11	**Comment②**	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

Unit of Measure		*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Category	SOWS Score at Titration Day 2	4.0	0-25	4.0	0-13
	SOWS Score at Titration Day 3	4.0	0-23	2.0	0-33
	SOWS Score at Titration Day 4	0.0	0-14	0.0	0-3
	SOWS Score at Titration Day 5	1.0	0-12	0.0	0-2
	SOWS Score at Titration Day 6	1.0	0-7	0.0	0-4
Category Title	SOWS Score at Titration Day 7	0.0	0-4	1.0	0-3
Category	SOWS Score at Maintenance Day 2	0.0	0-6	1.0	0-6
Category	SOWS Score at Maintenance Day 7	0.0	0-1	0.0	0-3
Category	OOWS Score at Titration Day 2	1.0	0-9	0.0	0-4
	OOWS Score at Titration Day 3	0.0	0-5	1.0	0-4
	OOWS Score at Titration Day 4	0.0	0-7	0.0	0-1
	OOWS Score at Titration Day 5	0.0	0-5	0.0	0-2
	OOWS Score at Titration Day 6	0.0	0-2	0.0	0-1
Category	OOWS Score at Titration Day 7	0.0	0-1	0.0	0-1
Category	OOWS Score at Maintenance Day 2	0.0	0-1	0.0	0-1
Category	OOWS Score at Maintenance Day 7	0.0	0-1	0.0	0-1

Graphical Representation

Upload images containing the graphical representation relevant to the End point.

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Subjective and Objective Opioid Withdrawal Scales	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	
Statistical analysis description	The total SOWS and OOWS scores for each assessment were to be summarised (separately for each of the SOWS and OOWS) using standard descriptive statistics across each study period day, by treatment group. The intra-subject score changes from Baseline to Maintenance Days 2 and 7 were to be statistically compared using ANOVA.		
Comparison group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets	**Selection of Reporting groups:**_____ ②	
Number of subjects	33		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		
Statistical hypothesis test			
P-value	***[Circle one]*** = < ≤ > ≥ ③	Value:_____	**Comment** ④ SOWS D2 : p= 0.8336 / D7 P = 0,8963 OOSW D2 : p=1 / D7 P = 0,7609
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify)_____		
Parameter Estimate			

Point estimate	SOWS and OOWS scores							
Confidence interval	**Level**	**95%; 90%; Other:_____%**	**Sides**	***[Circle one]*** **1 2**	**Lower limit**		**Upper limit**	
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_____							
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean			**Dispersion Value**				

End points form

End Point Type	***[Circle one]*** ***Primary*** ***Secondary*** ***Other Pre-specified*** ***Post-Hoc***
End Point Title	Efficacy Endpoints
End Point Description **[Max. 999 characters]**	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 Time Frame **[Max 255 characters]**	From baseline to end of study.
Arm(s)/Subjects analysis sets	Evaluable population

Reporting Group Title	**Xprenor group**			**Subutex group**		
Reporting Group Description ①	Subjects of the study who received at least on doses of Xprenor during the study			Subjects of the study who received at least on doses of Subutex during the study		
Overall Number of Baseline Subjects	23	**Comment②**		13	**Comment②**	
	Measure type		**Dispersion / Precision type**	**Measure type**		**Dispersion / Precision type**

Les lignes des autres jours de suivi à rajouter SVP		*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).	*[Circle One]* number, arithmetic mean, least squares mean, geometric mean, log mean, median.	*[Circle One]* ③ not applicable, standard deviation, inter-quartile range, range, sample min/max, standard error, confidence interval (percentage).
Unit of Measure	Minutes				
Category Title	Partial disintegration at Titration D1	0.3	[0.25-0.50]	0.3	[0.25-1.00]
Category Title	Complete disintegration at Titration D1	2.0	[1.00-15.00]	5.0	[2.00-15.00]
Category Title	Partial disintegration at Titration D7	0.3	[0.25-0.50]	0.3	[0.25-0.50]
Category Title	Complete disintegration at Titration D7	2.0	[1.00-10.00]	10.0	[3.00-10.00]
Category Title	Partial disintegration at Maintenance D2	0.25	[0.25-0.25]	0.3	[0.25-0.50]
Category Title	Complete disintegration at Maintenance D2	2.0	[1.00-10.00]	10.0	[3.00-15.00]
Category Title	Partial disintegration at Maintenance D7	0.3	[0.25-0.50]	0.3	[0.25-2.00]
Category Title	Complete disintegration at Maintenance D7	2.0	[1.00-10.00]	7.5	[3.00-15.00]
Category Title	Partial disintegration All Periods	0.3	[0.25-0.50]	0.3	[0.25-2.00]
Category Title	Complete disintegration All Periods	2.0	[1.00-15.00]	10.0	[2.00-15.00]

Graphical Representation

Upload images containing the graphical representation relevant to the End point.

Below is the definition of the statistical analysis details for this variable

Statistical Analysis of End Point ①

Statistical analysis title	Drug Disintegration Status Post-dose	**Analysis Type**	***[Circle one]*** Non-Inferiority; Equivalence; Superiority; Other
		Comment	
Statistical analysis description	The times of both partial and complete oral disintegration for each study drug were to be summarised separately using descriptive statistics. The proportion of all treatments at each time point with whole (not disintegrated), partial disintegration, and complete disintegration was to be determined separately for Xprenor and Subutex for all treatments regardless of phase and dose. Disintegration time records which were inadvertently recorded after a second dose on Titration Day 1 (Titration Day 1.1) were not included in the analysis but were summarised in the Listings. In addition, the mean and median time to whole, partial, and complete disintegration was to be determined separately for Xprenor and Subutex and compared using a Cox proportional hazards model for multiple events.		
Comparison group	**Omnibus analysis:** ***[Circle one]*** All reporting groups, All subject analysis sets		**Selection of Reporting groups:**_____ ②
Number of subjects	36		
Analysis specification	***[Circle one]*** Pre-specified; Post hoc		
Statistical hypothesis test			
P-value	***[Circle one]*** = < ≤ > ≥ ③	Value: 0.0001	**Comment** ④
Method **[Required if P-value provided]**	***[Circle one]*** ANCOVA; ANOVA; Chi-squared; Chi squared Corrected; Cochran-Mantel-Haenszel; Fisher Exact; Kruskal-Wallis; Logrank; Mantel-Haenszel ; McNemar; Mixed Models Analysis; Regression, Cox; Regression, Linear; Regression, Logistic; Sign Test; t-Test 1-sided; t-Test 2-sided; Wilcoxon (Mann-Whitney); Other method name: (specify)_____		
Parameter Estimate			

Point estimate	Study Drug Oral Disintegration Time							
Confidence interval	**Level**	**95%; 90%; Other:_____%**	**Sides**	***[Circle one]*** **1 2**	**Lower limit**		**Upper limit**	
Parameter type	***[Circle one]*** Cox Proportional Hazard; Hazard Ratio(HR); Hazard Ratio Log, Mean Difference (Final Values); Mean Difference (Net); Median Difference (Final Values); Median Difference (Net); Odds Ratio (OR); Odds Ratio log; Risk Difference (RD); Risk Ratio (RR); Risk Ratio log; Slope Other effect estimate: (specify)_____							
Variability estimate	***[Circle one]*** Standard Deviation; Standard Error of the Mean			**Dispersion Value**				

Time Frame for Adverse Event Reporting [max 255 characters]	Adverse events were to be monitored throughout the study from the time the subject signed the ICF.			
Adverse Event Reporting Additional Description [max 350 characters]	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 sitee 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.			
Dictionary Used ①	**Dictionary Name**	*[Circle One]* MedDRA; SNOMED CT; Other:(specify)_____	**Dictionary Version**	Version 15
Method	*[Circle one]* Systematic; Non-Systematic		**Frequency threshold for reporting non-serious adverse events** ②	_____% NA

Reporting Group Title	Subutex group	Xprenor goup	Extension group
Reporting Group Description ③	Subjects who had received Subutex	Subjects who had received Xprenor	Subjects entered to the Extension period (during which all Xprenor randomized subjects were to be transferred to Subutex).
Number of subjects exposed	13	23	32
Number of subjects affected by serious adverse events	0	0	0

Number of subject affected by non-serious adverse events	4	17	13
Number of deaths (all causes)	0	0	0
Number of deaths resulting from adverse events	0	0	0

Serious Adverse Events

System Organ Class	**Event Term**	**Additional Description**	**Dictionary**	*Number of Subjects **affected***	*Number of Subjects **exposed***	***Event term Occurrences - all***	*Event Term Occurrences - causally related to the treatment*	*Number of Subjects **Affected***	*Number of Subjects **exposed***	*Event term Occurrences - all*	*Event term Occurrences- causally related to the treatment*	*Number of Subjects **Affected***	*Number of Subjects **exposed***	*Event term occurrences - all*	*Event term Occurrences- causally related to the treatment*
NA					④				④				④		
NA					④				④				④		
NA					④				④				④		
NA					④				④				④		

FATALITIES

System Organ Class	**Event Term**		*Fatalities - all*	*Fatalities - causally related to the treatment*	*Fatalities - all*	*Fatalities - causally related to the treatment*	*Fatalities - all*	*Fatalities - causally related to the treatment*

NA	⑤							
NA	⑤							
NA	⑤							
NA	⑤							

Non-serious adverse events

Reporting group title	Subutex group				Xprenor group				Extension group			
Reporting group description	Subjects who had received Subutex				Subjects who had received Xprenor				Subjects entered to the Extension period (during which all Xprenor randomized subjects were to be transferred to Subutex).			
Number of subjects affected by non-serious adverse events	4				17				32			
Non-serious Adverse Events												
	Number of ***Subjects affected***	*Number of* ***Subjects exposed***	***Event term Occurrences - all***	*Event Term Occurrences - causally related to the treatment*	*Number of* ***Subjects Affected***	*Number of* ***Subjects exposed***	*Event term Occurrences - all*	*Event term Occurrences- causally related to the treatment*	*Number of* ***Subjects Affected***	*Number of* ***Subjects exposed***	*Event term occurrences - all*	*Event term Occurrences- causally related to the treatment*
System Organ Class / **Event Term** / **Additional Description** / **Dictionary**												
Ear and labyrinth disorders / Ear discomfort / / MedDRA	0		0	0	1		1	1	0		0	0
Eye disorders / Foreign body sensation in eyes / / MedDRA	0		0	0	1		1	0	0		0	0
Eye disorders / Lacrimation increased / / MedDRA	0		0	0	1		1	1	0		0	0
Eye disorders / Vision blurred / / MedDRA	0		0	0	1		1	1	0		0	0
Gastrointestinal disorders / Abdominal discomfort / / MedDRA	1		1	1	0		0	0	0		0	0

Gastrointestinal disorders	Abdominal pain upper		MedDRA	0		0	0	1		1	1	0		0	0
Gastrointestinal disorders	Constipation		MedDRA	0		0	0	2		3	2	1		3	1
Gastrointestinal disorders	Hypoaesthesia oral		MedDRA	0		0	0	2		2	2	0		0	0
Gastrointestinal disorders	Nausea		MedDRA	1		2	1	0		0	0	1		2	1
Gastrointestinal disorders	Toothache		MedDRA	0		0	0	1		2	0	1		2	1
Gastrointestinal disorders	Vomiting		MedDRA	1		3	1	0		0	0	2		3	2
General disorders and administration site conditions	Asthenia		MedDRA	0		0	0	1		1	1	0		0	0
General disorders and administration site conditions	Chest discomfort		MedDRA	0		0	0	0		0	0	1		1	0
General disorders and administration site conditions	Chest pain		MedDRA	0		0	0	1		2	1	1		2	0
General disorders and administration site conditions	Fatigue		MedDRA	0		0	0	2		4	1	2		4	2

General disorders and administration site conditions	Feeling hot		MedDRA	0		0	0	1		1	0	0		0	0
General disorders and administration site conditions	Influenza like illness		MedDRA	0		0	0	0		0	0	1		1	0
General disorders and administration site conditions	Vessel puncture site reaction		MedDRA	0		0	0	1		1	1	0		0	0
Infections and infestations	Abscess		MedDRA	0		0	0	1		1	0	0		0	0
Infections and infestations	Cellulitis		MedDRA	0		0	0	0		0	0	1		1	0
Infections and infestations	Influenza		MedDRA	0		0	0	1		1	1	0		0	0
Injury, poisoning and procedural complications	Alcohol poisoning		MedDRA	1		1	0	0		0	0	0		0	0
Injury, poisoning and procedural complications	Arthropod bite		MedDRA	0		0	0	0		0	0	1		1	0
Injury, poisoning and procedural complications	Laceration		MedDRA	0		0	0	1		1	0	0		0	0

Injury, poisoning and procedural complications	Muscle strain		MedDRA	0		0	0	1		1	0	0		0	0
Investigations	Alanine aminotransferase increased		MedDRA	1		3	0	0		0	0	2		3	0
Investigations	Aspartate aminotransferase increased		MedDRA	1		1	0	0		0	0	0		0	0
Investigations	Blood creatinine phosphokinase increased		MedDRA	0		0	0	1		1	1	0		0	0
Investigations	Blood pressure diastolic decreased		MedDRA	1		3	0	1		3	0	1		3	1
Investigations	Blood pressure increased		MedDRA	0		0	0	1		2	1	1		2	1
Investigations	Electrocardiogram abnormal		MedDRA	0		0	0	2		2	2	0		0	0
Investigations	Heart rate decreased		MedDRA	0		0	0	1		1	1	0		0	0
Investigations	Mean cell volume abnormal		MedDRA	0		0	0	0		0	0	1		1	0
Investigations	Platelet count decreased		MedDRA	0		0	0	0		0	0	1		1	1
Metabolism and nutrition disorders	Decreased appetite		MedDRA	1		1	1	0		0	0	0		0	0

Musculoskeletal and connective disorders	Arthralgia		MedDRA	0		0	0	3		4	3	1		4	0
Musculoskeletal and connective disorders	Back pain		MedDRA	0		0	0	1		1	1	0		0	0
Musculoskeletal and connective disorders	Muscle twitching		MedDRA	0		0	0	1		1	1	0		0	0
Musculoskeletal and connective disorders	Muscular weakness		MedDRA	0		0	0	1		1	0	0		0	0
Musculoskeletal and connective disorders	Musculoskeletal chest pain		MedDRA	0		0	0	1		1	1	0		0	0
Musculoskeletal and connective disorders	Myalgia		MedDRA	0		0	0	1		1	1	0		0	0
Musculoskeletal and connective disorders	Pain in extremity		MedDRA	0		0	0	1		2	0	1		2	0

Nervous system disorders	Burning sensation		MedDRA	0		0	0	1		1	1	0		0	0
Nervous system disorders	Dizziness		MedDRA	0		0	0	1		1	1	0		0	0
Nervous system disorders	Headache		MedDRA	1		6	1	4		6	4	1		6	1
Nervous system disorders	Hyperaesthesia		MedDRA	0		0	0	1		1	1	0		0	0
Nervous system disorders	Migraine		MedDRA	1		1	0	0		0	0	0		0	0
Psychiatric disorders	Anxiety		MedDRA	1		2	0	0		0	0	1		2	1
Psychiatric disorders	Depressed mood		MedDRA	0		0	0	0		0	0	1		1	1
Psychiatric disorders	Restlessness		MedDRA	1		1	1	0		0	0	0		0	0
Renal and urinary disorders	Micturition urgency		MedDRA	0		0	0	1		1	1	0		0	0
Reproductive system and breast	Dysmenorrhoea		MedDRA	0		0	0	1		1	0	0		0	0
Respiratory, thoracic and mediastinal disorders	Cough		MedDRA	0		0	0	1		3	1	2		3	0

Respiratory, thoracic and mediastinal disorders	Nasal congestion		MedDRA	0		0	0	2		2	2	0		0	0
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain		MedDRA	0		0	0	2		2	1	0		0	0
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea		MedDRA	0		0	0	3		4	3	1		4	1
Skin and subcutaneous tissue disorders	Eczema		MedDRA	1		1	0	0		0	0	0		0	0
Skin and subcutaneous tissue disorders	Hyperhidrosis		MedDRA	0		0	0	2		3	2	1		3	0
Skin and subcutaneous tissue disorders	Pruritus		MedDRA	0		0	0	1		1	1	0		0	0
Skin and subcutaneous tissue disorders	Rash		MedDRA	0		0	0	1		1	1	0		0	0

Skin and subcutaneous tissue disorders	Skin irritation		MedDRA	0		0	0	1		1	1	0		0	0
Vascular disorders	Hot flush		MedDRA	0		0	0	0		0	0	1		1	0
Vascular disorders	Hypotension		MedDRA	0		0	0	1		1	1	0		0	0

① The table defaults provide a short-cut for entering the dictionary used for recording all Adverse events in a study. If entered, the table default values respectively apply to any Adverse Event with a blank Dictionary name.

② The frequency of non-serious adverse events that, when exceeded within any arm or comparison group, are reported in the results database for all arms or comparison groups. The number must be less than or equal to the allowed maximum expressed as a percentage. For example, a threshold of 5 per cent indicates that all non-serious adverse events with a frequency greater than 5 per cent within at least one arm or comparison group are reported.

③ Reporting group description contains details about subjects in this group.

④ Number of subjects exposed for a single Adverse event in a reporting group is only required when the value differs from the Total number of subjects at exposed in the reporting group.

⑤ The event terms used for reporting fatalities must also appear in the serious adverse events table.

*Global Substantial Protocol Amendments*①

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

*Global Interruptions and Restarts*②

Interruption Date	Description	Restart Date

*Limitations and Caveats*③

Limitations and Caveats that apply to the results

① Provide details of the substantial amendments to the protocol that affected the trial globally. There may not have been any global substantial protocol amendments, so their presence is optional. However if a global substantial protocol amendment is created, then both the date and the description are necessary. There is sufficient provision to support the presence of any number of global substantial protocol amendments to the trial.

② Provide details of the interruptions that affected the trial globally. There may not have been any global interruptions, so their presence is optional. If a global amendment is created it must have an interruption date and a description. The restart date is provided only if the trial was restarted globally after the interruption. There is sufficient provision to support the presence of any number of global interruptions and restarts to the trial.

③ Based on the conduct of the trial provide any limitations or caveats to the results of the trial.

Xprenor

Period and Assessment Day	0 min N	mean	(SD)	15 min N	mean	(SD)	30 min N	mean	(SD)	60 min N	mean	(SD)
Respiratory rate (breaths/min)												
TitrationD1	23	15.3	(2.03)	23	14.8	(2.28)	23	14.7	(2.20)	15	14.0	(2.07)
TitrationD1.1	12	15.2	(1.40)	12	15.4	(1.38)	12	15.8	(1.90)	12	15.3	(1.06)
TitrationD2	17	15.2	(2.84)	17	14.6	(2.60)	17	14.4	(2.40)	17	14.8	(2.51)
TitrationD3	10	15.7	(1.25)	10	14.3	(1.42)	9	15.3	(0.87)	9	14.9	(0.78)
TitrationD4	5	16.0	(1.41)	5	16.2	(2.28)	5	15.8	(2.49)	5	15.8	(2.68)
TitrationD5	4	16.5	(1.00)	4	15.8	(2.06)	4	15.8	(2.06)	4	15.3	(1.50)
TitrationD6	5	15.6	(0.89)	5	15.8	(1.10)	5	15.4	(1.34)	5	15.2	(1.92)
TitrationD7	3	16.0	(0.00)	3	16.3	(1.15)	3	15.3	(0.58)	2	15.0	(1.41)
MaintenanceD2	22	15.1	(1.98)	22	14.9	(2.02)	21	14.6	(1.77)	22	14.7	(1.73)
MaintenanceD7	21	15.3	(2.74)	21	14.9	(2.20)	21	15.0	(1.67)	21	14.9	(1.67)
P-value[1]	0.8734			0.6072			0.8969			0.8986		
O2 Saturation (%)												
TitrationD 1	23	97.2	(1.41)	23	96.5	(1.65)	23	96.6	(1.41)	15	97.0	(1.46)
TitrationD 1.1	12	97.0	(1.21)	12	96.0	(1.65)	12	96.7	(1.15)	12	95.8	(1.40)
TitrationD 2	17	97.2	(1.48)	17	96.9	(1.09)	17	97.0	(1.00)	17	96.9	(0.99)
TitrationD 3	10	97.1	(1.10)	10	96.7	(1.25)	9	96.3	(1.50)	9	96.2	(1.48)
TitrationD 4	5	96.8	(1.10)	5	96.8	(1.10)	5	96.4	(1.52)	5	96.2	(0.84)
TitrationD 5	4	97.0	(1.41)	4	96.3	(2.22)	4	97.0	(1.41)	4	96.5	(2.38)
TitrationD 6	5	97.2	(0.84)	5	96.8	(0.84)	5	96.8	(0.84)	5	96.6	(1.14)
TitrationD 7	3	97.0	(1.00)	3	96.7	(1.15)	3	97.3	(1.53)	2	96.5	(0.71)
MaintenanceD2	22	97.0	(1.29)	22	96.8	(1.34)	21	96.6	(1.36)	22	96.0	(1.66)
MaintenanceD7	21	96.7	(1.27)	21	96.4	(1.66)	21	96.1	(1.74)	21	96.3	(1.59)
P-value[1]	0.2788			0.8058			0.7327			0.3159		

Subutex

Period and Assessment Day	0 min N	mean	(SD)	15 min N	mean	(SD)	30 min N	mean	(SD)	60 min N	mean	(SD)
Respiratory rate (breaths/min)												
TitrationD1	12	15.6	(2.97)	12	15.1	(2.47)	11	14.7	(2.10)	7	14.3	(2.14)
TitrationD1.1	7	13.7	(2.21)	7	14.4	(2.37)	7	13.9	(2.48)	7	14.9	(2.04)
TitrationD2	7	15.7	(1.38)	7	15.0	(2.24)	7	14.4	(2.44)	7	14.7	(2.21)
TitrationD3	4	15.0	(1.15)	4	14.3	(0.50)	4	14.8	(2.22)	4	15.3	(1.50)
TitrationD4	3	14.3	(0.58)	3	14.7	(2.31)	3	15.3	(1.15	3	15.0	(1.00)
TitrationD5	2	18.0	(2.83)	2	15.5	(3.54)	2	12.5	(3.54)	2	17.0	(2.83)
TitrationD6	1	16.0		1	17.0		1	16.0		1	18.0	
TitrationD7	2	17.0	(1.41)	2	16.0	(2.83)	2	15.0	(1.41)	2	16.0	(2.83)
MaintenanceD2	11	15.0	(1.84)	11	15.0	(1.84)	11	14.2	(2.09)	11	14.5	(2.34)
MaintenanceD7	10	15.5	(2.59)	10	15.3	(2.26)	10	14.9	(2.56)	10	15.0	(2.40)
O2 Saturation (%)												
TitrationD 1	12	95.9	(3.85)	12	95.3	(3.62)	11	95.5	(3.56)	7	97.1	(0.90)
TitrationD 1.1	7	95.1	(3.89)	7	95.3	(3.35)	7	95.3	(3.50)	7	95.6	(3.31)
TitrationD 2	7	96.9	(1.21)	7	97.0	(1.15)	7	97.0	(1.15)	7	96.4	(1.40)
TitrationD 3	4	96.0	(2.16)	4	95.8	(1.71)	4	95.3	(1.50)	4	95.5	(1.73)
TitrationD 4	3	97.7	(1.53)	3	97.7	(1.53)	3	96.7	(1.53)	3	97.0	(1.00)
TitrationD 5	2	97.0	(1.41)	2	97.5	(0.71)	2	97.0	(0.00)	2	95.0	(0.00)
TitrationD 6	1	98.0		1	97.0		1	96.0		1	96.0	
TitrationD 7	2	97.5	(0.71)	2	97.0	(1.41)	2	96.5	(0.71)	2	96.5	(0.71)
MaintenanceD2	11	96.4	(2.16)	11	95.4	(3.23)	11	95.7	(3.41)	11	95.1	(2.30)
MaintenanceD7	10	96.0	(2.36)	10	96.2	(2.35)	10	95.9	(2.02)	10	95.6	(2.07)

Résultats SpO2 et RR pour toutes les priodes et tous les jours de suivi