Clinical trial results:
A randomised, double blind, placebo controlled, cross over study of the effects of Buprenorphine Hemiadipate Hydrochloride/Naloxone Hydrochloride Dihydrate intravenous challenges in opioid dependent subjects stabilisied on sublingual Buprenorphine Hydrochloride/Naloxone Hydrochloride Dihydrate (Suboxone)

Summary

EudraCT number	2011-002229-23
Trial protocol	GB
Global end of trial date	11 October 2013

Results information

Result version number	v1 (current)
This version publication date	28 September 2016
First version publication date	28 September 2016

Trial information

Trial identification

Sponsor protocol code	RB-UK-11-0018

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Reckitt Benckiser Pharmaceuticals Inc
Sponsor organisation address	10710 Midlothian Turnpike, Suite 430, Richmond, VA, United States, 23235
Public contact	Director of Clinical Operations, Reckitt Benckiser Pharmaceuticals Inc., 01 (804) 594-2029,
Scientific contact	Director of Clinical Operations, Reckitt Benckiser Pharmaceuticals Inc., 01 (804) 594-2029,

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	30 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the behavioural and physiological effects of injecting buprenorphine hemiadipate hydrochloride (HCl)/naloxone HCl dihydrate both alone and in combination at three different dose ratios 1:1, 1:0.5 and 1:0.25, with placebo.

Protection of trial subjects:

This study was carried out in accordance with the study protocol, current ICH GCP guidelines, the European Clinical Trials Directive 2001/20/EC, 2005/28/EC, 95/46/EC, and other applicable regulatory and country-specific requirements.
Written informed consent was obtained from each subject prior to his/her enrolment in the study. Prior to entering the study, subjects were informed by the principal investigator (PI) or designated sub-investigator about the nature and purpose of the study, procedures, expected duration, alternative therapies available and the benefits and risks involved in study participation. Subjects reviewed consent documents and were given the opportunity to ask questions. Subjects were informed of their right to withdraw from the study at any time without prejudice.
It was intended that the potential subject be able to answer simple questions about the study after the ICF was reviewed and explained. After this explanation and before any study specific procedures were performed, the subject voluntarily signed and dated the ICF to indicate desire to participate in the study. The investigator or designee also signed and dated the ICF. The time (hour and minute) the consent was signed was recorded by the subject and the person obtaining the subject’s consent. Prior to participation in the study, the subject received a copy of the signed and dated ICF, along with a card noting site contact information in the event that a medical emergency occurred during the study.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	31 July 2012
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: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Forty-two subjects were screened.

Period 1

Period 1 title	Pre-Challenge Period (Day 1 - 7)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Pre-Challenge Period

Arm description:

A 7-day outpatient period during which subjects received Suboxone. The dose for Day 1 was 8mg, Day 2 was 12mg, and Days 3 to 7 were 16mg.

Arm type	Overall
Investigational medicinal product name	Suboxone
Investigational medicinal product code	
Other name	buprenorphine/naloxone
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual Suboxone was administered daily to all subjects, beginning with 8 mg on Day 1, 12 mg on Day 2 and 16 mg of Suboxone on Day 3. Subjects remained on 16 mg/day until the day after the administration of the final challenge.

Number of subjects in period 1	Overall Pre-Challenge Period
Started	36
Completed	31
Not completed	5
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Not specified	3

Period 2

Period 2 title	Challenge Period (Day 8 - 24)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Based on the randomisation code, the pharmacist dispensed challenge treatment to an unblinded research nurse, who prepared the individual challenge treatments. The challenge treatments were identical in appearance. Under normal circumstances, the blind was not to be broken until all subjects had completed the study and the database was finalised. The blind was allowed to be broken for specific subjects when specific emergency treatment would be dictated by knowing the treatment status.

Arms

Arm title	Overall Challenge Period

Arm description:

All subjects received open-label sublingual Suboxone 16 mg from Day 8 until the day after administration of the final challenge.

Subjects were administered each of the 8 blinded, intravenously injected challenges in a randomised order, at least 48 hours apart, starting on Study Day 9:
A: Placebo
B: Buprenorphine hemiadipate HCl 5 mg (delivering 3.7 mg of buprenorphine base)
C: Naloxone HCl dihydrate 5 mg (delivering 4.092 mg of naloxone base)
D: Buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 5 mg (delivering 3.7 mg of buprenorphine base and 4.092 mg of naloxone base)
E: Buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 2.5 mg (delivering 3.7 mg of buprenorphine base and 2.046 mg of naloxone base)
F: Buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 1.25 mg (delivering 3.7 mg of buprenorphine base and 1.023 mg of naloxone base)
G: Diamorphine HCl 10 mg
H: Buprenorphine HCl 4.0 mg (delivering 3.7 mg of buprenorphine base)

Arm type	Overall
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Challenges were administered using either direct puncture or a BD Adsyte Pro 18/20 gauge catheter or similar device over approximately 10 seconds via an IV push. Placebo for IV injection was provided by RBP as identical colourless 2 mL solutions for IV injection. The placebo comprised hydroxypropylbetadex and glucose monohydrate dissolved in water for injection pH adjusted to pH4.

Investigational medicinal product name	Buprenorphine hemiadipate HCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Buprenorphine hemiadipate HCl (2.5 mg/mL) was provided by RBP as a colourless solution identical in appearance to the other challenge treatments. Challenges were administered using either direct puncture or a BD Adsyte Pro 18/20 gauge catheter or similar device (2 mL (total volume for each treatment arm) over approximately 10 seconds via an IV push.

Investigational medicinal product name	Naloxone HCl dihydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

Naloxone HCl dihydrate in strengths of 2.5 mg/mL, 1.25 mg/mL, and 0.625 mg/mL was provided by RBP as a colourless solution identical in appearance to the other challenge treatments. Challenges were administered using either direct puncture or a BD Adsyte Pro 18/20 gauge catheter or similar device (2 mL (total volume for each treatment arm) over approximately 10 seconds via an IV push.

Investigational medicinal product name	Diamorphine HCl
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Diamorphine HCl was sourced commercially and diluted to 5 mg/mL as required. Challenges were administered using either direct puncture or a BD Adsyte Pro 18/20 gauge catheter or similar device (2 mL (total volume for each treatment arm) over approximately 10 seconds via an IV push.

Investigational medicinal product name	Suboxone
Investigational medicinal product code	
Other name	buprenorphine/naloxone
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual Suboxone was administered daily to all subjects, beginning with 8 mg on Day 1, 12 mg on Day 2 and 16 mg of Suboxone on Day 3. Subjects remained on 16 mg/day until the day after the administration of the final challenge.

Number of subjects in period 2	Overall Challenge Period
Started	31
Completed	24
Not completed	7
Adverse event, non-fatal	1
Not specified	6

Baseline characteristics

Reporting groups

Reporting group title	Pre-Challenge Period (Day 1 - 7)

Reporting group description: -

Reporting group values	Pre-Challenge Period (Day 1 - 7)	Total	
Number of subjects	36	36	
Age categorical Units: Subjects			
Adults (18-64 years)	36	36	
Age continuous Units: years			
arithmetic mean	42.9		
standard deviation	± 7.77	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	30	30	
Race Units: Subjects			
Asian	1	1	
Black or African American	10	10	
White	20	20	
Asian, White	1	1	
Black or African American, White	4	4	
Weight Units: kg			
arithmetic mean	71.51		
standard deviation	± 10.314	-	
Body Mass Index Units: kg/m^2			
arithmetic mean	23.41		
standard deviation	± 2.876	-	

End points reporting groups

Reporting group title	Overall Pre-Challenge Period

Reporting group description:

A 7-day outpatient period during which subjects received Suboxone. The dose for Day 1 was 8mg, Day 2 was 12mg, and Days 3 to 7 were 16mg.

Reporting group title	Overall Challenge Period

Reporting group description:

All subjects received open-label sublingual Suboxone 16 mg from Day 8 until the day after administration of the final challenge.

Subjects were administered each of the 8 blinded, intravenously injected challenges in a randomised order, at least 48 hours apart, starting on Study Day 9:
A: Placebo
B: Buprenorphine hemiadipate HCl 5 mg (delivering 3.7 mg of buprenorphine base)
C: Naloxone HCl dihydrate 5 mg (delivering 4.092 mg of naloxone base)
D: Buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 5 mg (delivering 3.7 mg of buprenorphine base and 4.092 mg of naloxone base)
E: Buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 2.5 mg (delivering 3.7 mg of buprenorphine base and 2.046 mg of naloxone base)
F: Buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 1.25 mg (delivering 3.7 mg of buprenorphine base and 1.023 mg of naloxone base)
G: Diamorphine HCl 10 mg
H: Buprenorphine HCl 4.0 mg (delivering 3.7 mg of buprenorphine base)

Subject analysis set title	A. Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the placebo challenge consisting of a single intravenous injection of placebo.

Subject analysis set title	B: Buprenorphine hemiadipate HCl
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg.

Subject analysis set title	C: Naloxone HCl dihydrate
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of naloxone HCl dihydrate 5 mg.

Subject analysis set title	D: BHA/NAL 1:1
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 5 mg.

Subject analysis set title	E. BHA/NAL 1:0.5
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 2.5 mg.

Subject analysis set title	F. BHA/NAL 1:0.25
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 1.25 mg.

Subject analysis set title	G: Diamorphine

Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of diamorphine HCl 10 mg.

Subject analysis set title	H. Buprenorphine HCL
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine HCl 4.0 mg.

Primary: Change from Baseline in the Clinical Opiate Withdrawal Scale (COWS) Overall Score from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Clinical Opiate Withdrawal Scale (COWS) Overall Score from 5 Minutes to 60 Minutes During the Challenge Period[1]

End point description:

The COWS is an 11-item instrument used to assess symptoms of opioid withdrawal (Wesson et al., 1999). The score is the sum of the response to each of the 11 items and cover a range of 0-48. The COWS is commonly used by clinicians treating patients with buprenorphine to monitor the severity of withdrawal. COWS scores below 5 are considered not indicative of withdrawal. Scores from 5 to 12 are considered mild withdrawal; from 13 to 24 moderate withdrawal; 25 to 36 moderate/severe withdrawal, and 37-48 severe withdrawal.

A repeated measures model was used to analyse the change from pre-challenge (-10 minutes) over the time frames of interest (assessment times from 5 through 60 minutes post-challenge). The repeated measures mixed model contained terms for the fixed effects for challenge (A to H), period (1 to 8), assessment (5, 15, 30, 45 and 60 minutes post challenge) and the challenge-by-assessment.

P-values available in attached file.

End point type	Primary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

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: The statistical analysis can be found in the attached file.

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	26	25	27
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.6 to 0.8)	0.1 (-0.6 to 0.8)	3.7 (3.1 to 4.4)	0.9 (0.3 to 1.6)

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25	27	26	26
Units: units on a scale				
least squares mean (confidence interval 95%)	1 (0.3 to 1.7)	0.2 (-0.5 to 0.9)	0.3 (-0.4 to 1)	0.1 (-0.5 to 0.8)

Attachments (see zip file)	COWS Change from Baseline through 60 minutes/RB-UK-11-

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Clinical Opiate Withdrawal Scale (COWS) Overall Score from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Clinical Opiate Withdrawal Scale (COWS) Overall Score from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

The COWS is an 11-item instrument used to assess symptoms of opioid withdrawal (Wesson et al., 1999). The score is the sum of the response to each of the 11 items and cover a range of 0-48. The COWS is commonly used by clinicians treating patients with buprenorphine to monitor the severity of withdrawal. COWS scores below 5 are considered not indicative of withdrawal. Scores from 5 to 12 are considered mild withdrawal; from 13 to 24 moderate withdrawal; 25 to 36 moderate/severe withdrawal, and 37-48 severe withdrawal.

A repeated measures model was used to analyse the change from pre-challenge (-10 minutes) = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for challenge within subject, and subject as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[2]	26[3]	25[4]	27[5]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.6 to 0.5)	0.1 (-0.5 to 0.6)	2.7 (2.2 to 3.3)	0.4 (-0.1 to 1)

Notes:

[2] - Efficacy population

[3] - Efficacy population

[4] - Efficacy population

[5] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine

				HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[6]	27[7]	26[8]	26[9]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.6 (0 to 1.1)	0 (-0.5 to 0.5)	0 (-0.5 to 0.6)	0 (-0.5 to 0.5)

Notes:

[6] - Efficacy population

[7] - Efficacy population

[8] - Efficacy population

[9] - Efficacy population

Attachments (see zip file)	COWS Change from Baseline through 300 minutes/RB-UK-11-

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Clinical Opiate Withdrawal Scale (COWS) Overall Score for Each Post-Baseline Assessment During the Challenge Period

End point title	Change from Baseline in the Clinical Opiate Withdrawal Scale (COWS) Overall Score for Each Post-Baseline Assessment During the Challenge Period

End point description:

The COWS is an 11-item instrument used to assess symptoms of opioid withdrawal (Wesson et al., 1999). The score is the sum of the response to each of the 11 items and cover a range of 0-48. The COWS is commonly used by clinicians treating patients with buprenorphine to monitor the severity of withdrawal. COWS scores below 5 are considered not indicative of withdrawal. Scores from 5 to 12 are considered mild withdrawal; from 13 to 24 moderate withdrawal; 25 to 36 moderate/severe withdrawal, and 37-48 severe withdrawal.

The first row of data represents actual values for baseline. All other rows of data are change from baseline to time point figures.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[10]	26[11]	25[12]	27[13]
Units: units on a scale				
arithmetic mean (standard deviation)				
Actual values at baseline (-10 minutes)	0.8 (± 0.94)	0.7 (± 1.19)	0.7 (± 1.21)	0.5 (± 0.64)
Change from baseline: 5 minutes	0.1 (± 0.68)	0.2 (± 0.83)	0.3 (± 1.25)	0.5 (± 1.6)
Change from baseline: 15 minutes	-0.1 (± 0.93)	0 (± 1.33)	1.6 (± 2.43)	1.3 (± 2.16)
Change from baseline: 30 minutes	-0.1 (± 1.08)	0.1 (± 1.99)	4.6 (± 4.25)	1.6 (± 2.45)
Change from baseline: 45 minutes	-0.1 (± 1.18)	0.1 (± 2.15)	6.7 (± 5.71)	1.3 (± 2.11)
Change from baseline: 60 minutes	-0.2 (± 1.31)	-0.1 (± 1.76)	6.2 (± 6.12)	0.7 (± 1.88)

Change from baseline: 120 minutes	-0.2 (± 1.18)	0 (± 2.07)	4 (± 5)	0 (± 1.19)
Change from baseline: 180 minutes	-0.4 (± 0.78)	-0.3 (± 1.76)	0.8 (± 2.82)	-0.1 (± 0.89)
Change from baseline: 240 minutes	-0.4 (± 0.72)	-0.2 (± 1.63)	0.6 (± 3.01)	-0.1 (± 0.85)
Change from baseline: 300 minutes	-0.3 (± 0.7)	-0.2 (± 2.05)	-0.2 (± 1.57)	-0.3 (± 0.71)

Notes:

[10] - Efficacy population

[11] - Efficacy population

[12] - Efficacy population

[13] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[14]	27[15]	26[16]	26[17]
Units: units on a scale				
arithmetic mean (standard deviation)				
Actual values at baseline (-10 minutes)	0.5 (± 0.71)	0.4 (± 0.58)	0.7 (± 0.94)	0.6 (± 0.58)
Change from baseline: 5 minutes	1.1 (± 2.74)	0.3 (± 0.95)	0.2 (± 0.86)	0.2 (± 0.94)
Change from baseline: 15 minutes	1.9 (± 2.96)	0.8 (± 2.03)	0.3 (± 1.29)	0.1 (± 0.74)
Change from baseline: 30 minutes	1.1 (± 2.34)	0.1 (± 1.49)	0.2 (± 1.12)	0.2 (± 1.41)
Change from baseline: 45 minutes	0.7 (± 2.39)	0.1 (± 1.46)	0.2 (± 1.16)	0.2 (± 1.36)
Change from baseline: 60 minutes	0.5 (± 2.8)	0.2 (± 1.85)	0 (± 1.34)	0.2 (± 1.54)
Change from baseline: 120 minutes	0.1 (± 2.18)	0.3 (± 1.81)	-0.2 (± 0.95)	-0.1 (± 1.32)
Change from baseline: 180 minutes	0.1 (± 1.94)	-0.1 (± 0.86)	-0.3 (± 0.72)	-0.1 (± 1.6)
Change from baseline: 240 minutes	0 (± 1.81)	-0.2 (± 0.68)	-0.3 (± 0.61)	-0.1 (± 1.31)
Change from baseline: 300 minutes	-0.1 (± 1.63)	-0.3 (± 0.54)	-0.3 (± 0.68)	-0.3 (± 0.75)

Notes:

[14] - Efficacy population

[15] - Efficacy population

[16] - Efficacy population
n=25 for the diamorphine challenge at 240 mins and 300 mins.

[17] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scale Good Effect (VAS-G) Repeated Measures Analysis of Variance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Visual Analogue Scale Good Effect (VAS-G) Repeated Measures Analysis of Variance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Visual Analogue Scale (VAS)-B, VAS-G, and VAS-high: 100 mm visual analogue scales assessing subject reported 'bad', 'good', and 'high' effects respectively. The
scales are anchored with the terms none on the zero end and most ever on the 100 mm end.

Repeated Measures Model: Post Challenge = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time,
and Challenge x Period, using the Toeplitz covariance structure for repeating Assessment Time for Challenge within subject, and subject
as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

5, 15, 30, 45, and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[18]	26[19]	25[20]	27[21]
Units: units on a scale				
least squares mean (confidence interval 95%)	2.7 (-4.9 to 10.2)	6.9 (-0.3 to 14)	3.3 (-3.6 to 10.3)	4.9 (-1.9 to 11.7)

Notes:

[18] - Efficacy population

[19] - Efficacy population

[20] - Efficacy population

[21] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[22]	27[23]	26[24]	26[25]
Units: units on a scale				
least squares mean (confidence interval 95%)	5.2 (-1.9 to 12.4)	4.8 (-2 to 11.6)	7.5 (0.4 to 14.6)	12.4 (5.5 to 19.2)

Notes:

[22] - Efficacy population

[23] - Efficacy population

[24] - Efficacy population

[25] - Efficacy population

Attachments (see zip file)	VAS-G through 60 minutes/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scale Good Effect (VAS-G) Repeated Measures Analysis of Variance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Visual Analogue Scale Good Effect (VAS-G) Repeated Measures Analysis of Variance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Visual Analogue Scale (VAS)-B, VAS-G, and VAS-high: 100 mm visual analogue scales assessing subject reported ‘bad’, ‘good’, and ‘high’ effects respectively. The
scales are anchored with the terms none on the zero end and most ever on the 100 mm end.

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for challenge within subject, and subject as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[26]	26[27]	25[28]	27[29]
Units: units on a scale				
least squares mean (confidence interval 95%)	2.5 (-3.2 to 8.1)	4.3 (-1.1 to 9.7)	2.2 (-3 to 7.4)	3.2 (-1.9 to 8.2)

Notes:

[26] - Efficacy population

[27] - Efficacy population

[28] - Efficacy population

[29] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[30]	27[31]	26[32]	26[33]
Units: units on a scale				
least squares mean (confidence interval 95%)	4.1 (-1.3 to 9.4)	4 (-1 to 9.1)	5.7 (0.4 to 11)	8.5 (3.3 to 13.6)

Notes:

[30] - Efficacy population

[31] - Efficacy population

[32] - Efficacy population

[33] - Efficacy population

Attachments (see zip file)	VAS-G through 300 minutes/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scale Bad Effect (VAS-B) Repeated Measures Analysis of Variance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Visual Analogue Scale Bad Effect (VAS-B) Repeated Measures Analysis of Variance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Visual Analogue Scale (VAS)-B, VAS-G, and VAS-high: 100 mm visual analogue scales assessing subject reported ‘bad’, ‘good’, and ‘high’ effects respectively. The
scales are anchored with the terms none on the zero end and most ever on the 100 mm end.

Repeated Measures Model: Post Challenge = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, and Challenge x Period, using the Toeplitz covariance structure for repeating Assessment Time for Challenge within subject, and subject as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

5, 15, 30, 45, and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[34]	26[35]	25[36]	27[37]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-3.6 to 3.5)	0.3 (-3.1 to 3.6)	19.7 (16.4 to 22.9)	2.6 (-0.5 to 5.8)

Notes:

[34] - Efficacy population

[35] - Efficacy population

[36] - Efficacy population

[37] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[38]	27[39]	26[40]	26[41]
Units: units on a scale				
least squares mean (confidence interval 95%)	2.1 (-1.2 to 5.4)	0.5 (-2.7 to 3.6)	0.9 (-2.4 to 4.2)	1.1 (-2.1 to 4.3)

Notes:

[38] - Efficacy population

[39] - Efficacy population

[40] - Efficacy population

[41] - Efficacy population

Attachments (see zip file)	VAS-B through 60 minutes/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scale Bad Effect (VAS-B) Repeated Measures Analysis of Variance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Visual Analogue Scale Bad Effect (VAS-B) Repeated Measures Analysis of Variance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Visual Analogue Scale (VAS)-B, VAS-G, and VAS-high: 100 mm visual analogue scales assessing subject reported ‘bad’, ‘good’, and ‘high’ effects respectively. The
scales are anchored with the terms none on the zero end and most ever on the 100 mm end.

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, Challenge x Period and Within Period Baseline Value,

using the Toeplitz covariance structure for repeating Assessment Time for challenge within subject, and subject as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[42]	26[43]	25[44]	27[45]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-2.7 to 2.7)	0.2 (-2.4 to 2.7)	16 (13.5 to 18.5)	1.4 (-1 to 3.8)

Notes:

[42] - Efficacy population

[43] - Efficacy population

[44] - Efficacy population

[45] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[46]	27[47]	26[48]	26[49]
Units: units on a scale				
least squares mean (confidence interval 95%)	1.3 (-1.2 to 3.8)	0.3 (-2.1 to 2.7)	0.3 (-2.2 to 2.9)	1.4 (-1 to 3.8)

Notes:

[46] - Efficacy population

[47] - Efficacy population

[48] - Efficacy population

[49] - Efficacy population

Attachments (see zip file)	VAS-B through 300 minutes/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scale High Effect (VAS-H) Repeated Measures Analysis of Variance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Visual Analogue Scale High Effect (VAS-H) Repeated Measures Analysis of Variance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Visual Analogue Scale (VAS)-B, VAS-G, and VAS-high: 100 mm visual analogue scales assessing subject reported ‘bad’, ‘good’, and ‘high’ effects respectively. The
scales are anchored with the terms none on the zero end and most ever on the 100 mm end.

Repeated Measures Model: Post Challenge = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, and Challenge x Period, using the Toeplitz covariance structure for repeating Assessment Time for Challenge within subject, and subject as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

5, 15, 30, 45, and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[50]	26[51]	25[52]	27[53]
Units: units on a scale				
least squares mean (confidence interval 95%)	1.5 (-4.7 to 7.8)	7.3 (1.3 to 13.3)	4.7 (-1.2 to 10.6)	4.5 (-1.3 to 10.2)

Notes:

[50] - Efficacy population

[51] - Efficacy population

[52] - Efficacy population

[53] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[54]	27[55]	26[56]	26[57]
Units: units on a scale				
least squares mean (confidence interval 95%)	4.9 (-1.1 to 10.9)	3.3 (-2.5 to 9)	4.4 (-1.5 to 10.4)	10.8 (5 to 16.6)

Notes:

[54] - Efficacy population

[55] - Efficacy population

[56] - Efficacy population

[57] - Efficacy population

Attachments (see zip file)	VAS-H through 60 minutes/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Visual Analogue Scale High Effect (VAS-H) Repeated Measures Analysis of Variance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Visual Analogue Scale High Effect (VAS-H) Repeated Measures Analysis of Variance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Visual Analogue Scale (VAS)-B, VAS-G, and VAS-high: 100 mm visual analogue scales assessing subject reported ‘bad’, ‘good’, and ‘high’ effects respectively. The
scales are anchored with the terms none on the zero end and most ever on the 100 mm end.

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for challenge within subject, and subject as a random effect.

P-values available in attached file.

End point type	Secondary

End point timeframe:

5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[58]	26[59]	25[60]	27[61]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.9 (-3.6 to 5.4)	4.5 (0.1 to 8.8)	3 (-1.2 to 7.2)	2.5 (-1.7 to 6.6)

Notes:

[58] - Efficacy population

[59] - Efficacy population

[60] - Efficacy population

[61] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[62]	27[63]	26[64]	26[65]
Units: units on a scale				
least squares mean (confidence interval 95%)	3.3 (-1 to 7.6)	2.2 (-1.9 to 6.3)	3.3 (-1 to 7.6)	7.3 (3.1 to 11.5)

Notes:

[62] - Efficacy population

[63] - Efficacy population

[64] - Efficacy population

[65] - Efficacy population

Attachments (see zip file)	VAS-H through 300 minutes/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Flushing Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Flushing Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Flushing

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[66]	26[67]	25[68]	27[69]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.3)	0.1 (-0.1 to 0.3)	0.7 (0.5 to 0.9)	0.4 (0.2 to 0.6)

Notes:

[66] - Efficacy population

[67] - Efficacy population

[68] - Efficacy population

[69] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[70]	27[71]	26[72]	26[73]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.3 (0.1 to 0.5)	0.2 (0 to 0.3)	0.2 (0 to 0.4)	0.2 (0.1 to 0.4)

Notes:

[70] - Efficacy population

[71] - Efficacy population

[72] - Efficacy population

[73] - Efficacy population

Attachments (see zip file)	AEC Flushing 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Flushing Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Flushing Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Flushing

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[74]	26[75]	25[76]	27[77]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.2)	0.1 (0 to 0.2)	0.5 (0.4 to 0.6)	0.2 (0.1 to 0.3)

Notes:

[74] - Efficacy population

[75] - Efficacy population

[76] - Efficacy population

[77] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[78]	27[79]	26[80]	26[81]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.2 (0.1 to 0.3)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0.2 (0.1 to 0.3)

Notes:

[78] - Efficacy population

[79] - Efficacy population

[80] - Efficacy population

[81] - Efficacy population

Attachments (see zip file)	AEC Flushing 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Itchy Skin Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Itchy Skin Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Itchy skin

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[82]	26[83]	25[84]	27[85]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.3)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.2)

Notes:

[82] - Efficacy population

[83] - Efficacy population

[84] - Efficacy population

[85] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[86]	27[87]	26[88]	26[89]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.2)	0 (-0.2 to 0.1)	0.4 (0.3 to 0.6)	0.2 (0 to 0.3)

Notes:

[86] - Efficacy population

[87] - Efficacy population

[88] - Efficacy population

[89] - Efficacy population

Attachments (see zip file)	AEC Itchy Skin 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Itchy Skin Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Itchy Skin Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Itchy skin

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[90]	26[91]	25[92]	27[93]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)	0 (-0.1 to 0.2)

Notes:

[90] - Efficacy population

[91] - Efficacy population

[92] - Efficacy population

[93] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[94]	27[95]	26[96]	26[97]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.2)	0 (-0.1 to 0.1)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)

Notes:

[94] - Efficacy population

[95] - Efficacy population

[96] - Efficacy population

[97] - Efficacy population

Attachments (see zip file)	AEC Itchy Skin 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Nausea Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Nausea Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Nausea

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[98]	26[99]	25[100]	27[101]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0.1 (-0.1 to 0.2)	0.4 (0.3 to 0.5)	0.1 (0 to 0.2)

Notes:

[98] - Efficacy population

[99] - Efficacy population

[100] - Efficacy population

[101] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[102]	27[103]	26[104]	26[105]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)	0 (-0.1 to 0.1)	0 (-0.1 to 0.2)

Notes:

[102] - Efficacy population

[103] - Efficacy population

[104] - Efficacy population

[105] - Efficacy population

Attachments (see zip file)	AEC Nausea 60 min/RB-UK-11-0018 Summary table 14.2.7.1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Nausea Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Nausea Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Nausea

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[106]	26[107]	25[108]	27[109]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (0 to 0.1)	0 (0 to 0.1)	0.3 (0.2 to 0.4)	0.1 (0 to 0.1)

Notes:

[106] - Efficacy population

[107] - Efficacy population

[108] - Efficacy population

[109] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[110]	27[111]	26[112]	26[113]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.1)	0 (0 to 0.1)	0 (0 to 0.1)	0.1 (0 to 0.1)

Notes:

[110] - Efficacy population

[111] - Efficacy population

[112] - Efficacy population

[113] - Efficacy population

Attachments (see zip file)	AEC Nausea 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Nodding Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Nodding Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Nodding
Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[114]	26[115]	25[116]	27[117]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0.1)	0.1 (-0.1 to 0.2)	0.1 (-0.1 to 0.2)	0.2 (0.1 to 0.3)

Notes:

[114] - Efficacy population

[115] - Efficacy population

[116] - Efficacy population

[117] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[118]	27[119]	26[120]	26[121]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.3)	0.1 (0 to 0.3)	0.1 (0 to 0.3)	0.1 (0 to 0.3)

Notes:

[118] - Efficacy population

[119] - Efficacy population

[120] - Efficacy population

[121] - Efficacy population

Attachments (see zip file)	AEC Nodding 60 min/RB-UK-11-0018 Summary table 14.2.8.1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Nodding Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Nodding Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Nodding

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for

repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[122]	26[123]	25[124]	27[125]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0.1)	0.1 (0 to 0.1)	0.1 (0 to 0.2)	0.1 (0 to 0.2)

Notes:

[122] - Efficacy population

[123] - Efficacy population

[124] - Efficacy population

[125] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[126]	27[127]	26[128]	26[129]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0.1 (0 to 0.2)

Notes:

[126] - Efficacy population

[127] - Efficacy population

[128] - Efficacy population

[129] - Efficacy population

Attachments (see zip file)	AEC Nodding 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Relaxed Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Relaxed Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or

spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Relaxed

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[130]	26[131]	25[132]	27[133]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.2 to 0.4)	0.3 (0 to 0.6)	-0.3 (-0.6 to 0)	0 (-0.3 to 0.3)

Notes:

[130] - Efficacy population

[131] - Efficacy population

[132] - Efficacy population

[133] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[134]	27[135]	26[136]	26[137]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.3 to 0.3)	0.1 (-0.2 to 0.4)	0.2 (-0.1 to 0.5)	0.4 (0.2 to 0.7)

Notes:

[134] - Efficacy population

[135] - Efficacy population

[136] - Efficacy population

[137] - Efficacy population

Attachments (see zip file)	AEC Relaxed 60 min/RB-UK-11-0018 Summary table 14.2.9.1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Relaxed Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Relaxed Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Relaxed

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[138]	26[139]	25[140]	27[141]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.2 to 0.3)	0.2 (-0.1 to 0.5)	-0.4 (-0.6 to -0.1)	0 (-0.3 to 0.2)

Notes:

[138] - Efficacy population

[139] - Efficacy population

[140] - Efficacy population

[141] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[142]	27[143]	26[144]	26[145]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.3 to 0.2)	0 (-0.2 to 0.3)	0.1 (-0.2 to 0.3)	0.4 (0.1 to 0.6)

Notes:

[142] - Efficacy population

[143] - Efficacy population

[144] - Efficacy population

[145] - Efficacy population

Attachments (see zip file)	AEC Relaxed 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Pleasant Sick Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Pleasant Sick Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Pleasant Sick

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[146]	26[147]	25[148]	27[149]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0.1)	0 (0 to 0.1)	0.1 (0.1 to 0.2)	0.1 (0 to 0.1)

Notes:

[146] - Efficacy population

[147] - Efficacy population

[148] - Efficacy population

[149] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[150]	27[151]	26[152]	26[153]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (0 to 0.1)	0 (-0.1 to 0.1)	0 (0 to 0.1)	0 (0 to 0.1)

Notes:

[150] - Efficacy population

[151] - Efficacy population

[152] - Efficacy population

[153] - Efficacy population

Attachments (see zip file)	AEC Pleasand Sick 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Pleasant Sick Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Pleasant Sick Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Pleasant Sick

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[154]	26[155]	25[156]	27[157]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0)	0 (0 to 0.1)	0.1 (0.1 to 0.2)	0 (0 to 0.1)

Notes:

[154] - Efficacy population

[155] - Efficacy population

[156] - Efficacy population

[157] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[158]	27[159]	26[160]	26[161]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (0 to 0.1)	0 (0 to 0.1)	0 (0 to 0.1)	0 (0 to 0.1)

Notes:

[158] - Efficacy population

[159] - Efficacy population

[160] - Efficacy population

[161] - Efficacy population

Attachments (see zip file)	AEC Pleasant Sick 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Coasting or Spaced Out Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Coasting or Spaced Out Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Coasting or Spaced Out

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[162]	26[163]	25[164]	27[165]
Units: units on a scale				
least squares mean (confidence interval	0.1 (-0.1 to	0.4 (0.1 to 0.6)	0.3 (0.1 to 0.5)	0.2 (-0.1 to

95%)	0.4)	0.4)

Notes:

[162] - Efficacy population

[163] - Efficacy population

[164] - Efficacy population

[165] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[166]	27[167]	26[168]	26[169]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.2 (0 to 0.5)	0.2 (0 to 0.4)	0.3 (0 to 0.5)	0.5 (0.3 to 0.7)

Notes:

[166] - Efficacy population

[167] - Efficacy population

[168] - Efficacy population

[169] - Efficacy population

Attachments (see zip file)	AEC Coasting/Spaced Out 60 min/RB-UK-11-0018 Summary

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Coasting or Spaced Out Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Coasting or Spaced Out Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Coasting or Spaced Out

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[170]	26[171]	25[172]	27[173]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.2)	0.2 (0.1 to 0.3)	0.2 (0 to 0.3)	0.1 (-0.1 to 0.2)

Notes:

[170] - Efficacy population

[171] - Efficacy population

[172] - Efficacy population

[173] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[174]	27[175]	26[176]	26[177]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.3)	0.1 (0 to 0.3)	0.2 (0 to 0.3)	0.3 (0.2 to 0.5)

Notes:

[174] - Efficacy population

[175] - Efficacy population

[176] - Efficacy population

[177] - Efficacy population

Attachments (see zip file)	AEC Coasting/Spaced Out 300 min/RB-UK-11-0018 Summary

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Talkative Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Talkative Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Talkative

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge

within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[178]	26[179]	25[180]	27[181]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.2 to 0.2)	0.2 (0 to 0.4)	-0.3 (-0.5 to -0.1)	-0.1 (-0.3 to 0.1)

Notes:

[178] - Efficacy population

[179] - Efficacy population

[180] - Efficacy population

[181] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[182]	27[183]	26[184]	26[185]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.3)	-0.1 (-0.3 to 0.1)	0.1 (-0.1 to 0.3)	0.1 (0 to 0.3)

Notes:

[182] - Efficacy population

[183] - Efficacy population

[184] - Efficacy population

[185] - Efficacy population

Attachments (see zip file)	AEC Talkative 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Talkative Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Talkative Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood,

tingling and energetic.

This item: Talkative

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[186]	26[187]	25[188]	27[189]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.2 to 0.2)	0.2 (0 to 0.4)	-0.3 (-0.5 to -0.1)	-0.1 (-0.3 to 0.1)

Notes:

[186] - Efficacy population

[187] - Efficacy population

[188] - Efficacy population

[189] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[190]	27[191]	26[192]	26[193]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.3)	0 (-0.2 to 0.2)	0 (-0.2 to 0.2)	0.1 (-0.1 to 0.3)

Notes:

[190] - Efficacy population

[191] - Efficacy population

[192] - Efficacy population

[193] - Efficacy population

Attachments (see zip file)	AEC Talkative 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Heavy or Sluggish Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Heavy or Sluggish Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Heavy or Sluggish

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[194]	26[195]	25[196]	27[197]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.2 (-0.1 to 0.4)	0.2 (-0.1 to 0.4)	0.7 (0.5 to 1)	0.5 (0.2 to 0.7)

Notes:

[194] - Efficacy population

[195] - Efficacy population

[196] - Efficacy population

[197] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[198]	27[199]	26[200]	26[201]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.2 (0 to 0.5)	0.2 (0 to 0.5)	0.2 (-0.1 to 0.5)	0.3 (0 to 0.5)

Notes:

[198] - Efficacy population

[199] - Efficacy population

[200] - Efficacy population

[201] - Efficacy population

Attachments (see zip file)	AEC Heavy/Sluggsh 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Heavy or Sluggish Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Heavy or Sluggish Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Heavy or Sluggish

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[202]	26[203]	25[204]	27[205]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.4)	0.1 (-0.1 to 0.3)	0.6 (0.3 to 0.8)	0.3 (0.1 to 0.5)

Notes:

[202] - Efficacy population

[203] - Efficacy population

[204] - Efficacy population

[205] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[206]	27[207]	26[208]	26[209]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.4)	0.1 (-0.1 to 0.3)	0.2 (-0.1 to 0.4)	0.2 (0 to 0.4)

Notes:

[206] - Efficacy population

[207] - Efficacy population

[208] - Efficacy population

[209] - Efficacy population

Attachments (see zip file)	AEC Heavy/Sluggsh 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Dry Mouth Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Dry Mouth Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Dry Mouth

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[210]	26[211]	25[212]	27[213]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.2 (0 to 0.3)	0.1 (-0.1 to 0.2)	0.1 (0 to 0.3)	0 (-0.1 to 0.2)

Notes:

[210] - Efficacy population

[211] - Efficacy population

[212] - Efficacy population

[213] - Efficacy population

End point values	E. BHA/NAL 1:	F. BHA/NAL 1:	G:	H.

	0.5	0.25	Diamorphine	Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[214]	27[215]	26[216]	26[217]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.3)	0.1 (-0.1 to 0.2)	0.1 (0 to 0.2)	0.4 (0.2 to 0.5)

Notes:

[214] - Efficacy population

[215] - Efficacy population

[216] - Efficacy population

[217] - Efficacy population

Attachments (see zip file)	AEC Dry Mouth 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Dry Mouth Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Dry Mouth Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Dry Mouth

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[218]	26[219]	25[220]	27[221]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0 (-0.1 to 0.2)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)

Notes:

[218] - Efficacy population

[219] - Efficacy population

[220] - Efficacy population

[221] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[222]	27[223]	26[224]	26[225]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)	0 (-0.1 to 0.2)	0.3 (0.2 to 0.4)

Notes:

[222] - Efficacy population

[223] - Efficacy population

[224] - Efficacy population

[225] - Efficacy population

Attachments (see zip file)	AEC Dry Mouth 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Drive Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Drive Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Drive

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[226]	26[227]	25[228]	27[229]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.1)	-0.6 (-0.8 to -0.4)	-0.2 (-0.4 to 0)

Notes:

[226] - Efficacy population

[227] - Efficacy population

[228] - Efficacy population

[229] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[230]	27[231]	26[232]	26[233]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.2 (-0.4 to 0)	-0.1 (-0.3 to 0.1)	-0.2 (-0.4 to 0)	0.1 (-0.1 to 0.2)

Notes:

[230] - Efficacy population

[231] - Efficacy population

[232] - Efficacy population

[233] - Efficacy population

Attachments (see zip file)	AEC Drive 60 min/RB-UK-11-0018 Summary table 14.2.15.1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Drive Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Drive Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Drive

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[234]	26[235]	25[236]	27[237]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.3 to 0.2)	-0.1 (-0.4 to 0.1)	-0.5 (-0.7 to -0.3)	-0.2 (-0.4 to 0)

Notes:

[234] - Efficacy population

[235] - Efficacy population

[236] - Efficacy population

[237] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[238]	27[239]	26[240]	26[241]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.2 (-0.4 to 0)	-0.2 (-0.4 to 0.1)	-0.2 (-0.4 to 0)	0 (-0.2 to 0.2)

Notes:

[238] - Efficacy population

[239] - Efficacy population

[240] - Efficacy population

[241] - Efficacy population

Attachments (see zip file)	AEC Drive 300 min/RB-UK-11-0018 Summary table 14.2.15.2.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Sleepy Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Sleepy Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Sleepy

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[242]	26[243]	25[244]	27[245]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.2 to 0.3)	0 (-0.3 to 0.2)	0.8 (0.5 to 1)	0.4 (0.1 to 0.6)

Notes:

[242] - Efficacy population

[243] - Efficacy population

[244] - Efficacy population

[245] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[246]	27[247]	26[248]	26[249]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.4)	0.2 (0 to 0.4)	0.2 (0 to 0.4)	0.2 (-0.1 to 0.4)

Notes:

[246] - Efficacy population

[247] - Efficacy population

[248] - Efficacy population

[249] - Efficacy population

Attachments (see zip file)	AEC Sleepy 60 min/RB-UK-11-0018 Summary table 14.2.16.1.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Sleepy Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Sleepy Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Sleepy

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[250]	26[251]	25[252]	27[253]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (-0.1 to 0.3)	0 (-0.2 to 0.2)	0.7 (0.5 to 0.9)	0.2 (0 to 0.4)

Notes:

[250] - Efficacy population

[251] - Efficacy population

[252] - Efficacy population

[253] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[254]	27[255]	26[256]	26[257]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.2 to 0.3)	0.1 (0 to 0.3)	0.2 (0 to 0.4)	0.2 (0 to 0.4)

Notes:

[254] - Efficacy population

[255] - Efficacy population

[256] - Efficacy population

[257] - Efficacy population

Attachments (see zip file)	AEC Sleepy 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Carefree Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Carefree Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Carefree

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[258]	26[259]	25[260]	27[261]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.3)	0.2 (-0.1 to 0.5)	-0.3 (-0.6 to 0)	-0.1 (-0.4 to 0.3)

Notes:

[258] - Efficacy population

[259] - Efficacy population

[260] - Efficacy population

[261] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[262]	27[263]	26[264]	26[265]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.3)	0.1 (-0.2 to 0.4)	0.1 (-0.2 to 0.4)	0.4 (0.1 to 0.7)

Notes:

[262] - Efficacy population

[263] - Efficacy population

[264] - Efficacy population

[265] - Efficacy population

Attachments (see zip file)	AEC Carefree 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Carefree Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Carefree Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Carefree

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[266]	26[267]	25[268]	27[269]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.2)	0.1 (-0.2 to 0.4)	-0.3 (-0.6 to 0)	0 (-0.3 to 0.3)

Notes:

[266] - Efficacy population

[267] - Efficacy population

[268] - Efficacy population

[269] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[270]	27[271]	26[272]	26[273]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.3 to 0.3)	0 (-0.3 to 0.3)	0.1 (-0.2 to 0.4)	0.3 (0 to 0.6)

Notes:

[270] - Efficacy population

[271] - Efficacy population

[272] - Efficacy population

[273] - Efficacy population

Attachments (see zip file)	AEC Carefree 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Drunken Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Drunken Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Drunken

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[274]	26[275]	25[276]	27[277]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.2 to 0.1)	0.1 (-0.1 to 0.2)	0 (-0.1 to 0.2)	0 (-0.1 to 0.2)

Notes:

[274] - Efficacy population

[275] - Efficacy population

[276] - Efficacy population

[277] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[278]	27[279]	26[280]	26[281]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.3)	0.1 (0 to 0.2)	0 (-0.1 to 0.2)	0.2 (0 to 0.3)

Notes:

[278] - Efficacy population

[279] - Efficacy population

[280] - Efficacy population

[281] - Efficacy population

Attachments (see zip file)	AEC Drunken 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Drunken Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Drunken Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Drunken

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[282]	26[283]	25[284]	27[285]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.2 to 0.1)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)	0 (-0.1 to 0.1)

Notes:

[282] - Efficacy population

[283] - Efficacy population

[284] - Efficacy population

[285] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[286]	27[287]	26[288]	26[289]
Units: units on a scale				
least squares mean (confidence interval 95%)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)	0 (-0.1 to 0.1)	0.1 (0 to 0.2)

Notes:

[286] - Efficacy population

[287] - Efficacy population

[288] - Efficacy population

[289] - Efficacy population

Attachments (see zip file)	AEC Drunken 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Good Mood Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Good Mood Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Good Mood

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[290]	26[291]	25[292]	27[293]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.2)	0.2 (-0.1 to 0.5)	-0.5 (-0.8 to -0.3)	-0.2 (-0.4 to 0.1)

Notes:

[290] - Efficacy population

[291] - Efficacy population

[292] - Efficacy population

[293] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[294]	27[295]	26[296]	26[297]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.1)	-0.1 (-0.3 to 0.2)	0.1 (-0.2 to 0.4)	0.3 (0.1 to 0.6)

Notes:

[294] - Efficacy population

[295] - Efficacy population

[296] - Efficacy population

[297] - Efficacy population

Attachments (see zip file)	AEC Good Mood 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Good Mood Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Good Mood Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Good Mood

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[298]	26[299]	25[300]	27[301]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.1)	0.1 (-0.1 to 0.4)	-0.6 (-0.8 to -0.3)	-0.2 (-0.4 to 0.1)

Notes:

[298] - Efficacy population

[299] - Efficacy population

[300] - Efficacy population

[301] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[302]	27[303]	26[304]	26[305]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.4 to 0.2)	-0.1 (-0.4 to 0.2)	0 (-0.3 to 0.3)	0.2 (0 to 0.5)

Notes:

[302] - Efficacy population

[303] - Efficacy population

[304] - Efficacy population

[305] - Efficacy population

Attachments (see zip file)	AEC Good Mood 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Tingling Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Tingling Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Tingling

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[306]	26[307]	25[308]	27[309]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0.2)	0.1 (0 to 0.3)	0.2 (0 to 0.3)	0 (-0.1 to 0.2)

Notes:

[306] - Efficacy population

[307] - Efficacy population

[308] - Efficacy population

[309] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[310]	27[311]	26[312]	26[313]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0.2)	0.2 (0 to 0.3)	0.2 (0 to 0.3)	0.2 (0 to 0.3)

Notes:

[310] - Efficacy population

[311] - Efficacy population

[312] - Efficacy population

[313] - Efficacy population

Attachments (see zip file)	AEC Tingling 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Tingling Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Tingling Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Tingling

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[314]	26[315]	25[316]	27[317]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.1 to 0.1)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0 (-0.1 to 0.1)

Notes:

[314] - Efficacy population

[315] - Efficacy population

[316] - Efficacy population

[317] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[318]	27[319]	26[320]	26[321]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (0 to 0.1)	0.1 (0 to 0.2)	0.1 (0 to 0.2)	0.1 (0.1 to 0.2)

Notes:

[318] - Efficacy population

[319] - Efficacy population

[320] - Efficacy population

[321] - Efficacy population

Attachments (see zip file)	AEC Tingling 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Energetic Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Energetic Repeated Measures Analysis of Covariance from 5 Minutes to 60 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Energetic

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45 and 60 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[322]	26[323]	25[324]	27[325]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.2 to 0.2)	0 (-0.2 to 0.2)	-0.4 (-0.6 to -0.2)	-0.2 (-0.4 to 0)

Notes:

[322] - Efficacy population

[323] - Efficacy population

[324] - Efficacy population

[325] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[326]	27[327]	26[328]	26[329]
Units: units on a scale				
least squares mean (confidence interval 95%)	-0.1 (-0.3 to 0.1)	0.1 (-0.1 to 0.2)	-0.2 (-0.4 to 0)	0.1 (-0.1 to 0.3)

Notes:

[326] - Efficacy population

[327] - Efficacy population

[328] - Efficacy population

[329] - Efficacy population

Attachments (see zip file)	AEC Energetic 60 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Agonist Effects Checklist (AEC) Energetic Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point title	Change from Baseline in the Agonist Effects Checklist (AEC) Energetic Repeated Measures Analysis of Covariance from 5 Minutes to 300 Minutes During the Challenge Period

End point description:

Agonist Effects Checklist (AEC): a 17 item, subject completed checklist consisting of terms and phrases typical of opioid agonist effects. Subjects rated each of the following items on a 5-point scale from 0 (no effect) to 4 (maximum effect): flushing, itchy skin, nausea, nodding, relaxed, pleasant sick, coasting or spaced out, talkative, heavy or sluggish, dry mouth, drive, sleepy, carefree, drunken, good mood, tingling and energetic.

This item: Energetic

Repeated Measures Model: Change from Baseline = Challenge, Period, Assessment Time, Challenge x Assessment Time, Period x Assessment
Time, Challenge x Period and Within Period Baseline Value, using the Toeplitz covariance structure for repeating Assessment Time for Challenge
within subject, and subject as a random effect.
P-values available in attached file.

End point type	Secondary

End point timeframe:

-10 minutes (pre-dose), 5, 15, 30, 45, 60, 120, 180, 240 and 300 minutes post dose on dosing days during the challenge period (Study days 9, 11, 13, 15, 17, 19, 21 , 23, dependent upon randomization order)

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[330]	26[331]	25[332]	27[333]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.2 to 0.2)	0 (-0.2 to 0.2)	-0.4 (-0.6 to -0.2)	-0.1 (-0.3 to 0.1)

Notes:

[330] - Efficacy population

[331] - Efficacy population

[332] - Efficacy population

[333] - Efficacy population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	25[334]	27[335]	26[336]	26[337]
Units: units on a scale				
least squares mean (confidence interval 95%)	0 (-0.3 to 0.2)	0 (-0.2 to 0.3)	-0.2 (-0.4 to 0.1)	0.1 (-0.2 to 0.3)

Notes:

[334] - Efficacy population

[335] - Efficacy population

[336] - Efficacy population

[337] - Efficacy population

Attachments (see zip file)	AEC Energetic 300 min/RB-UK-11-0018 Summary table

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Treatment-Emergent Adverse Events (TEAEs)

End point title	Patients with Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment.
TEAE: Treatment-Emergent Adverse Event is a new adverse event or an event that worsens in intensity after the first dose of Suboxone is administered.
An adverse event is associated with a challenge if the onset of the AE occurs after the start of the administration of the challenge but prior to the start of the administration of the next challenge.
Relation to study treatment was assessed by the investigator.
Serious AE Criteria: 1 = Results in death 2 = Is life-threatening 3 = Requires in-patient hospitalisation or prolongation of existing hospitalisation 4 = Results in persistent or significant disability/incapacity 5 = Is a congenital anomaly/birth defect

End point type	Secondary

End point timeframe:

Days 1-24

End point values	A. Placebo	B: Buprenorphine hemiadipate HCl	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24[338]	23[339]	22[340]	23[341]
Units: patients				
Any TEAE	2	5	5	1
Related TEAE	1	3	2	1
Serious TEAE	0	0	0	0
Serious Related TEAE	0	0	0	0
TEAE leading to d/c of treatment	0	0	0	0
TEAE leading to death	0	0	0	0

Notes:
[338] - Safety population
[339] - Safety population
[340] - Safety population
[341] - Safety population

End point values	E. BHA/NAL 1:0.5	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	23[342]	22[343]	23[344]	22[345]
Units: patients				
Any TEAE	5	4	5	3
Related TEAE	0	1	1	0
Serious TEAE	0	0	0	0
Serious Related TEAE	0	0	0	0
TEAE leading to d/c of treatment	0	0	0	0
TEAE leading to death	0	0	0	0

Notes:
[342] - Safety population
[343] - Safety population
[344] - Safety population
[345] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 - 24

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	Pre-Challenge Period (Day 1 - 7)

Reporting group description:

A 7-day outpatient period during which subjects received Suboxone. The dose for Day 1 was 8mg, Day 2 was 12mg, and Days 3 to 7 was 16mg.

Reporting group title	A. Placebo

Reporting group description:

Subjects who completed the placebo challenge consisting of a single intravenous injection of placebo.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	B: Buprenorphine hemiadipate HCl

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	C: Naloxone HCl dihydrate

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of naloxone HCl dihydrate 5 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	D: BHA/NAL 1:1

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 5 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	E. BHA/NAL 1:0.5

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 2.5 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	F. BHA/NAL 1:0.25

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine hemiadipate HCl 5 mg /naloxone HCl dihydrate 1.25 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	G: Diamorphine

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of diamorphine HCl 10 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Reporting group title	H. Buprenorphine HCL

Reporting group description:

Subjects who completed the challenge consisting of a single intravenous injection of buprenorphine HCl 4.0 mg.
The time frame for the Challenge Period was between days 8-24 during which patients continued taking 16mg of Suboxone daily.

Serious adverse events	Pre-Challenge Period (Day 1 - 7)	A. Placebo	B: Buprenorphine hemiadipate HCl
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 36 (0.00%)	0 / 24 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1	E. BHA/NAL 1:0.5
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 27 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Pre-Challenge Period (Day 1 - 7)	A. Placebo	B: Buprenorphine hemiadipate HCl
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 36 (13.89%)	0 / 24 (0.00%)	4 / 26 (15.38%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 36 (2.78%)	0 / 24 (0.00%)	3 / 26 (11.54%)
occurrences (all)	1	0	3
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all)	4 / 36 (11.11%) 4	0 / 24 (0.00%) 0	1 / 26 (3.85%) 1
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	0 / 24 (0.00%) 0	0 / 26 (0.00%) 0

Non-serious adverse events	C: Naloxone HCl dihydrate	D: BHA/NAL 1:1	E. BHA/NAL 1:0.5
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 25 (12.00%)	1 / 27 (3.70%)	1 / 25 (4.00%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	0 / 27 (0.00%) 0	0 / 25 (0.00%) 0
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 27 (3.70%) 1	1 / 25 (4.00%) 1
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 27 (0.00%) 0	0 / 25 (0.00%) 0

Non-serious adverse events	F. BHA/NAL 1:0.25	G: Diamorphine	H. Buprenorphine HCL
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	0 / 26 (0.00%)
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 February 2012	• Exclusion criteria 7, 9, 12 and 13 were revised. • Definition and reporting of AEs and SAEs were revised. • Pregnancy related section was added to the study procedures. • Prohibited medications were described.
19 July 2012	• A clarification was provided regarding the administration of the first challenge dose. It was clarified that the first challenge could be administered on a Monday if it was not possible to administer it on the weekend. It was also clarified that the investigator was allowed to use discretion to dispense sublingual Suboxone for 2 days to cover the weekend dose. • It was clarified that clinical laboratory safety tests would be performed 21-24 hours prior to the first challenge dose and at 24 h after the final challenge. The schedule of these tests was revised to Day -14 to Day -1, Day 1, Day 8 ("first challenge day -1"), the day after the final challenge ("final challenge day +1") and at Follow-up. • The dose of test product on Day 3 was revised to 16 mg and it was clarified that the duration of the dose would be extended until the day after the last challenge administration. • It was clarified that subjects would receive Suboxone from Day 1 until the day after the last challenge administration (inclusive). • Figure 1 was corrected with the clarification of Screening visit to be Day-14 to Day-1 and that Day 8 was considered Challenge Day -1. The timing of the challenges was changed to be between 9 and 11 AM. • Duration of participation for each subject was changed to 43 days; the out patient period was changed to 7 days; the duration of the residential period was changed to a minimum of 17 days which was allowed to be extended up to 28 days if the subject was kept in house during the out patient period. • Inclusion criterion No. 9 was modified to include subjects who continued to abuse opioids at least 3 times per week. • The method of administration of challenges was modified to include either direct puncture or a BD Adsyte Pro 18/20 gauge catheter or similar device over approximately 10 seconds via an IV push. • Other changes were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported