

**Clinical trial results:****A Phase I, Open-Label, Multicentre Study to Assess the Pharmacokinetics and Safety of Naloxegol in Paediatric Patients Ages 6 Months to < 18 Years Receiving Treatment with Opioids****Summary**

EudraCT number	2013-003935-32
Trial protocol	GB ES NO DK
Global end of trial date	22 April 2021

Results information

Result version number	v1 (current)
This version publication date	28 July 2022
First version publication date	28 July 2022

Trial information**Trial identification**

Sponsor protocol code	D3820C00016
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02099591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kyowa Kirin Pharmaceutical Development Ltd
Sponsor organisation address	Galabank Business Park, Galashiels, United Kingdom, TD1 1QH
Public contact	Clinical Trial Information , Kyowa Kirin Pharmaceutical Development Ltd., +44 1896664000, kkd.clintrial.82@kyowakirin.com
Scientific contact	Clinical Trial Information, Kyowa Kirin Pharmaceutical Development Ltd., +44 1896664000, kkd.clintrial.82@kyowakirin.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001146-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2021
Global end of trial reached?	Yes
Global end of trial date	22 April 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize the pharmacokinetics (PK) of naloxegol after single oral dose and through population PK in paediatric patients with opioid induced constipation (OIC) or at risk of OIC.

Protection of trial subjects:

The Principal Investigators were responsible for the conduct and administration of the study in accordance with the protocol and ICH E6-GCP (CPMP/ICH/135/95) guidelines, for collecting, recording, and reporting the data accurately and properly as well as the applicable country-specific requirements and in accordance with the ethical principles enunciated in the current version of the Declaration of Helsinki.

The Investigator's staff was responsible for preparing the study-specific written consent document for this study. The documents incorporated the required elements for informed consent, including the possible treatment risks and necessary documentation as required by the Declaration of Helsinki, 21 CFR Part 50, and the ICH-GCP (CPMP/ICH/135/95) guidelines. The ICF also was to contain any additional information required by local laws relating to IRB/IEC review. The ICF was approved by the IRB/IEC and the Sponsor.

The subject's willingness to participate in the study was documented in writing (signed and dated by the subject and by the person who conducted the ICF discussion) with a copy provided to the subject. The Investigators kept the original consent forms.

A Safety and Pharmacokinetic Review Committee oversaw safety in the study, including a staggered enrolment scheme, which began with the oldest paediatric subjects before proceeding to the youngest.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 July 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 19
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Israel: 2
Worldwide total number of subjects	61
EEA total number of subjects	59

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)	5
Children (2-11 years)	26
Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 14 investigative sites located centers in Denmark, Norway, Spain, the United Kingdom, and Israel with Investigators experienced in conducting clinical studies paediatric studies. The study was initiated 12-Nov-14 and all subjects were screened for eligibility to participate in the trial. Recruitment closed in April 2021.

Pre-assignment

Screening details:

Subjects were screened for study entry after the subject, parent or legal guardian signed the ICF. A subject was enrolled into the study only if all inclusion criteria and none of the exclusion criteria were fulfilled. A total of 61 subjects were screened for inclusion, 57 subjects were enrolled and assigned treatment and 46 subjects were treated.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

≥12 years to <18 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg

Arm type	Experimental
Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	Moventig
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Naloxegol (12.5 mg adult equivalent dose) was administered once daily as an oral dose and was taken on an empty stomach in the morning at the same time of day throughout the study. Subjects were dosed with a single oral dose of naloxegol on Day 1 (Visit 2) in the clinic. Subjects stayed in the clinic overnight or for at least 10 hours following the first dose of naloxegol for PK sampling and for post first dose safety and tolerability assessments. If a subject continued treatment with naloxegol beyond Day 1, the second dose was administered in the clinic on Day 2 (Visit 3). Subjects could have continued treatment for up to 6 months (26 weeks) depending on duration of opioid treatment and tolerability of study drug as determined by the investigator and Study Physician.

Arm title	Cohort 2
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Arm description:

≥12 years to <18 years higher dose targeted to achieve similar exposure to adults dosed at 25 mg

Arm type	Experimental
Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	Moventig
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Naloxegol (25 mg adult equivalent dose) was administered once daily as an oral dose and was taken on an empty stomach in the morning at the same time of day throughout the study. Subjects were dosed with a single oral dose of naloxegol on Day 1 (Visit 2) in the clinic. Subjects stayed

in the clinic overnight or for at least 10 hours following the first dose of naloxegol for PK sampling and for post first dose safety and tolerability assessments. If a subject continued treatment with naloxegol beyond Day 1, the second dose was administered in the clinic on Day 2 (Visit 3). Subjects could have continued treatment for up to 6 months (26 weeks) depending on duration of opioid treatment and tolerability of study drug as determined by the investigator and Study Physician.

Arm title	Cohort 3
Arm description: ≥6 years to <12 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg	
Arm type	Experimental
Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	Moventig
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Naloxegol (12.5 mg adult equivalent dose) was administered once daily as an oral dose and was taken on an empty stomach in the morning at the same time of day throughout the study. Subjects were dosed with a single oral dose of naloxegol on Day 1 (Visit 2) in the clinic. Subjects stayed in the clinic overnight or for at least 10 hours following the first dose of naloxegol for PK sampling and for post first dose safety and tolerability assessments. If a subject continued treatment with naloxegol beyond Day 1, the second dose was administered in the clinic on Day 2 (Visit 3). Subjects could have continued treatment for up to 6 months (26 weeks) depending on duration of opioid treatment and tolerability of study drug as determined by the investigator and Study Physician.

Arm title	Cohort 4
Arm description: ≥6 years to <12 years higher dose targeted to achieve similar exposure to adults dosed at 25 mg	
Arm type	Experimental
Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	Moventig
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Naloxegol (25 mg adult equivalent dose) was administered once daily as an oral dose and was taken on an empty stomach in the morning at the same time of day throughout the study. Those subjects already enrolled in Cohort 4 prior to Protocol Version 6.0, were dosed with a single oral dose of naloxegol on Day 1 (Visit 2) in the clinic. Subjects stayed in the clinic overnight or for at least 10 hours following the first dose of naloxegol for PK sampling and for post first dose safety and tolerability assessments. If a subject continued treatment with naloxegol beyond Day 1, the second dose was administered in the clinic on Day 2 (Visit 3). Those subjects enrolled in Cohort 4 after Protocol Version 6.0 were dosed with a single oral dose of naloxegol on Day 1 in the clinic. Subjects could have continued treatment for up to 6 months (26 weeks) depending on duration of opioid treatment and tolerability of study drug as determined by the investigator and Study Physician.

Arm title	Cohort 5
Arm description: ≥6 months to <6 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg	
Arm type	Experimental
Investigational medicinal product name	Naloxegol
Investigational medicinal product code	
Other name	Moventig
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Naloxegol (12.5 mg adult equivalent dose) was administered once daily as an oral dose and was taken

on an empty stomach in the morning at the same time of day throughout the study.
 Subjects in Cohort 5 were dosed with a single oral dose of naloxegol on Day 1 in the clinic.
 Subjects could have continued treatment for up to 6 months (26 weeks) depending on duration of opioid treatment and tolerability of study drug as determined by the investigator and Study Physician.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	12	18	10
Completed	8	12	9
Not completed	4	6	1
Consent withdrawn by subject	-	-	-
Screen Failure	1	3	1
Adverse event, non-fatal	-	1	-
Difficulty swallowing tablets	-	-	-
Stopped Analgesia	1	1	-
Failed Blood Draw	-	-	-
Protocol deviation	2	1	-

Number of subjects in period 1	Cohort 4	Cohort 5
Started	9	12
Completed	4	6
Not completed	5	6
Consent withdrawn by subject	1	2
Screen Failure	3	1
Adverse event, non-fatal	-	-
Difficulty swallowing tablets	1	-
Stopped Analgesia	-	-
Failed Blood Draw	-	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
Reporting group description: ≥12 years to <18 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg	
Reporting group title	Cohort 2
Reporting group description: ≥12 years to <18 years higher dose targeted to achieve similar exposure to adults dosed at 25 mg	
Reporting group title	Cohort 3
Reporting group description: ≥6 years to <12 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg	
Reporting group title	Cohort 4
Reporting group description: ≥6 years to <12 years higher dose targeted to achieve similar exposure to adults dosed at 25 mg	
Reporting group title	Cohort 5
Reporting group description: ≥6 months to <6 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	12	18	10
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Adolescents (12-17 years)	12	18	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
6 months to < 6 years	0	0	0
6 yrs to < 12 years	0	0	10
Gender categorical			
Units: Subjects			
Female	11	15	5
Male	1	3	5

Reporting group values	Cohort 4	Cohort 5	Total
Number of subjects	9	12	61
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Adolescents (12-17 years)	0	0	30
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0

85 years and over	0	0	0
6 months to < 6 years	0	12	12
6 yrs to < 12 years	9	0	19
Gender categorical			
Units: Subjects			
Female	3	6	40
Male	6	6	21

Subject analysis sets

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who:

- received at least 1 dose of naloxegol on the administration of study drug CRF page, and
- for whom any postdose data were available

Subject analysis set title	Acceptability Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects who:

- received at least 1 dose of naloxegol on the administration of study drug CRF page, and
- for whom any postdose palatability or ability to swallow tablet data were available on the CRF

Reporting group values	Safety Analysis	Acceptability Analysis Set	
Number of subjects	46	29	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Adolescents (12-17 years)	26	23	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
6 months to < 6 years	6	3	
6 yrs to < 12 years	14	3	
Gender categorical			
Units: Subjects			
Female	33		
Male	13		

End points

End points reporting groups

Reporting group title	Cohort 1
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Reporting group description:

≥12 years to <18 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg

Reporting group title	Cohort 2
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Reporting group description:

≥12 years to <18 years higher dose targeted to achieve similar exposure to adults dosed at 25 mg

Reporting group title	Cohort 3
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Reporting group description:

≥6 years to <12 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg

Reporting group title	Cohort 4
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Reporting group description:

≥6 years to <12 years higher dose targeted to achieve similar exposure to adults dosed at 25 mg

Reporting group title	Cohort 5
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Reporting group description:

≥6 months to <6 years lower dose targeted to achieve similar exposure to adults dosed at 12.5 mg

Subject analysis set title	Safety Analysis
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All subjects who:

- received at least 1 dose of naloxegol on the administration of study drug CRF page, and
- for whom any postdose data were available

Subject analysis set title	Acceptability Analysis Set
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Subject analysis set type	Per protocol
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Subject analysis set description:

All subjects who:

- received at least 1 dose of naloxegol on the administration of study drug CRF page, and
- for whom any postdose palatability or ability to swallow tablet data were available on the CRF

Primary: AUC 0-∞

End point title	AUC 0-∞ ^{[1][2]}
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End point description:

End point type	Primary
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End point timeframe:

Day 1 to Day 7

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 objective was to evaluate naloxegol exposures, full statistical analysis was not performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Summary Statistics: Naloxegol exhibited dose-linear kinetics across the adult equivalent 12.5 and 25mg doses in pediatric subjects receiving opioids from ≥6 yrs to <18 yrs. The geometric mean C_{max} and AUC_{0-∞} values for pediatric subjects from ≥12 yrs to <18 yrs receiving the adult equivalent 12.5mg dose was 11.6 ng/mL and 96.6 hr*ng/mL. The geometric mean C_{max} and AUC values for pediatric subjects from ≥6 yrs to <12 yrs receiving the adult equivalent 12.5mg dose was 9.26 ng/mL and 46.1 hr*ng/mL

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	4
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	96.6 (± 48.3)	182 (± 53.5)	46.1 (± 90.9)	65.4 (± 67.8)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax

End point title	Cmax ^{[3][4]}
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End point description:

End point type	Primary
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End point timeframe:

Day 1 to Day 7

Notes:

[3] - 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 objective was to evaluate naloxegol exposures, full statistical analysis was not performed.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Summary Statistics: Naloxegol exhibited dose-linear kinetics across the adult equivalent 12.5 and 25mg doses in pediatric subjects receiving opioids from ≥6 yrs to <18 yrs. The geometric mean Cmax and AUC_{0-∞} values for pediatric subjects from ≥12 yrs to <18 yrs receiving the adult equivalent 12.5mg dose was 11.6 ng/mL and 96.6 hr*ng/mL. The geometric mean Cmax and AUC values for pediatric subjects from ≥6 yrs to <12 yrs receiving the adult equivalent 12.5mg dose was 9.26 ng/mL and 46.1 hr*ng/mL

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	8	4
Units: ng/mL				
geometric mean (geometric coefficient of variation)	11.6 (± 40.6)	31.7 (± 81.4)	9.26 (± 95.0)	21.5 (± 60.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability of Liquid Formulation

End point title	Palatability of Liquid Formulation ^[5]
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End point description:

Subjects ≥6 years old were asked to evaluate palatability immediately after dosing using the visual analogue scale (VAS) with 100 mm facial hedonic scale. For subjects under 6 years of age down to 6 months, a nurse's assessment of the subject's willingness to swallow and how the subject's response compared to the subject's response to all other oral medication currently being given was performed.

End point type	Secondary
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End point timeframe:

Day 1 and Day 2

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Mean palatability score of naloxegol liquid oral formulation at Visit 2 was reported as 59.6 for subjects in the age group ≥ 6 yrs to < 12 yrs, and 50.0 in the age group ≥ 12 yrs to < 18 yrs. At Visit 3, results were available for only 1 subject, age group ≥ 6 yrs to < 12 yrs, who scored 100. For acceptability, all subjects in the age group ≥ 12 yrs to < 18 yrs were able to swallow tablets on Day 1 and data were only available for 2 subjects for low dose and 5 subjects for high-dose on Day 2.

End point values	Cohort 2	Cohort 3		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	5		
Units: Visual Analogue Scale				
number (not applicable)	50	59.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected from the time of signature of informed consent/assent, throughout the treatment period, and up to and including the follow up visit (Visit 12)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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Reporting groups

Reporting group title	Safety Analysis Set
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Reporting group description:

All subjects who:

- received at least 1 dose of naloxegol on the administration of study drug CRF page, and
- for whom any postdose data were available

Serious adverse events	Safety Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 46 (2.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Laryngeal obstruction			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Withdrawal Syndrome			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 46 (76.09%)		

Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 4		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 46 (8.70%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	10 / 46 (21.74%) 10 8 / 46 (17.39%) 8 7 / 46 (15.22%) 7 4 / 46 (8.70%) 4		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2014	Protocol Version 2.0, 13 May 2014 The key changes to Version 2.0 of the protocol included: <ul style="list-style-type: none">• An adjustment to the palatability of formulation assessments to include subjects who switch from 1 formulation to another;• Changes to the exclusion criteria for absolute neutrophil count and hemoglobin levels;• Clarification to the restricted concomitant treatment section;• An update to the blood volume schedule.
25 October 2016	Protocol Version 4.0, 09 Sep 2016 Version 4.0 of the protocol updated the name of the Sponsor from AstraZeneca AB to Kyowa Kirin Pharmaceutical Development Ltd. Protocol version 3.0 (20 Jun 2016) was included in the submissions as a non-substantial amendment
19 June 2019	Protocol Version 5.0, 21 Mar 2019 The key changes to Version 5.0 of the protocol included: <ul style="list-style-type: none">• An update to the commonly reported ADRs;• Updates to the exclusion criteria;• Addition of the ability to conduct the follow-up visit by telephone if necessary.
28 November 2019	Protocol Version 6.0, 07 Nov 2019 The key changes to Version 6.0 of the protocol included: <ul style="list-style-type: none">• Updated safety profile of naloxegol;• Modification of exclusion criteria to allow more flexible subject enrollment;• Reduction in the number of subjects in some cohorts;• Changes to the PK dosing schedule for some cohorts;• Changes to food restrictions and fasting requirements to aid recruitment;• Follow-ups in the form of phone calls instead of site visits for some cohorts;• Clarification of primary and secondary objectives following changes to the protocol;• Clarification of what constitutes a formal BM.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 March 2020	Recruitment was temporarily halted on 31 Mar 2020 due to the Coronavirus disease-19 pandemic. Sites were then reopened individually from late Jun 2020 to early Nov 2020.	19 June 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The last subject visit was 22 April 2021, however the study remained open until a modification to the PIP to reduce the number of subjects was accepted in December 2021.

Notes: