10 November 2022
EMA/914876/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Moventig

naloxegol

Procedure no: EMEA/H/C/002810/P46/011

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 4/7/2022, the MAH submitted a completed paediatric study for Moventig, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the SAFARI study is part of a clinical development program, PIP EMEA-001146-PIP01-11. The variation application is expected to be submitted after October 2022.

2.2. Information on the pharmaceutical formulation used in the studies

For this pediatric study, the subject was administered naloxegol oral tablets or naloxegol liquid oral formulation (Table 1).

Table 1. Identity of the investigational product

Investigational Product	Dosage form and Strength	Manufacturer Name	Manufacturer Country
Naloxegol	5 mg, round tablet (as oxalate salt)	AstraZeneca AB	Sweden
Naloxegol	12.5 mg, oval tablet (as oxalate salt)	AstraZeneca AB	Sweden
Naloxegol	25 mg, oval tablet (as oxalate salt)	AstraZeneca AB	Sweden
Naloxegol	oral solution, 0.8 mg/mL (as oxalate salt)	AstraZeneca AB	Sweden
Naloxegol	oral solution, 2.5 mg/mL (as oxalate salt)	AstraZeneca AB	Sweden

The naloxegol liquid oral formulation was used when the available tablets could not accommodate the dosing algorithm, as well as in cases when a subject could not swallow solid tablets. For the youngest age group, only liquid oral formulation was administered. Liquid formulation was taken orally or given through a naso-gastric or gastric tube.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- D3820C00016 (SAFARI): A Phase 1, Open-label, Multicenter Study to Assess the Pharmacokinetics and Safety of Naloxegol in Pediatric Patients Ages ≥6 Months to <18 Years Receiving Treatment with Opioids

2.3.2. Clinical study

D3820C00016 (SAFARI): A Phase 1, Open-label, Multicenter Study to Assess the Pharmacokinetics and Safety of Naloxegol in Pediatric Patients Ages ≥6 Months to <18 Years Receiving Treatment with Opioids

Description

Methods

Study participants

This is a phase I, open-label study to assess the pharmacokinetics (PK) and safety of naloxegol in paediatric patients ages ≥6 months to <18 years receiving treatment with opioids and presenting with opioid-induced constipation (OIC) or at risk of OIC. There are 3 different age groups and initially it was planned for each age group to have 2 cohorts.

Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Written informed consent for study participation must be obtained prior to any study-related procedures being performed (local regulations are to be followed in determining the assent/consent requirements for children and parent[s]/guardian[s]) and according to international guidelines and/or applicable European Union guidelines;

2. Patients between the ages of ≥6 months and <18 years;

3. Patients with malignant or non-malignant pain who are receiving (or are about to receive) acute or chronic treatment with opioids;

4. In the investigator's judgment, patients must be either newly diagnosed with constipation or patients must have a history of constipation treated with laxatives or be expected to develop constipation after initiation of opioid treatment;

5. Patients must have the ability to be present in the clinic for at least 10 hours following the first dose of naloxegol for PK sampling and post first dose tolerability observations;

6. Female patients of childbearing potential must have a negative urine pregnancy test at screening. Females of childbearing potential must either not be sexually active or be using an adequate birth control method throughout the duration of the study;

7. Provision of informed consent prior to any study specific procedures.

Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement of a parent or guardian in the planning and/or conduct of the study (applies to both KKI staff and/or staff at the study site);

2. Previous enrolment in the present study with intake of naloxegol IP;

3. Current acute or chronic use of methadone;

4. For patients 6-12 months old, history of major corrective or reconstructive GI surgery (except pyloric stenosis) in the last 6 months or possible need for corrective or reconstructive GI surgery in the

next month, or history of post-surgical ileus. For patients over 1 year of age, history of previous GI surgery in the last 6 months (does not include placement of enteral tubes or liver biopsies);

5. History of an intra-abdominal or peritoneal neoplasm or an ongoing GI-related issue (e.g., inflammatory bowel disease, connective tissue disorders like Ehler Danlos, dermatomyositis, scleroderma) which, in the opinion of the investigator, may be contributing to constipation as a result of mechanical obstruction or may place the patient at increased risk for intestinal perforation by impairing the local or global structural integrity of the GI tract;

6. Signs or symptoms of GI obstruction including faecal impaction requiring medical intervention. History of GI obstructive conditions (e.g. Hirschsprung's disease, malrotation, volvulus, pseudo-obstruction syndromes);

7. Currently active medical conditions or ongoing treatments (e.g. irinotecan) that may result in diarrhoea or intermittent loose stools during the screening or treatment period;

8. Significant cardiorespiratory dysfunction or haemodynamic instability;

9. Evidence of known widespread cancer metastases in the CNS;

10. Radiotherapy between the diaphragm and the pelvis in the 4 weeks prior to screening or planned to be initiated during the treatment period;

11. Any of the following findings and/or conditions:

(i) For patients 6-12 months old, any elevation of serum direct or indirect bilirubin, and/or elevation of LFTs not associated with their underlying disease and associated treatment, that have not undergone a medical work up. For patients over 1 year old, serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 x upper limit of normal (ULN) and/or serum bilirubin >1.2 x ULN (unless known to be due to Gilbert’s syndrome or sickle cell disease).

(ii) Creatinine clearance <60 ml/min/1.73 m2 (using the Schwartz formula*).

(iii) Absolute neutrophil count <1.0 x 10^9/L; haemoglobin <9 g/dL (or <7 g/dL if known to be related to sickle cell disease) or, platelet count <50,000/µL.

For oncology patients, excursions below these limits may be considered on a case-by-case basis following discussion between the investigator and the Medical Monitor, and agreement of the Sponsor.

12. History (within past 3 months) of prolonged (>10 days) neutropenia or thrombocytopenia with clinical sequelae;

13. Treatment with another experimental medication for which there is no current labelled therapy (adult or paediatric), currently or within the last 30 days;

14. Patients with cancer currently receiving the first cycle of chemotherapy, or due to receive a chemotherapeutic agent for the first time;

15. Life expectancy of <3 months;

16. Treatment within 7 days of naloxegol dosing with any concomitant medications known or expected to be significantly affected by naloxegol administration or known to significantly affect naloxegol PK;

17. Patients with clinically significant BBB disruptions (e.g., active multiple sclerosis, recent brain injury);

18. Patients with known hypersensitivity to other opioid antagonists;

19. Patients with cancer-related pain who are at heightened risk of GI perforation.

Treatments

Treatments Administered

For this pediatric study, the subject was administered naloxegol oral tablets or naloxegol liquid oral formulation (Table 1).

The naloxegol liquid oral formulation was used when the available tablets could not accommodate the dosing algorithm, as well as in cases when a subject could not swallow solid tablets. For the youngest age group, only liquid oral formulation was administered. Liquid formulation was taken orally or given through a naso-gastric or gastric tube.

On PK sampling days (Day 1, Day 2, and Day 7 [as appropriate]), the IP was taken on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal. All subjects could have eaten solid or liquid food 1 hour after dosing (Protocol Version 6.0) or 2 hours after dosing (prior to Protocol Version 6.0). A moderate amount of water was allowed up to 1 hour prior to dosing and could have been resumed 1 hour after dosing. Subjects were encouraged to avoid consumption of grapefruit or grapefruit juice during the treatment of naloxegol.

Dose and Treatment Regimens

Naloxegol 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 Cohorts 1 to 3, and 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, and 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.

Treatment Groups and Cohort Size

There were 3 age groups: ≥12 years to <18 years; ≥6 years to <12 years, and ≥6 months to <6 years. The study proceeded sequentially from the oldest to the youngest age group. Each age group had 2 dose cohorts planned (Figure 1).

For the first age group (≥12 years to <18 years), the first 11 subjects (lower dose cohort) were given a dose targeted to achieve similar exposure to the exposure in adults dosed at 12.5 mg based on PBPK modeling. Subjects continued treatment for up to 6 months and were evaluated for PK, safety, and tolerability. The SPRC reviewed PK and safety data and made decisions regarding approving the enrollment of subjects for the higher dose of naloxegol and for a lower age group.

The SPRC was an independent, external, expert group that reviewed PK study data, evaluated adverse effects and other safety data, and made recommendations about enrollment of new subjects of the same age group to be administered a higher dose or enrollment of a younger age group. The SPRC consisted of 3 voting members with the following expertise: Chair: Physician with pediatric background and clinical trial experience; Pharmacokineticist: clinical pharmacologist with pharmacokinetic background, clinical trial experience, and opioid withdrawal expertise; Physician: with clinical training and experience in opioid withdrawal.

The next subjects were enrolled to receive the higher dose to achieve similar exposure to that for 25 mg in the adults. This dose was based on the actual PK measurements from the lower dose and did not start until the characterization of the PK and tolerability of the lower dose cohort had been completed (Figure 1). In parallel to dosing the same age group with the higher dose, a new cohort from the lower age group was enrolled and dosed with the 12.5 mg adult equivalent dose. Following PK characterization and the safety assessment of this age group, the same dosing and assessment procedure was sequentially followed for the subsequent age groups.

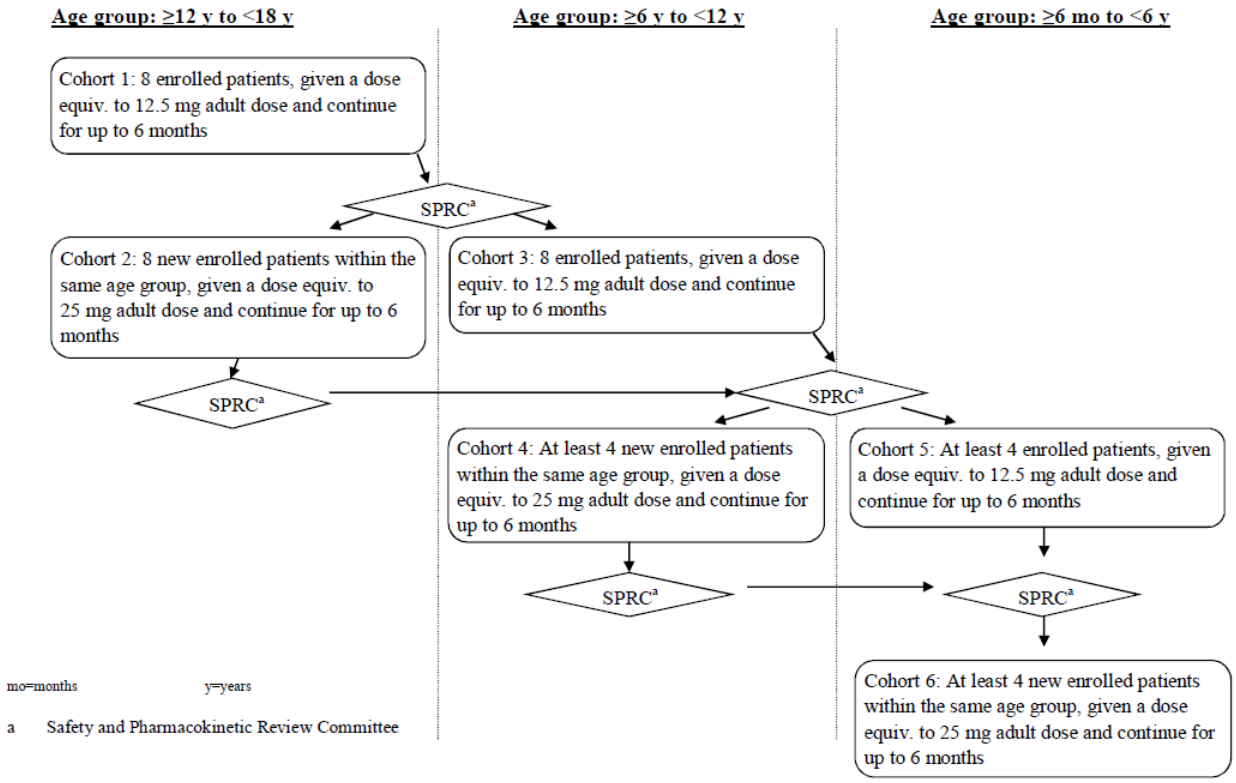


Figure 1. Study flow chart

Lower dose cohort

The planned lower doses (starting doses) of naloxegol are presented in Table 2. The doses in the various age groups were based on PBPK modeling using established in vitro and in vivo metabolic and PK information. The planned starting doses were projected to provide similar exposure (ie, area under the plasma concentration-time curve [AUC]) to that achieved in adults at 12.5 mg. Body-weight-based dosing was used to accommodate the variations in body size in pediatric subjects. Multiple tablets were administered to achieve a desired dose (eg, 17.5 mg=12.5 mg+5 mg). The naloxegol liquid oral formulation was used when the available tablets could not accommodate the dosing algorithm, as well as in cases when children could not swallow solid tablets. For the youngest age group, only liquid oral formulation was administered. The investigator provided appropriate oral and written study drug instruction to subject or parent(s)/guardian(s).

Table 2. Lower IP Dose Stratified by Age Groups and Weight

Age Group	Age	Weight Range (kg)	Planned Starting Dose (mg)	IP Oral Formulation
≥12 Y to <18 Y		>60	12.5	tablet 12.5 mg or liquid formulation 2.5 mg/mL
		40-60	10	tablet 2x5 mg or liquid formulation 2.5 mg/mL
		<40	6.25	liquid formulation 2.5 mg/mL
≥6 Y to <12 Y		>35	6.25	liquid formulation 2.5 mg/mL
		25-35	3.75	liquid formulation 2.5 mg/mL
		<25	2.5	liquid formulation 2.5 mg/mL
≥6 M to <6 Y	≥2 Y to <6 Y	>18	2.5	liquid formulation 2.5 mg/mL
		14-18	1.6	liquid formulation 0.8 mg/mL
		<14	1.2	liquid formulation 0.8 mg/mL
	≥6 M to <2 Y	>11	1.2	liquid formulation 0.8 mg/mL
		9-11	0.8	liquid formulation 0.8 mg/mL
		<9	0.4	liquid formulation 0.8 mg/mL

IP=investigational product; M=months; Y=years.

Higher dose cohort

Administration of the higher dose of naloxegol in each age group was based on SPRC review of available safety and PK data from the previous (lower) dose.

The higher dose in each age group was proposed taking into consideration the exposure observed in the previous (lower) dose, extrapolation from adult PK and age-related characteristics in PBPK modeling. The recommended dose was predicted to result in an exposure approximately corresponding to that for 25 mg naloxegol in the adult population. It was the responsibility of the SPRC to review and accept or reject the proposed dose.

KKPD communicated the decision of SPRC to the investigators and provided appropriate body-weight-based dosing schedule if applicable.

Objectives and endpoints

Primary Objective:	**Outcome Measure:**
To characterise the PK of naloxegol after single oral dose and through population PK in paediatric patients presenting with OIC or at risk of OIC.	Standard non-compartmental analysis approach (Cohorts 1 to 4 only: patients in Cohorts 4 with sparse sampling will be excluded from this analysis): • Area under the plasma concentration-time curve from zero extrapolated to infinity (AUC) • Area under the plasma concentration-time curve from zero to the last quantifiable concentration ($AUC_{(0-t)}$) • Maximum plasma concentration (C_{max}) • Terminal half-life ($t_{1/2\lambda z}$) • Time to maximum plasma concentration (t_{max}) • Mean residence time (MRT) • Oral clearance (CL/F) • Apparent Volume of distribution during the terminal phase (Vz/F) Population PK modelling approach using PK data from all cohorts: • Population estimated structural PK parameters (i.e., CL/F, Vz/F and other parameters as appropriate) • Influence of potential covariates (i.e., age, weight, etc).

Secondary Objective:	Outcome Measure:
To characterise the PK of naloxegol after multiple, once-daily, oral dosing in paediatric patients with or at risk of OIC who continue participation beyond Day 1 where data is available (Cohorts 1 to 4 only). A minimum of 3 days of dosing is required for multiple-dose PK analysis.	• As above • Other additional multiple-dose PK parameters, e.g., Rac(C_{4h})
To assess the acceptability of the study medication through assessment of: 1) palatability of liquid formulation and, 2) the ability of the patient to swallow the tablet.	Palatability of liquid formulation: For age group ≥6 years to <18 years: • Visual analogue scale (VAS) with facial hedonic scale at Day 1 and Day 2 immediately after dosing. For age group ≥6 months to <6 years: • A nurse's assessment of the patient's willingness to swallow and how the patient's response compares to the patient's response to all other oral medication currently being given assessed at Day 1 and Day 2 immediately after dosing. For patients who switch from one formulation to another (e.g., tablet to liquid) in Cohorts 1 and 2, the acceptability is to be assessed when patients come to the clinic to receive their study medication.

Safety Objective:	Outcome Measure:
To assess the safety and tolerability of naloxegol in paediatric patients with or at risk of OIC.	• Adverse events (AEs) • Laboratory assessments (clinical chemistry, haematology, urinalysis) • Physical examination • Vital signs • Electrocardiogram (ECG) • Opioid withdrawal symptoms • Pain

Clinical Outcome Objective:	Outcome Measure:
To collect information on time to first post-dose bowel movement, laxative use within 24 hours prior to first dose, number of days with BM, number of days with laxative use, while patients are taking opioids and naloxegol concurrently.	• Laxative use within 24 hours prior to first dose • Time (in hours) to first post-dose BM • Number of days with bowel movement per week • Number of days with laxative use per week • Percentage of days with bowel movement during treatment • Percentage of days with laxative use during treatment

Sample size

It was anticipated that approximately 60 subjects would be enrolled to obtain at least 36 evaluable PK subjects.

Randomisation and blinding (masking)

The study is open label.

Statistical Methods

There is no formal Statistical Analysis Plan for this study.

For Cohorts 1 to 3, at least 8 paediatric patients and for Cohort 4, at least 4 paediatric patients, were enrolled in each dose cohort with evaluable PK data (i.e., AUC). In these cohorts, rich PK sampling was utilised to characterise the PK disposition of naloxegol. This sample size in the original study protocol was determined to provide at least 80% power to target a 95% CI within 60% to 140% of geometric mean estimates of clearance and volume of distribution in each age group for naloxegol, based on an approximate geometric coefficient of variation at 45.6% for AUC (estimated from naloxegol pooled clinical pharmacology data in adults) (Wang Y et al 2012). However, based on the preliminary analysis of the population PK data from Cohorts 1 to 4, the Sponsor has re-evaluated the study design including the sample size and PK sampling scheme using Population Fisher Information Matrix. The results from this PK M&S support the reduction of sample size from 8 to at least 4 per cohort for Cohorts 4, 5 and 6. In addition, the M&S indicates that sparse PK sampling can be used to provide additional PK data needed for population PK analysis. Thus, data from Cohorts 5 and 6 and data from patients enrolled in Cohort 4 who had sparse PK sampling will not be used to derive traditional PK endpoints, but will be used in combination with data from Cohorts 1 to 4 for population PK modelling purposes.

Results

Participant flow

The disposition of subjects is provided in Table 3.

A total of 12 subjects were enrolled and assigned treatment in the age group ≥6 months to <6 years, 17 subjects in the age group ≥6 years to <12 years, and 28 subjects in the age group ≥12 years to <18 years.

Of these, 6 (50.0%) subjects in the age group ≥6 months to <6 years received treatment (all low-dose), 14 (82.4%) subjects in the age group ≥6 years to <12 years received treatment (9 [52.9%] low-dose and 5 [29.4%] high-dose), and 26 (92.9%) subjects in the age group ≥12 years to <18 years received treatment (11 [39.3%] low-dose and 15 [53.6%] high-dose).

No subjects were enrolled and assigned to the high-dose treatment in the age group ≥6 months to <6 years (ie, Cohort 6). The decision to not include any subjects in this age and dose cohort was approved as modifications to the PIPs by the EMA and MHRA.

In the Safety Analysis Set, none of the subjects were withdrawn from the study in the age group ≥6 months to <6 years. One (7.1%) subject in the age group ≥6 years to <12 years was withdrawn from the study, for the reason "Other". Six (23.1%) subjects in the age group ≥12 years to <18 years were withdrawn from the study; reasons for study withdrawal were severe noncompliance to protocol in 3 (11.5%) subjects, AE in 1 (3.8%) subject, and "Other" in 2 (7.7%) subjects. The "Other" reasons were specified as difficulty swallowing tablets.

Table 3. Subject Disposition (All Enrolled Subjects)

	Number (%) of subjects							
	Age group/Dose group							
	≥6M to <6Y			≥6Y to <12Y		≥12Y to <18Y		
Subject disposition	L	T (N=12)	L	H	T (N=19)	L	H	T (N=30)
Subject enrolled		12			19			30
Subjects enrolled and assigned to treatment [a]	12	12	10	7	17	12	16	28
Subjects who received treatment	6 (50.0)	6 (50.0)	9 (52.9)	5 (29.4)	14 (82.4)	11 (39.3)	15 (53.6)	26 (92.9)
Subjects who did not receive treatment	6 (50.0)	6 (50.0)	1 (5.9)	2 (11.8)	3 (17.6)	1 (3.6)	1 (3.6)	2 (7.1)
Subjects who completed study [b]	6 (100)	6 (100)	9 (100)	4 (80.0)	13 (92.9)	8 (72.7)	12 (80.0)	20 (76.9)
Subjects withdrawn from study	0	0	0	1 (20.0)	1 (7.1)	3 (27.3)	3 (20.0)	6 (23.1)
Main reason for premature withdrawal	0	0	0	0	0	0	0	0
Subject decision	0	0	0	0	0	0	0	0
Eligibility criteria not fulfilled	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
Adverse event	0	0	0	0	0	0	1 (6.7)	1 (3.8)
Severe noncompliance to protocol	0	0	0	0	0	2 (18.2)	1 (6.7)	3 (11.5)
Lack of therapeutic response	0	0	0	0	0	0	0	0
Development of study-specific withdrawal criteria	0	0	0	0	0	0	0	0
Subject lost to follow-up	0	0	0	0	0	0	0	0
Other	0	0	0	1 (20.0)	1 (7.1)	1 (9.1)	1 (6.7)	2 (7.7)
Missing	0	0	0	0	0	0	0	0

H=high-dose; L=low-dose; M=months; T=total; Y=years.
[a] Some subjects were enrolled (signed informed consent) but not assigned to a treatment. See Appendix 16.2.1.
[b] Percentages for subjects who completed/withdrew prematurely from study, and main reason for premature withdrawal are calculated out of the total number of subjects in the Safety Analysis Set.
Note: Subjects who failed screening although did not receive a treatment but were assigned with a subject number.
Note: No subjects were enrolled and assigned to the high-dose treatment in the age group ≥6M to <6Y. The decision to not include any subjects in this age and dose group was approved by the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA).
Source: Table 14.1.1.

Rapporteur comment:

Although 12 patients have been recruited in the age group ≥6 months to <6 years, only 50% of them received the actual treatment resulting in 6 patients receiving low dose treatment in cohort 1. The MAH is requested to discuss the reasons why such a high percentage of patients in this age group eventually did not receive the assigned treatment.

Baseline data

Demographics

Demographic characteristics are provided in Table 4.

The median age was 3.5 years (range: 0.5 to 5 years) in the age group ≥6 months to <6 years; 10.0 years (range: 7 to 11 years) in the age group ≥6 years to <12 years, and 14.0 years (range: 12 to 17 years) in the age group ≥12 years to <18 years.

Half of the subjects were male and half were female in the age group ≥6 months to <6 years and ≥6 years to <12 years (3 [50.0%] subjects in the age group ≥6 months to <6 years and 7 [50.0%] subjects in the age group ≥6 years to <12 years), whereas most of the subjects 23 (88.5%) in the age

group ≥12 years to <18 years were female. The majority of subjects in the study were White (12 [85.7%] subjects in the age group ≥6 years to <12 years and 26 [100.0%] subjects in the age group ≥12 years to <18 years).

All subjects were not Hispanic or Latino with the exception of 1 subject who was Hispanic or Latino in the age group ≥12 years to <18 years (high-dose group).

Table 4. Demographic Characteristics (Safety Analysis Set)

	Age group/Dose group							
	≥6M to <6Y		≥6Y to <12Y			≥12Y to <18Y		
Variable/ Category	L (N=6)	T (N=6)	L (N=9)	H (N=5)	T (N=14)	L (N=11)	H (N=15)	T (N=26)
Age (years)								
n	6	6	9	5	14	11	15	26
Mean	2.8	2.8	9.6	9.8	9.6	14.1	15	14.6
SD	1.94	1.94	1.33	1.64	1.39	1.81	1.2	1.53
Median	3.5	3.5	10	10	10	14	15	14
Minimum	0	0	8	7	7	12	13	12
Maximum	5	5	11	11	11	17	17	17
Sex n (%)								
Female	3 (50.0)	3 (50.0)	5 (55.6)	2 (40.0)	7 (50.0)	10 (90.9)	13 (86.7)	23 (88.5)
Male	3 (50.0)	3 (50.0)	4 (44.4)	3 (60.0)	7 (50.0)	1 (9.1)	2 (13.3)	3 (11.5)
Race n (%)								
Black or African American	0	0	0	0	0	0	0	0
White	2 (33.3)	2 (33.3)	8 (88.9)	4 (80.0)	12 (85.7)	11 (100)	15 (100)	26 (100)
Asian	0	0	0	0	0	0	0	0
Native Hawaiian or Pacific Islander	0	0	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Other	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Missing	3 (50.0)	3 (50.0)	1 (11.1)	1 (20.0)	2 (14.3)	0	0	0
Ethnicity n (%)								
Hispanic or Latino	0	0	0	0	0	0	1 (6.7)	1 (3.8)
Not Hispanic or Latino	6 (100)	6 (100)	9 (100)	5 (100)	14 (100)	11 (100)	14 (93.3)	25 (96.2)

H=high-dose; L=low-dose; M=months; SD=standard deviation; T=total; Y=years.
Note: Percentages are calculated out of the number of subjects in the Safety Analysis Set.
Note: Age = (date of informed consent minus DOB plus 1 day) / 365.25 and using the floored integer for rounding.

Subject Characteristics

Subject characteristics data are provided in Post-text Table 14.1.3 (not shown here).

The mean height was 97.2 cm (range: 67 to 119 cm) in the age group ≥6 months to <6 years; 140 cm (range: 121 to 167 cm) in the age group ≥6 years to <12 years; 161.4 cm (range: 125 to 187 cm) in the age group ≥12 years to <18 years.

The mean weight was 15.2 kg (range: 8 to 23 kg) in the age group ≥6 months to <6 years; 37.4 kg (range: 22 to 76 kg) in the age group ≥6 years to <12 years; 53.5 kg (range: 26 to 80 kg) in the age group ≥12 years to <18 years.

The mean BMI was 15.8 kg/m2 (range: 14.8 to 17.8 kg/m2) in the age group ≥6 months to <6 years; 18.86 kg/m2 (range: 13.6 to 27.3 kg/m2) in the age group ≥6 years to <12 years; 20.36 kg/m2 (range: 16.2 to 28 kg/m2) in the age group ≥12 years to <18 years.

Medical History

Medical history data are provided in Post-text Table 14.1.4 (not shown here).

The most commonly reported medical history conditions (≥2% subjects) by system organ class (SOC) level in the age group ≥6 months to <6 years were congenital, familial, and genetic disorder reported in a total of 4 (66.7%) subjects, followed by injury, poisoning, and procedural complications in a total

of 2 (33.3%) subjects, and respiratory, thoracic and mediastinal disorder in a total of 2 (33.3%) subjects.

The most commonly reported medical history conditions (≥2% subjects) by SOC level in the age group ≥6 years to <12 years were congenital, familial and genetic disorder and respiratory, thoracic and mediastinal disorders reported in a total of 7 (50.0%) subjects, followed by gastrointestinal disorder in a total of 5 (35.7%) subjects, and musculoskeletal and connective tissue disorders and neoplasm benign, malignant and unspecified (including cyst and polyps) in a total of 4 (28.6%) subjects.

The most commonly reported medical history conditions (≥2% subjects) by SOC level in the age group ≥12 years to <18 years were musculoskeletal and connective tissue disorder in a total of 19 (73.1%) subjects, followed by congenital, familial and genetic disorder reported in a total of 7 (26.9%) subjects, and gastrointestinal disorder in a total of 5 (19.2%) subjects.

Surgical History

Surgical history data are provided in Post-text Table 14.1.5 (not shown here).

The most commonly reported surgical history conditions (≥2% subjects) by SOC level in the age group ≥6 months to <6 years were surgical and medical procedure reported in a total of 4 (66.7%) subjects. No other surgical history condition was reported in >1 subject.

The most commonly reported surgical history conditions (≥2% subjects) by SOC level in the age group ≥6 years to <12 years were surgical and medical procedure reported in a total of 12 (85.7%) subjects, followed by congenital, familial, and genetic disorders in a total of 2 (14.3%) subjects, and eye disorders and investigations in a total of 2 (14.3%) subjects each.

The most commonly reported surgical history conditions (≥2% subjects) by SOC level in the age group ≥12 years to <18 years were surgical and medical procedure reported in a total of 25 (96.2%) subjects. No other surgical history condition was reported in >1 subject.

Prior and Concomitant Medications

Prior medications data are provided in Post-text Table 14.1.6.1 and concomitant medications data are provided in Post-text Table 14.1.6.2 (not shown here).

The most frequently used prior medication was paracetamol, which was used by 6 (100%) subjects in the age group ≥6 months to <6 years, 12 (85.7%) subjects in the age group ≥6 years to <12 years, and 22 (84.6%) subjects in the age group ≥12 years to <18 years, followed by fentanyl, used in 6 (100%) subjects in the age group ≥6 months to <6 years, 8 (57.1%) subjects in the age group ≥6 years to <12 years, and 14 (53.8%) subjects in the age group ≥12 years to <18 years.

The most frequently used concomitant medication was paracetamol, which was used by 6 (100%) subjects in the age group ≥6 months to <6 years, 13 (92.9%) subjects in the age group ≥6 years to <12 years, and 24 (92.3%) subjects in the age group ≥12 years to <18 years, followed by ondansetron used in 3 (50.0%) subjects in the age group ≥6 months to <6 years, 4 (28.6%) subjects in the age group ≥6 years to <12 years and 18 (69.2%) subjects in the age group ≥12 years to <18 years, and ibuprofen used in 3 (50.0%) subjects in the age group ≥6 months to <6 years, 8 (57.1%) subjects in the age group ≥6 years to <12 years, and 11 (42.3%) subjects in the age group ≥12 years to <18 years.

Number analysed

The number of subjects included in each population analysis set is provided in Table 5.

Table 5. Subject Disposition (All Enrolled Subjects)

	Number (%) of subjects							
	Age group/Dose group							
	≥6M to <6Y		≥6Y to <12Y			≥12Y to <18Y		
Subject disposition	L	T (N=12)	L	H	T (N=19)	L	H	T (N=30)
Safety Analysis Set	6 (50.0)	6 (50.0)	9 (52.9)	5 (29.4)	14 (82.4)	11 (39.3)	15 (53.6)	26 (92.9)
PK Analysis Set [a]	0	0	9 (100)	5 (29.4)	14 (82.4)	10 (35.7)	13 (46.4)	23 (82.1)
Clinical Outcome Analysis Set	5 (41.7)	5 (41.7)	7 (41.2)	5 (29.4)	12 (70.6)	8 (28.6)	14 (50.0)	22 (78.6)
Acceptability Analysis Set	3 (25.0)	3 (25.0)	2 (11.8)	1 (5.9)	3 (17.6)	10 (35.7)	13 (46.4)	23 (82.1)

H=high-dose; L=low-dose; M=months; PK=pharmacokinetic; PPK=population pharmacokinetic(s); T=total; Y=years.
[a] Percentages were calculated out of the total number of subjects enrolled and assigned to a treatment.
Note: No subjects were enrolled and assigned to the high-dose treatment in the age group ≥6M to <6Y. The decision to not include any subjects in this age and dose group was approved by the European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA).
Source: Table 14.1.1 and Attachment 10 of naloxegol Pediatric Population Pharmacokinetic (PPK) Report.

Efficacy results

Primary Objective Results

Single-dose Pharmacokinetic Results

PK results are summarized from the naloxegol PPK final report dated 08 Jul 2021. Dipotassium ethylenediaminetetraacetic acid human plasma samples were analyzed for naloxegol concentration using a validated high pressure liquid chromatography-mass spectrometry/mass spectrometry method by Labcorp Early Development Laboratories Inc. The sample analysis data met acceptance criteria. See the Bioanalytical Report in Appendix 16.1.13 for more detail.

Non-compartmental analysis

The observed pediatric naloxegol Cmax and AUC0-∞ values are provided in Table 6.

Observed naloxegol AUC0-∞ values for the ≥12 years to <18 years pediatric age group at the 12.5 and 25 mg adult equivalent dose of naloxegol were comparable with the healthy adult values. However, naloxegol AUC0-∞values for the ≥6 years to <12 years pediatric age group at the 12.5 mg, and 25 mg adult equivalent doses of naloxegol were only 56% and 39% of the AUC0-∞ in adults, respectively. Lower naloxegol exposure for the ≥6 years to <12 year pediatric age group were due to lower doses of naloxegol given according to their age and body weight. The %CVs of naloxegol AUC0-∞ at the 12.5 mg adult equivalent dose were 48.3% and 90.9% for the 2 pediatric age groups, respectively.

Table 6. Observed Pediatric Naloxegol Cmax and AUC0-∞ Values

	Descriptive Statistics	12.5 mg equivalent dose			25 mg equivalent dose		
		Healthy Adults	≥12 Y to <18 Y	≥6 Y to <12 Y	Healthy Adults	≥12 Y to <18 Y	≥6 Y to <12 Y
$AUC_{0-\infty}$ (hr*ng/mL)	n	6	7	8	282	8	4
	Geo Mean	81.9	96.6	46.1	168.8	182	65.4
	%CV	38.3	48.3	90.9	52	53.5	67.8
	Min	60.7	43.9	18.0	48.6	99.6	34.7
	Max	151.7	157	146	749	451	142
	Ratio to Adult	**1.00**	**1.18**	**0.563**	**1.00**	**1.08**	**0.387**
C_{max} (ng/mL)	n	6	7	8	282	8	4
	Geo Mean	18.3	11.6	9.26	41.3	31.7	21.5
	%CV	27	40.6	95.0	51.3	81.4	60.9
	Min	10.2	6.67	3.48	7.4	10.7	11.5
	Max	25.7	21.9	30.2	180	110	37.9
	Ratio to Adult	**1.00**	**0.635**	**0.506**	**1.00**	**0.768**	**0.521**

%CV=geometric coefficient of variation; Geo Mean=geometric mean; Max=maximum; Min=minimum; Y=years.
Reference: Naloxegol PPK final report dated 08 Jul 2021

Rapporteur comment:

According to the protocol, the 12.5 mg equivalent doses in the various age groups were based on PBPK modeling and projected to provide similar exposure to that achieved in adults at 12.5mg. For the ≥6 years to <12 year pediatric age group, however, lower naloxegol exposure was observed compared to adults. The protocol further defines that for the higher dose (25 mg equivalent), the exposure observed in the previous (lower) dose will be taken into account. However, it seems like this was not the case as exposure for the ≥6 years to <12 year pediatric age group receiving the 25 mg equivalent dose is even lower (39% of AUC in adults). The MAH is asked to clarify.

In addition to AUC and Cmax of the actual dose, dose-normalized AUC and Cmax parameter estimates were derived based on the assumption of linear kinetics of naloxegol. Observed dose-normalized naloxegol AUC 0-∞ values for the 6 to < 12 and 12 to < 18 year pediatric age group were comparable to the healthy adult values (Table 7).

Table 7. Observed Pediatric Naloxegol Dose-normalized Cmax and AUC0-∞ Values Compared to Adults

	Descriptive Statistics	Normalized to 12.5 mg dose			Normalized to 25 mg dose		
		Healthy Adults	12 y to <18 y	6 y to <12 y	Healthy Adults	12 y to <18 y	6 y to <12 y
$AUC_{0-\infty}$ (hr*ng/mL)	N	6	7	8	282	8	4
	Geo Mean	81.9	121	140	168.8	209	169
	%CV	38.3	54.5	113	52	52.7	93.1
	Min	60.7	54.8	36.1	48.6	124	69.4
	Max	151.7	198	728	749	564	475
	Ratio to Adult	**1.00**	**1.48**	**1.71**	**1.00**	**1.24**	**1.00**
C_{max} (ng/mL)	n	6	7	8	282	8	4
	Geo Mean	18.3	14.6	28.2	41.3	36.5	55.6
	%CV	27	57.4	79.7	51.3	79.8	103
	Min	10.2	6.67	11.6	7.4	13.4	23.0
	Max	25.7	27.4	76.5	180	138	126
	Ratio to Adult	**1.00**	**0.797**	**1.54**	**1.00**	**0.883**	**1.35**

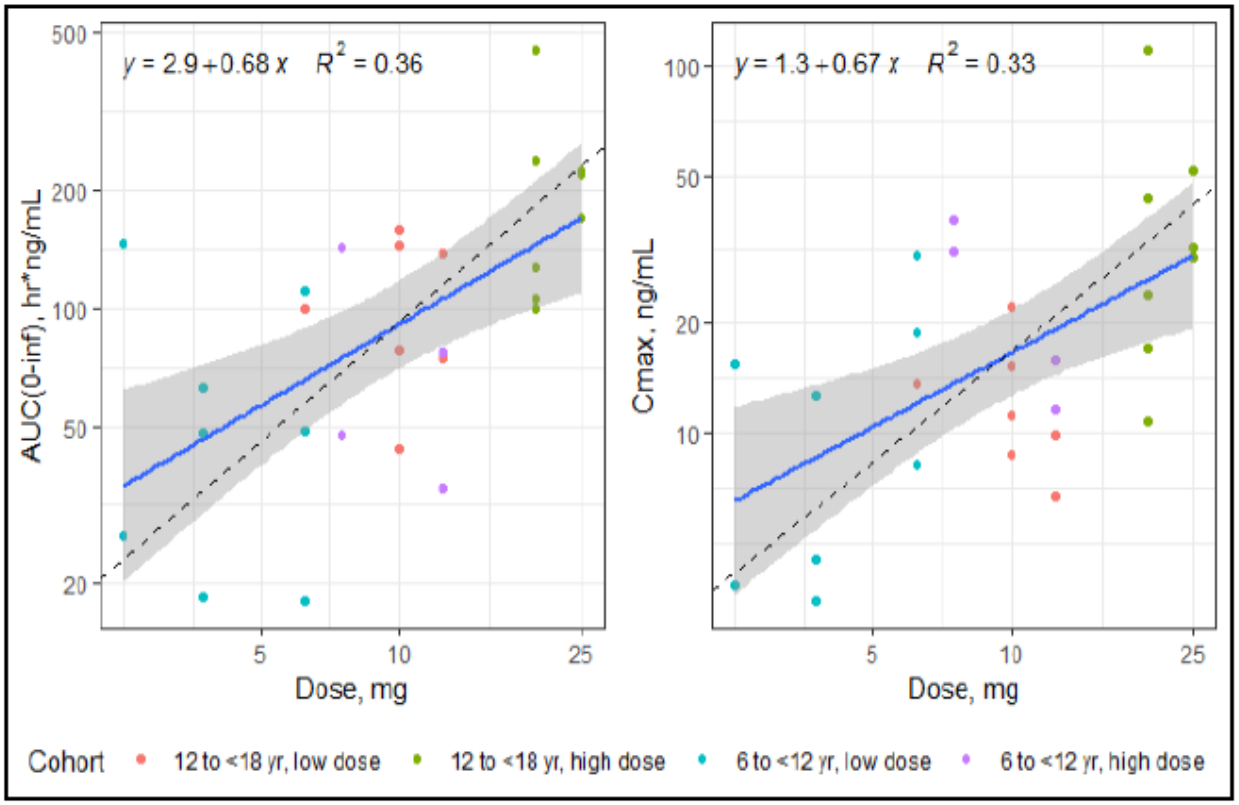
Key: Geo Mean= geometric mean; Max= maximum; Min= minimum; y= years; %CV= geometric coefficient of variation

Rapporteur comment:

Dose-normalized AUC and Cmax parameter estimates were in general higher for the pediatric subgroups compared to adults. Due to the small sample sizes and high variability, it is difficult to draw clear conclusions. Using a popPK approach (see further), exposure (6 to <12 years, and 12 to <18 years of age) normalized to a fixed dose seems comparable to adult exposure.

Dose proportionality of observed pediatric naloxegol Cmax and AUC0-∞ are provided in Figure 2. The reference line with slope of 1.00 coincide within the 90% confidence interval of the regression line (grey shaded area) for both Cmax and AUC0-∞. The slope of the regression line for Cmax and AUC0-∞ was not significantly different from 1.00, indicating a linear increase of exposure with increased dose of naloxegol.

Naloxegol exhibited dose-linear kinetics across the adult equivalent 12.5 and 25 mg doses in pediatric subjects receiving opioids from ≥6 years to <18 years of age. The geometric mean Cmax and AUC0-∞ values for pediatric subjects from ≥12 years to <18 years of age receiving the adult equivalent 12.5 mg dose was 11.6 ng/mL and 96.6 hr*ng/mL. The geometric mean Cmax and AUC values for pediatric subjects from ≥6 years to <12 years of age receiving the adult equivalent 12.5 mg dose was 9.26 ng/mL and 46.1 hr*ng/mL.



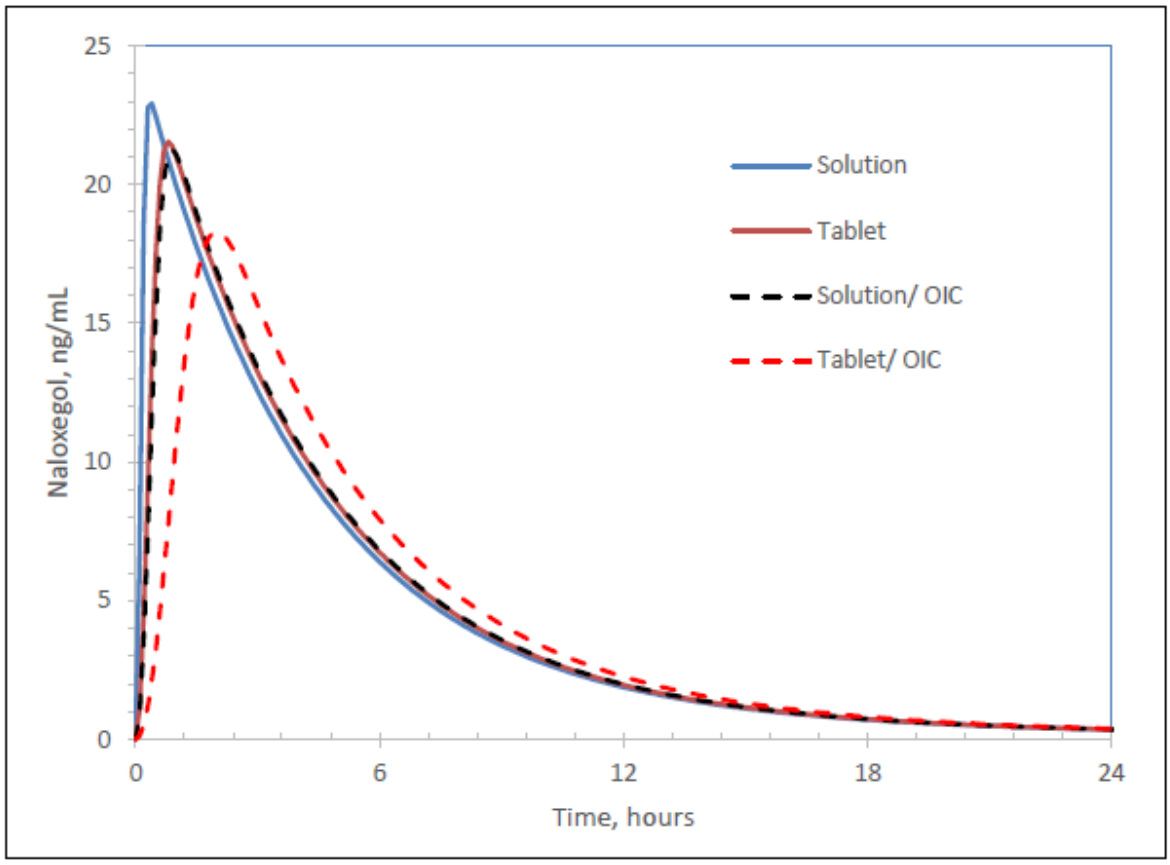
* Blue solid line is the linear regression of log-transformed naloxegol C_{max} and $AUC_{0-\infty}$ with respect to log-transformed doses of naloxegol. The grey shaded area is the 90% confidence interval of the regression line. The black dashed line is the reference line with slope of 1.00.

Reference: Naloxegol PPK final report dated 08 Jul 2021

Figure 2. Dose Proportionality of Observed Pediatric Naloxegol Cmax and AUC0-∞

Population PK analysis

Simulated PK profiles of naloxegol following a single-dose of 12.5 mg naloxegol oral solution or tablet in the typical healthy subjects or OIC subjects are provided in Figure 3. Naloxegol plasma PK profiles of oral administration of naloxegol solution or tablets in pediatrics and adults were best characterized by a 2-compartment PK model with Weibull-type absorption. Estimated CL/F of naloxegol was 109 L/hr and Vdss/F was 668 L (V1/F + V2/F). The between subject variability (BSV) of CL/F and V1/F was 50.7% and 63.7%, respectively. The median half-life of naloxegol in pediatric subjects receiving opioids (11.0 hour) was consistent to that in adults (10.6 hours). The rate of absorption of naloxegol oral tablets is ~2.55 times slower than that of naloxegol oral solution.

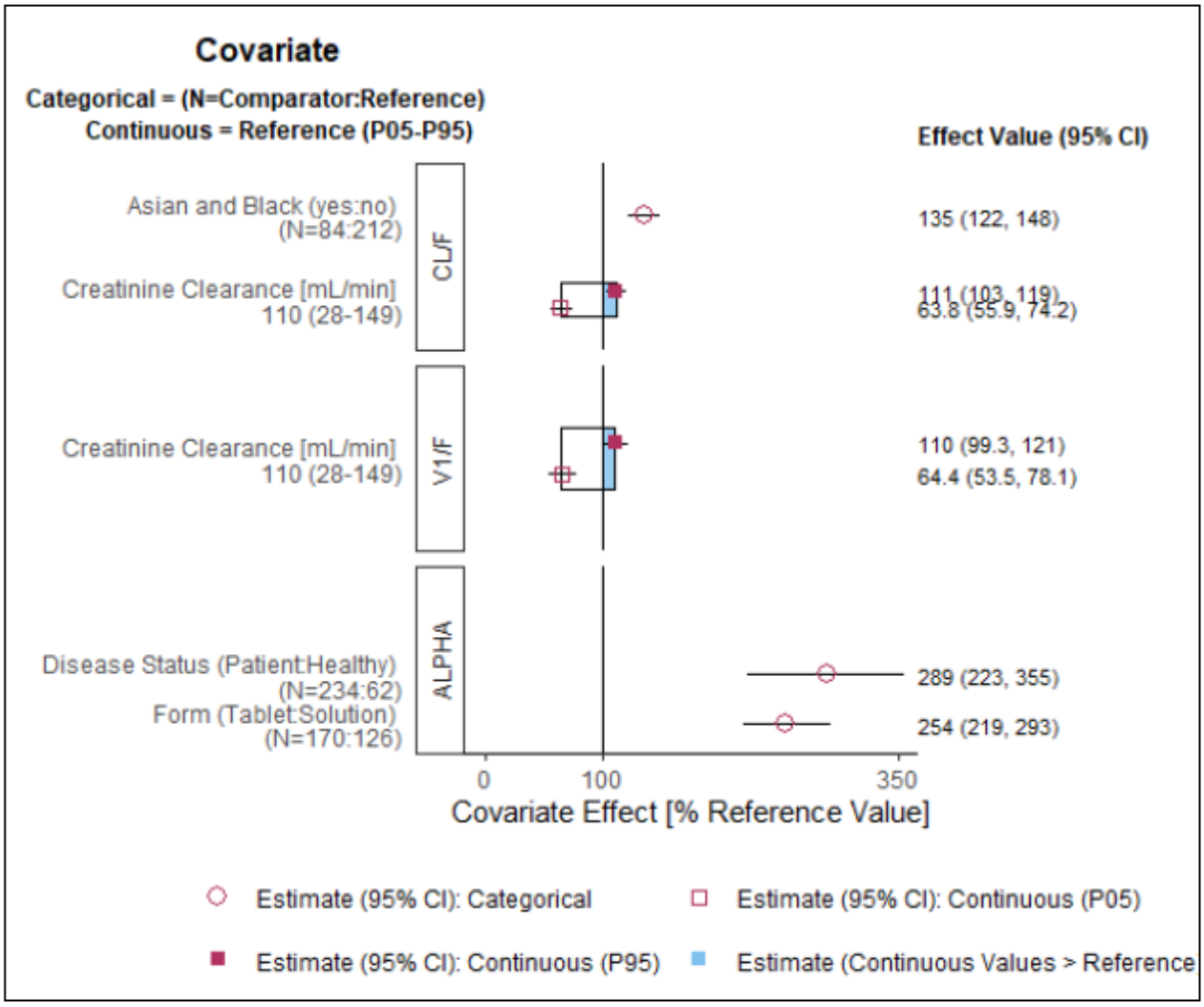


OIC=opioid-induced constipation; PK=pharmacokinetic.
Reference: Naloxegol PPK final report dated 08 Jul 2021

Figure 3. Simulated PK Profiles of Naloxegol Following a Single-Dose of 12.5 mg Naloxegol Oral Solution or Tablet in the Typical Healthy Subjects or OIC Patients

Covariate effects on CL/F, V1/F, and Alpha from the final PPK model are provided in Figure 4.

Key demographic parameters including age, body weight, race, hepatic impairment, renal impairment, disease state (OIC vs healthy subjects), etc. were evaluated as potential covariates. Body weight was not a significant covariate factor on the CL/F or V1/F of naloxegol. Creatinine clearance was a significant covariate factor on CL/F and V1/F of naloxegol. The CL/F of naloxegol in Asian and Black (n=84) was 35% higher than that of White. In addition, the rate of absorption of naloxegol in OIC adult patients and pediatric patients receiving opioid treatment was ~2.88 times slower than that of volunteer subjects. A forest plot was constructed to illustrate effects of the covariates meeting inclusion criteria on naloxegol parameters of CL/F, V1/F, and Alpha as shown below. The reference subject is an adult Caucasian subject with creatinine clearance of 110 mL/min/1.73 m2 and received oral administration of naloxegol solution. Parameter estimates in reference subjects are considered 100% (vertical solid line).

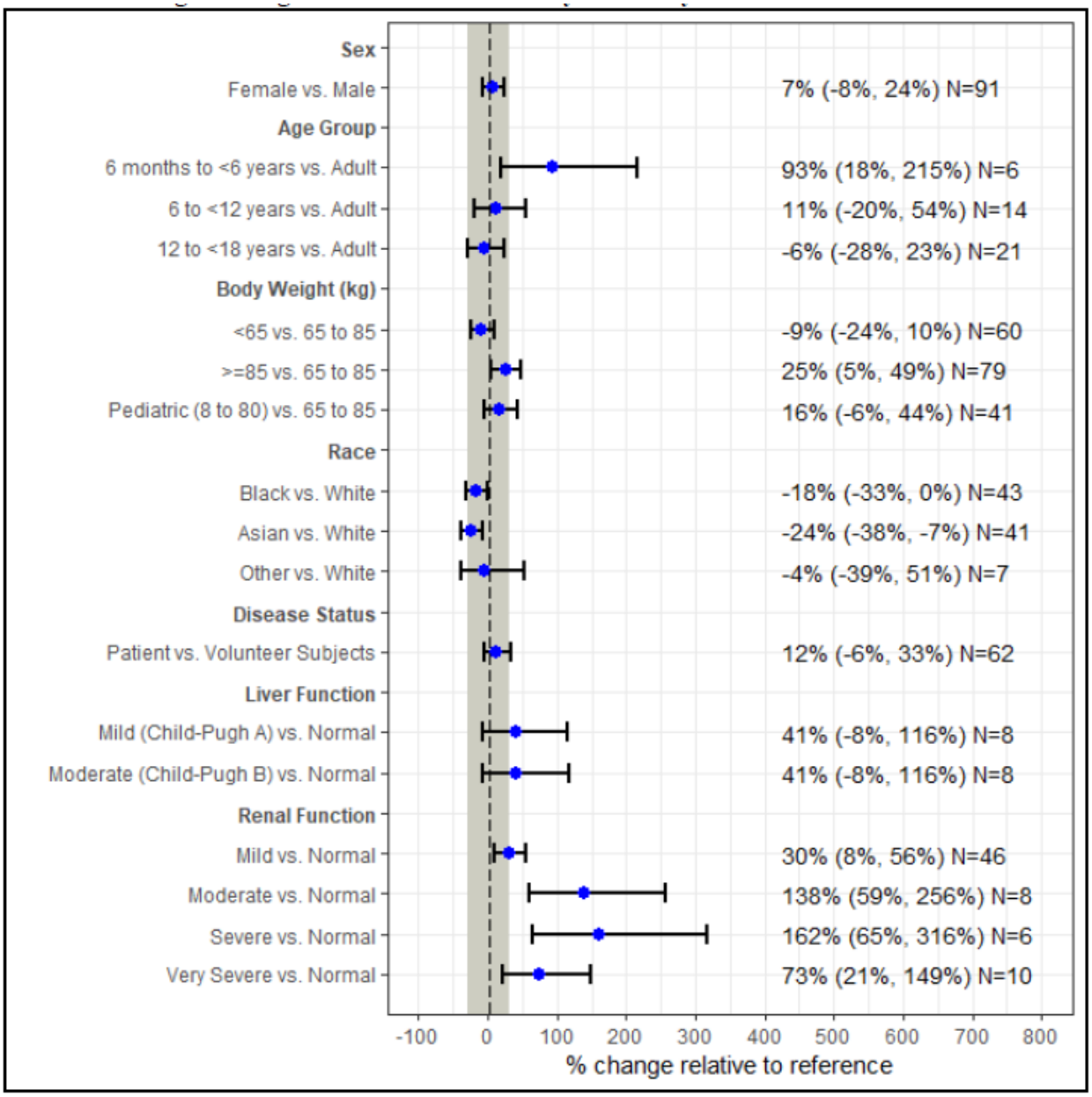


CI=confidence interval; CL/F=oral clearance; PPK=population pharmacokinetic; V1/F=volume of distribution during terminal phase.
Open/shaded area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate. Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented at the end of horizontal boxes by open/shaded squares (horizontal lines).
Reference: Naloxegol PPK final report dated 08 Jul 2021

Figure 4. Covariate Effects on CL/F, V1/F, and Alpha from the Final PPK Model

Forest plot of subgroup analyses on percent change relative to reference value of model-predicted steady-state naloxegol AUC values following a fixed 12.5 mg naloxegol oral dose once daily for 8 days are provided in Figure 5.

A forest plot was constructed to compare model-predicted steady-state naloxegol AUC in subgroups defined by specific intrinsic and extrinsic covariates as shown below. The difference in steady-state naloxegol AUC (ie, % change relative to reference) for each covariate are based on the forest plots subgroup analysis. Neither age nor body weight were identified as a significant covariate. However, exposure to naloxegol in ≥6 months to <6 years age group (N=6) was 93% greater for a fixed dose than that in adults, as this subgroup had lower Bayesian post-hoc estimates of CL (final PED report). Exposures to naloxegol in moderate, severe, and very severe renal impairment were predicted to be 138%, 162%, and 73% greater than that in normal subjects.



Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of 0. Numbers represent ratio, confidence interval, and number of subjects in the comparison groups. Grey shaded region represents ±30% from reference value. Note: Analyses assumed that all subjects received 12.5 mg once daily for 8 days. The number of subjects in the reference group: normal liver function (N=280); normal renal function (N=226); adults (N=255); male (N=205); volunteer subjects (N=234); White (N=205); body weight from 65 to 85 kg (N=116); three adult body weight subgroups are 42 to 65 kg, 65 to 85 kg, and 85 to 133.9 kg and pediatric body weight subgroup is 8 to 80 kg.
Reference: Naloxegol PPK final report dated 08 Jul 2021

Figure 5. Forest Plot of Subgroup Analyses on Percent Change Relative to Reference Value of Model-predicted Steady-state Naloxegol AUC Values Following a Fixed 12.5 mg Naloxegol Oral Dose Once Daily for 8 Days

Rapporteur comment:

A separate popPK report has been provided. In general, the popPK results are presented in line with CHMP/EWP/185990/06. An in-depth assessment of the model building, evaluation and simulations performed will be conducted at the time of submission of the planned type II variation.

Subgroup analysis based on simulations of naloxegol PK profiles for a 12.5 mg dose (once daily for 8 days) using empirical Bayesian estimates of individual PK parameters of the final popPK model, show a 93% higher exposure in subjects < 6 years old (n=6) compared to that in adults.

Monte Carlo simulations (see further) of the popPK model predict comparable exposure between the three pediatric age groups and adults following a fixed naloxegol dose.

PopPK predicted Naloxegol Exposures in Pediatric Subjects 6 Months to < 6 Years of Age

The geometric mean (% CV) AUC following single 12.5 mg dose administration to healthy adult volunteers was 81.9 (38.3%) hr*ng/mL and ranged from 60.7 to 151.7 hr*ng/mL. The corresponding value observed in pediatric subjects from 6 months to < 6 years of age (n= 6) receiving the 12,5 mg equivalent dose was 21.8 (86.7%) hr*ng/mL and ranged from 7.5 hr*ng/mL to 67.8 hr*ng/mL. The mean exposure to naloxegol in pediatric subjects was approximately 75% lower than that observed in adults. The geometric mean peak plasma concentration (Cmax) (%CV) in Cohort 5 subjects was 3.36 (61.9%) ng/mL, which was approximately 80% lower than that in adults receiving a 12.5 mg dose of naloxegol [18.3 (27.0%) ng/mL].

Rapporteur comment:

Since only sparse sampling was applied to pediatric subjects 6 Months to < 6 Years of Age, the PK parameters were estimated by popPK modeling. In line with observations for subjects aged 6 to <12 years, exposure after a single 12,5 mg equivalent dose was lower than that observed in adults.

Monte Carlo simulation in 3 pediatric age groups and adults

Model-predicted AUC0-∞ and Cmax of naloxegol in the three pediatric age groups, OIC adults and healthy adults were determined from Monte Carlo simulation of PK profiles after a single oral 25 mg dose of naloxegol based on the population PK parameters of the final PPK model of naloxegol. Model-predicted naloxegol AUC0-∞ of the three pediatric age groups was 106%, 112%, and 119% of the AUC0-∞ in OIC adults, respectively.

Table 8. Monte Carlo Simulations to Predicted Population Naloxegol Cmax and AUC0-∞ Values following a 25 mg Dose of Naloxegol

	Descriptive Statistics	OIC Adults	Healthy Adults	12 y to <18 y	6 y to <12 y	6 m to <6 y
$AUC_{0-\infty}$ (hr*ng/mL)	n	6218	6214	4072	2813	1343
	Median	208	204	220	234	248
	5th Pctl	91.0	89.3	96.2	105	107
	95th Pctl	485	467	515	554	551
	Ratio to Healthy Adults	**1.02**	**1.00**	**1.08**	**1.15**	**1.21**
	Ratio to OIC Adults	**1.00**	**0.981**	**1.06**	**1.12**	**1.19**
C_{max} (ng/mL)	n	6218	6214	4072	2813	1343
	Median	35.8	39.8	37.6	40.7	42.4
	5th Pctl	13.2	14.7	14.4	15.2	14.9
	95th Pctl	99.3	107	104	111	115
	Ratio to Healthy Adults	**0.900**	**1.00**	**0.947**	**1.02**	**1.07**
	Ratio to OIC Adults	**1.00**	**1.11**	**1.05**	**1.14**	**1.18**

Key: 5th Pctl = 5th percentile; 95th Pctl = 95th percentile; m= months; y= years;

Secondary Objective Results

Multiple-dose Pharmacokinetics Results

No multiple-dosing analysis was conducted.

Acceptability and Palatability Results

Palatability of Naloxegol Liquid Oral Formulation Measured by 5-Point Facial Hedonic VAS for Subjects ≥6 Years to <18 Years

The palatability of naloxegol liquid oral formulation as measured by the VAS with facial hedonic scale for subjects ≥6 years to <18 years in the safety analysis population is provided in Table 9.

At Visit 2, in the low-dose group, mean palatability score was 59.6 (SD=33.69) for 5 of 9 subjects in the age group ≥6 years to <12 years; and in the high-dose group, mean palatability score was 50.0 (SD=NA) for 1 of 15 subjects in the age group ≥12 years to <18 years.

At Visit 3, results were available only for 1 subject in the age group ≥6 years to <12 years in the low-dose group who scored 100.

Table 9. Summary of 5-Point Facial Hedonic VAS for Palatability by Age Group and Dose Group (Safety Analysis Set)

		Number (%) of subjects					
		Age group/Dose group					
		≥6Y to <12Y		≥12Y to <18Y		All subjects	
Time point	Statistic	L (N=9)	H (N=5)	L (N=11)	H (N=15)	L (N=20)	H (N=20)
Visit 2							
	n	5	0	0	1	5	1
	Mean	59.6			50	59.6	50
	SD	33.69			NA	33.69	NA
	Median	74			50	74	50
	Minimum	24			50	24	50
	Maximum	100			50	100	50
Visit 3	n	1	0	0	0	1	0
	Mean	100				100	
	SD	NA				NA	
	Median	100				100	
	Minimum	100				100	
	Maximum	100				100	

H=high-dose; IP=investigational product; L=low-dose; M=months; NA=not applicable; VAS=visual analogue scale; SD=standard deviation; Y=years.

All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Source: Table 14.3.1.2.

Palatability and Ability to Swallow Naloxegol Liquid Oral Formulation or Naloxegol Oral Tablets

The palatability and ability to swallow naloxegol liquid oral formulation or naloxegol oral tablets in the safety analysis population is provided in Table 10.

For oral solutions, on Day 1, 1 (50.0%) subject in the low-dose group and 1 (100%) subject in the high-dose group in the age group ≥6 years to <12 years swallowed without problem.

For oral solutions, on Day 1, 1 (100%) subject in the low-dose group in the age group ≥12 years to <18 years swallowed without problem.

For oral solutions, similar results were observed on Day 2; 1 (50.0%) subject in the low-dose group in the age group ≥6 years to <12 years swallowed without problem. Of the total subjects, 1 (16.7%) subject was able to swallow without problem.

For tablets, all subjects were able to swallow on Day 1, and all subjects with available data were able to swallow on Day 2.

Table 10. Summary of Palatability and Ability to Swallow by Age Group and Dose Group (Safety Analysis Set)

	Number (%) of subjects										
	Age group/Dose group										
	≥6M to <6Y	≥6y to <12Y		≥12Y to <18Y		≥12Y to <18Y		All Subjects		All Subjects	
Scheduled Day/ Assessment/ Response	Solution	Solution		Solution		Tablet		Solution		Tablet	
	L (N=3)	L (N=2)	H (N=1)	L (N=1)	H (N=0)	L (N=9)	H (N=13)	L (N=6)	H (N=1)	L (N=9)	H (N=13)
Day 1											
Palatability (oral solution)											
Swallowed without problem	0	1 (50.0)	1 (100)	1 (100)	0			2 (33.3)	1 (100)		
Some resistance but did swallow	0	0	0	0	0			0	0		
Spit out some/all medication	0	0	0	0	0			0	0		
Vomited up medication	0	0	0	0	0			0	0		
Ability to swallow (tablet)											
Able to swallow						9 (100)	13 (100)			9 (100)	13 (100)
Not able to swallow						0	0			0	0
Day 2											
Palatability (oral solution)											
Swallowed without problem	0	1 (50.0)	0	0	0			1 (16.7)	0		
Some resistance but did swallow	0	0	0	0	0			0	0		
Spit out some/all medication	0	0	0	0	0			0	0		
Vomited up medication	0	0	0	0	0			0	0		
Ability to swallow (tablet)											
Able to swallow						2 (22.2)	5 (38.5)			2 (22.2)	5 (38.5)
Not able to swallow						0	0			0	0

H=high-dose; IP=investigational product; L=low-dose; M=months; Y=years.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages are calculated out of the number of subjects in the Acceptability Analysis Set.
Source: Table 14.3.1.3.

Subjects' Behavior and Response to the Taste of Naloxegol Liquid Formulation in Subjects ≥6 Months to <6 Years of Age

No data were reported for any subject.

Rapporteur comment:

The study population is considered too limited to draw any meaningful conclusions on acceptability and palatability of the naloxegol formulations.

Clinical Outcome Results

Time (Hours) to First Postdose BM

The time in hours to the first postdose BM for subjects in the clinical outcome analysis population is provided in Table 11. The Kaplan-Meier estimates of time to first postdose BM for subjects in the Safety Analysis Set is provided in Figure 6.

First postdose BMs were observed in 4 (80.0%) subjects in the low-dose group in the age group ≥6 months to <6 years, 7 (100%) subjects in the low-dose group and 5 (100%) subjects in the high-dose

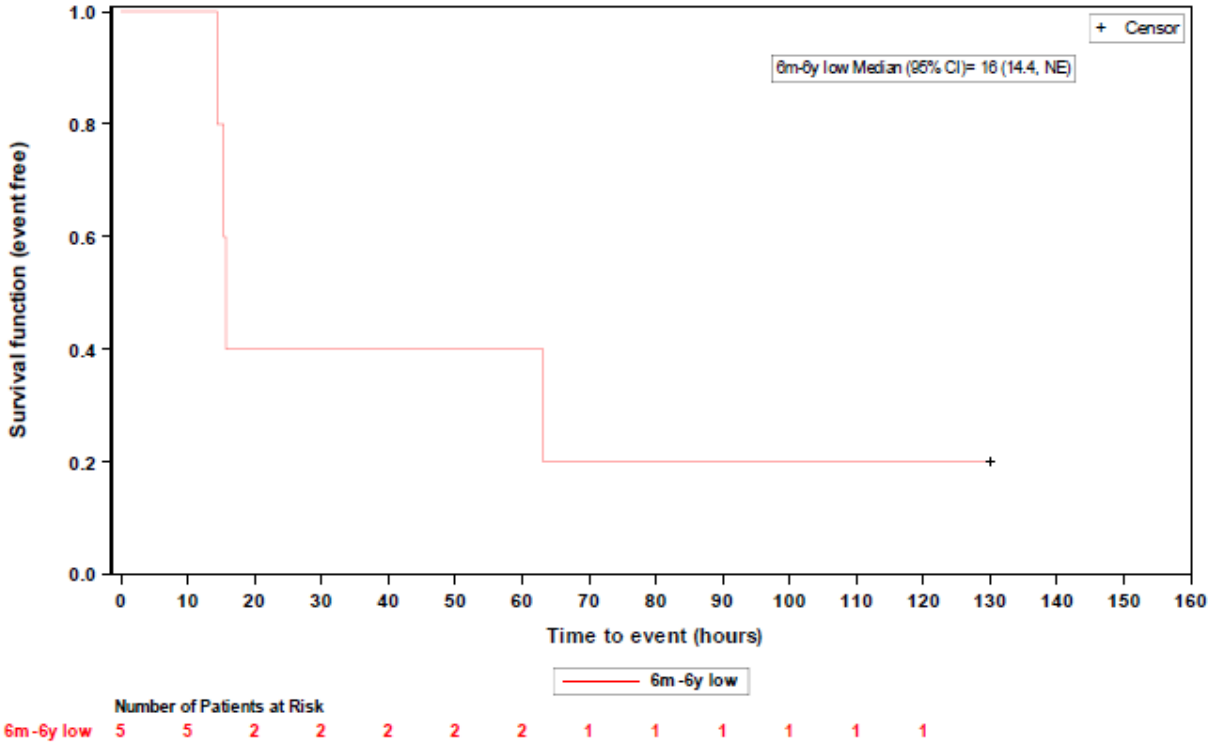
group in the age group ≥6 years to <12 years, and 6 (75.0%) subjects in the low-dose group and 9 (64.3%) subjects in the high-dose group in the age group ≥12 years to <18 years.

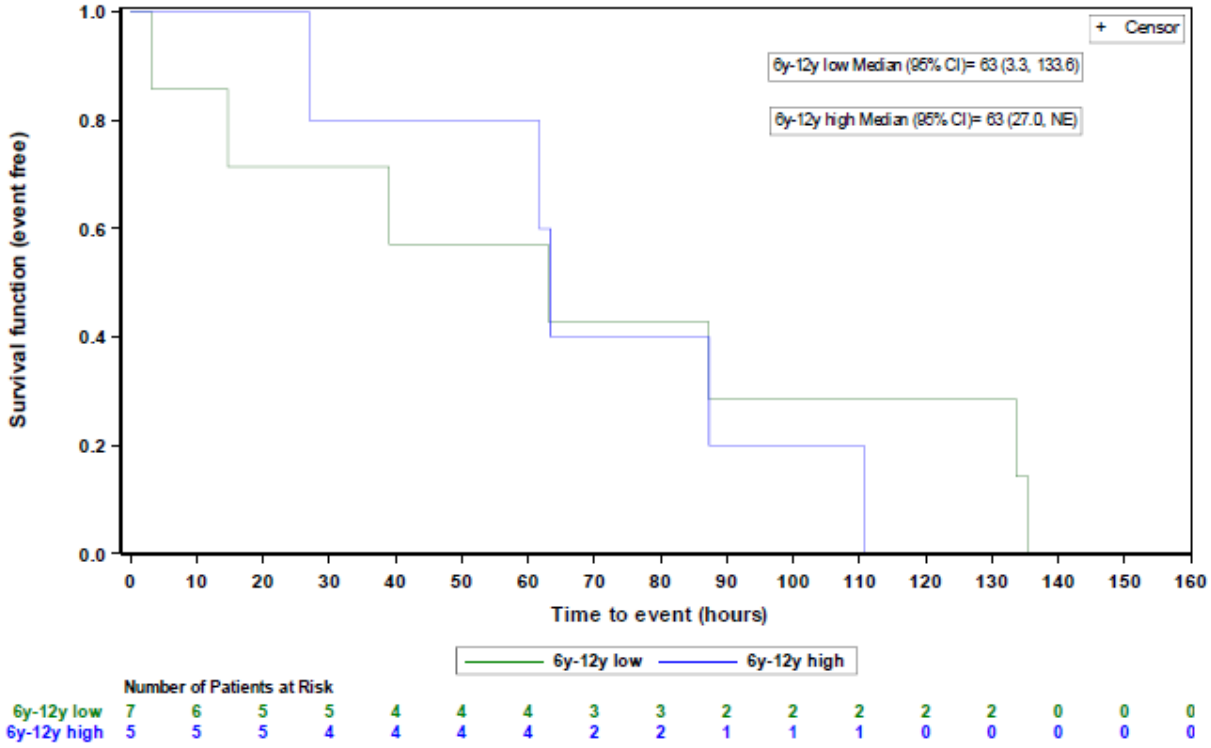
The median time (95% CI) to first BMs was 16 hours in the low-dose group in the age group ≥6 months to <6 years, 63 hours for both low-dose and high-dose group in the age group ≥6 years to <12 years, and 110 hours and 103 hours for low-dose and high-dose respectively, in the age group ≥12 years to <18 years.

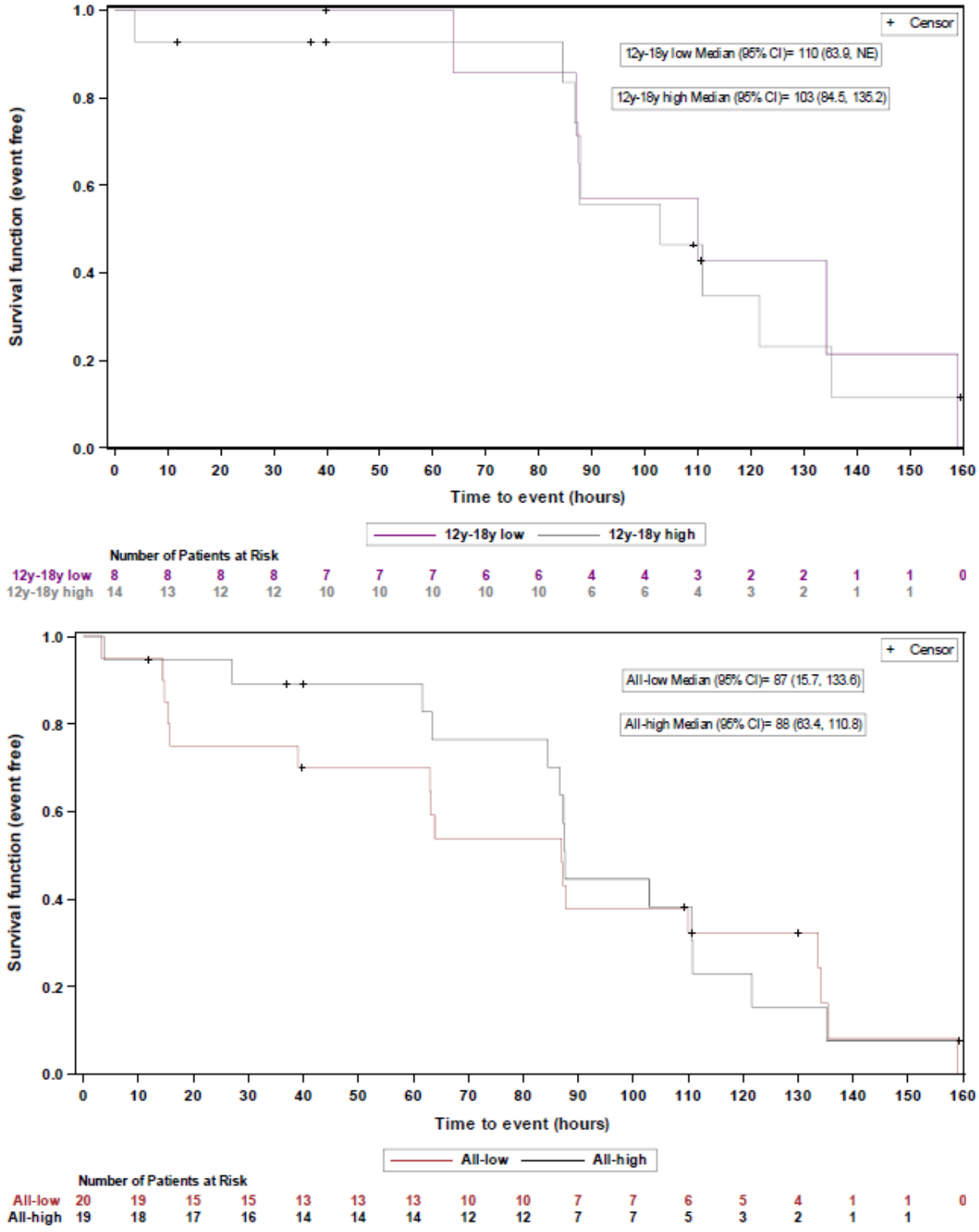
Table 11. Summary of Time (Hours) to First Postdose BM by Age Group and Dose Group (Clinical Outcome Analysis Set)

	Number (%) of subjects						
	Age group/Dose group						
	≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
Kaplan-Meier Statistic	L (N=5)	L (N=7)	H (N=5)	L (N=8)	H (N=14)	L (N=20)	H (N=19)
Subjects with first post dose BM	4 (80.0)	7 (100)	5 (100)	6 (75.0)	9 (64.3)	17 (85.0)	14 (73.7)
Censored subjects	1 (20.0)	0	0	2 (25.0)	5 (35.7)	3 (15.0)	5 (26.3)
25th percentile (95% CI)	15 (14.4, 63.2)	5 (3.3, 63.0)	62 (27.0, 87.3)	87 (63.9, 110.0)	87 (3.8, 102.9)	27 (3.3, 63.9)	84 (3.8, 87.5)
Median (95% CI)	16 (14.4, NE)	63 (3.3, 133.6)	63 (27.0, NE)	110 (63.9, NE)	103 (84.5, 135.2)	87 (15.7, 133.6)	88 (63.4, 110.8)
75th percentile (95% CI)	63 (14.4, NE)	134 (39.0, NE)	87 (27.0, NE)	134 (87.8, NE)	122 (87.6, NE)	134 (87.2, NE)	111 (87.6, NE)

BM=bowel movement; H=high-dose; IP=investigational product; L=low-dose; M=months; NE=not evaluable; Y=years.
Note: The denominator of percentage calculations was the number of subjects with first post-BM.
Note: Overflow diarrhea (watery stools) can occur in severe cases of constipation and was not considered as a formal BM.
Note: Percentiles were calculated using Kaplan-Meier estimation, where the event was the first postdose BM. For those subjects with a postdose BM while on study, the time to first postdose BM (in hours) was calculated as: Time of first BM after first dose – time of first dose.
Note: Subjects who did not have a postdose BM were censored at the time of study discontinuation.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Clinical Outcome Analysis Set.
Source: Table 14.2.1.1.


Censor
6m-6y low Median (95% CI)= 16 (14.4, NE)
Survival function (event free)
1.0
0.8
0.6
0.4
0.2
0.0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
Time to event (hours)
6m -6y low
Number of Patients at Risk
6m -6y low 5 5 2 2 2 2 2 1 1 1 1 1 1


Censor
6y-12y low Median (95% CI)= 63 (3.3, 133.6)
6y-12y high Median (95% CI)= 63 (27.0, NE)
Survival function (event free)
1.0
0.8
0.6
0.4
0.2
0.0
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160
Time to event (hours)
6y-12y low
6y-12y high
Number of Patients at Risk
6y-12y low 7 6 5 5 4 4 4 3 3 2 2 2 2 2 0 0 0
6y-12y high 5 5 5 4 4 4 4 2 2 1 1 1 0 0 0 0 0



BM=bowel movement; CI=confidence interval; NE=nonevaluable.

Figure 6. Kaplan-Meier Estimates of Time to First Postdose BM (Safety Analysis Set)

Number of Days with a BM Each Week and Percentage of Days with a BM During Treatment

The number of days with BM each week and the percentage of days with a BM during treatment for subjects in the clinical outcome analysis population is provided in Table 12.

The median number of days with a BM per week was 7 days for subjects in the age group ≥6 months to <6 years, 4 and 6 days for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years, and 2.04 and 1.28 days for subjects in the low-dose group and high-dose group, respectively, in the age group ≥12 years to <18 years.

The median percentages of days with BM during treatment was 100% of days for subjects in the age group ≥6 months to <6 years, 57.14% and 85.71% of days for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years, and 29.17% and 18.33% of days for subjects in the low-dose and high-dose groups, respectively, in the age group ≥12 years to <18 years.

Table 12. Summary of BM by Age Group and Dose Group (Clinical Outcome Analysis Set)

		Number (%) of subjects						
		Age group/Dose group						
		≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
	Statistic	L (N=5)	L (N=7)	H (N=5)	L (N=8)	H (N=14)	L (N=20)	H (N=19)
Number of days with BM per week [a]	n	5	7	5	8	14	20	19
	N	5	7	5	8	14	20	19
	Mean	5	4.12	5.31	2.18	1.81	3.57	2.73
	SD	3.082	2.155	1.997	1.835	2.146	2.484	2.594
	Median	7	4	6	2.04	1.28	3.75	2
	Minimum	0	1	2	0	0	0	0
	Maximum	7	7	7	4.7	7	7	7
Percentage of days with BM during treatment [b]	N	5	7	5	8	14	20	19
	Mean	71.43	58.92	75.89	31.13	25.8	50.93	38.98
	SD	44.032	30.786	28.53	26.212	30.656	35.492	37.057
	Median	100	57.14	85.71	29.17	18.33	53.57	28.57
	Minimum	0	14.3	28.6	0	0	0	0
	Maximum	100	100	100	66.7	100	100	100

BM=bowel movement; H=high-dose; IP=investigational product; L=low-dose; M=months; SD=standard deviation; Y=years.
Note: Overflow diarrhea (watery stools) can occur in severe cases of constipation and were not considered as a formal BM.
[a] = (total number of days with BMs during the period of interest/number of days in the period of interest) x 7
[b] = (the number of days with BM /the total number of days on treatment) x 100
Note: The period of interest was the number of days during the treatment period in which the subject records an entry in diary data.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Clinical Outcome Analysis Set.
Source: Table 14.2.1.2.

Number of Days with Laxative Use Each Week, and Percentage of Days with Laxative Use During Treatment

Number of days with laxative use each week and the percentage of days with laxative use during treatment for subjects in the clinical outcome analysis population is provided in Table 13.

The median number of days with laxative use per week was 0 and 3 days for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years, and 4.45 and 1.46 days for subjects in the low-dose and high-dose groups, respectively, in the age group ≥12 years to <18 years. No subjects used any laxative in the low-dose group in the age group ≥6 months to <6 years.

The median percentages of days with laxative use during treatment was 0% and 42.86% for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years, and 63.64% and 20.83% for subjects in the low-dose and high-dose groups, respectively, in the age group ≥12 years to <18 years.

Table 13. Summary of Use of Laxatives by Age Group and Dose Group (Clinical Outcome Analysis Set)

		Number (%) of subjects						
		Age group/Dose group						
		≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
	Statistic	L (N=5)	L (N=7)	H (N=5)	L (N=8)	H (N=14)	L (N=20)	H (N=19)
Number of days with laxative use per week [a]	n	5	7	5	8	14	20	19
	Mean	0	0.71	2.8	3.87	2.49	1.8	2.57
	SD	0	1.496	2.95	3.397	2.672	2.838	2.667
	Median	0	0	3	4.45	1.46	0	1.75
	Minimum	0	0	0	0	0	0	0
	Maximum	0	4	7	7	7	7	7
Percentage of days with laxative use during treatment [b]	n	5	7	5	8	14	20	19
	Mean	0	10.2	40	55.33	35.56	25.7	36.73
	SD	0	21.372	42.137	48.532	38.179	40.546	38.096
	Median	0	0	42.86	63.64	20.83	0	25
	Minimum	0	0	0	0	0	0	0
	Maximum	0	57.1	100	100	100	100	100

H=high-dose; IP=investigational product; L=low-dose; M=months; SD=standard deviation; Y=years.
[a] (sum of number of days with laxatives use during the period of interest/number of days in the period of interest) x 7
[b] (the number of days with laxative use/the total number of days on treatment) x 100
Note: The period of interest was the number of days during the treatment period in which the subject recorded an entry in diary data.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Clinical Outcome Analysis Set.
Source: Table 14.2.1.3.

Rapporteur comment:

The number of days with a BM appears very low in the low and high dose groups in the age category ≥12 years to <18 year. Because of the limited number of patients included, the clinical relevance of this observation is uncertain.

Pharmacokinetic Results Summary

The objective of the current study was to evaluate the naloxegol exposures of adult equivalent 12.5 and 25 mg doses in pediatric subjects receiving opioids from ≥6 months to <18 years of age. Naloxegol AUC and Cmax values for subject from ≥6 years to <18 years of age were derived by noncompartmental analysis (NCA). A PPK model was developed to derive the AUC and Cmax values for pediatric subjects 6 months to <18 years of age.

· The noncompartmental PK analysis of the 12.5 and 25 mg adult equivalent doses in adolescent subjects (≥12 to <18 years of age) revealed comparable naloxegol exposures compared to adult subjects. The AUC values for pediatric subjects ≥6 years to <12 years of age was approximately 45% lower for the 12.5 mg (46.1 hr*ng/mL) and approximately 60% lower for the 25 mg (65.4 hr*ng/mL) adult equivalent exposures. These findings are expected, since body weight was not identified as a significant covariate in the PPK analysis, and the dose adjustment by body weight is not needed in pediatric subjects.

• Body weight of the subjects in this analysis ranged from 8.0 to 133.9 kg. However, CL/F and V1/F of naloxegol were found to be independent on body weight in this analysis. Based on this, it would suggest that allometric scaling of CL/F and V1/F is not needed to extrapolate the exposure of naloxegol pediatric subject ≥6 years to <18 years of age.

• Although subgroup analysis indicated that exposure to naloxegol in subjects with mild/moderate hepatic impairment was 41% higher than that in subjects with normal hepatic function, impaired hepatic function was not found to be a significant factor on CL/F or V1/F of naloxegol. The BSV of CL/F

and V1/F of naloxegol in the base model was 54.5% and 66.3%, respectively. After covariate model building, the BSV of CL/F and V1/F of naloxegol in the final model was 50.7% and 63.7%, respectively. This suggested that the covariate factors described approximately 4% of the variability. The BSV at this level could result in difficulty to detect significance and thus not identify impaired hepatic function, and body weight on CL/F or V1/F of naloxegol.

• Strong CYP3A4 inducer, moderate CYP3A4 inhibitor, P-gp inhibitor, and P-gp inducer were found to be significant factors on CL/F of naloxegol in the previous PPK analysis of naloxegol in volunteer adult subjects and OIC adult patients. These factors were not available in the pediatric patients and were not investigated in this PPK analysis. However, the estimated BSV of CL/F of naloxegol was 48% in the previous PPK analysis, which is only 3% less than the estimate in this PPK analysis.

Efficacy Results Summary

· Mean palatability score of naloxegol liquid oral formulation at Visit 2 was reported as 59.6 for subjects in the age group ≥6 years to <12 years, and 50.0 in the age group ≥12 years to <18 years. At Visit 3, results were available for only 1 subject, age group ≥6 years to <12 years, who scored 100.

· For acceptability, all subjects in the age group ≥12 years to <18 years 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 (who also swallowed tablets). The number of subjects with the ability to swallow the oral solution was too small to draw conclusions (1 [16.7%] subject).

· The median time (95% CI) to first BM was 16 hours in the low-dose group in the ≥6 months to <6 years age group, 63 hours for both the low-dose and high-dose group in the ≥6 years to <12 years age group, 110 hours and 103 hours for low-dose and high-dose groups, respectively, in the ≥12 years to <18 years age group.

· The median number of days with a BM per week was 7 days for subjects in the age group ≥6 months to <6 years, 4 days for subjects in the low-dose group and 6 days in the high-dose group in the age group ≥6 years to <12 years, and 2.04 days for subjects in the low-dose group and 1.28 days in the high-dose group in the age group ≥12 years to <18 years.

· The median number of days with laxative use per week was 0 days for subjects in the low-dose group and 3 days in the high-dose group in the age group ≥6 years to <12 years, and 4.45 days for subjects in the low-dose group and 1.46 days in the high-dose group in the age group ≥12 years to <18 years. No subjects used any laxative in the low-dose group in the age group ≥6 months to <6 years.

Safety results

Extent of Exposure

Exposure data are provided in Table 14.

Oral Solution:

The mean duration on study drug was 1.5 days for subjects in the low-dose group in the age group ≥6 months to <6 years, 21.3 days and 2.2 days for subject in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years.

The median duration on study drug was 1.5 days for subjects in the low-dose group in the age group ≥6 months to <6 years, 1 day each, for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years.

The median duration on study drug was 2 days and 1 day each for subjects in the low-dose and high-dose groups, in the age group ≥12 years to <18 years. The mean duration on study drug was also 2 days and 1 day each for subjects in the low-dose and high-dose groups, in the age group ≥12 years to <18 years.

Among the subjects from all age groups, the mean duration on study drug was 12.1 days and 2 days in the low-dose and high-dose groups, respectively.

The median duration for all the subjects on study drug was 1 day each for both low-dose (range: 1 to 181 days) and high-dose (range: 1 to 5 days) groups.

The mean of total study drug consumed was 1.81 g for subjects in the low-dose group in the age group ≥6 months to <6 years.

The median of total study drug consumed was 2 g for subjects in the low-dose group in the age group ≥6 months to <6 years.

The mean of total study drug consumed was 48.84 g and 9.6 g for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years.

The median of total study drug consumed was 1.69 g and 4.09 g for subjects in the low-dose and high-dose groups, respectively, in the age group ≥6 years to <12 years.

The median of total study drug consumed was 7.75 g and 2.72 g in the low-dose and high-dose groups in the age group ≥12 years to <18 years, respectively. The mean of total study drug consumed was also same with 7.75 g and 2.72 g in the low-dose and high-dose groups in the age group ≥12 years to <18 years, respectively.

Among the subjects from all age groups, the mean of total study drug consumed was 27.41 g and 8.45 g for subjects in the low-dose and high-dose groups, respectively.

The median of total study drug consumed for all subjects administered with oral solution was 2.1 g (range: 0.6 to 417 g) for subject in the low-dose groups and 3.61 g (range: 2.7 to 27.1 g) for subjects in the high-dose groups.

Tablet:

The mean duration on study drug was 2.2 days and 14.3 days in the low-dose and high-dose groups, respectively, in the age group ≥12 years to <18 years.

The median duration on study drug for all subjects was 2 days for both low-dose (range: 1 to 4 days) and high-dose groups (range: 1 to 174 days).

The mean of total study drug consumed was 4.33 tablets and 18.71 tablets in the low-dose and high-dose groups, respectively, in the age group ≥12 years to <18 years.

Among the subjects from all age groups, the median of total study drug consumed was 4 tablets (range: 1 to 8 tablets) for subjects in the low-dose groups and 6 tablets (range: 1 to 173 tablets) for subjects in the high-dose groups.

Table 14. Summary of Study Drug Administration and Accountability by Age Group and Dose Group (Safety Analysis Set)

		Age group/Dose group										
		≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y				All subjects		All subjects	
		Oral solution	Oral solution		Oral solution		Tablet		Oral solution		Tablet	
		L (N=6)	L (N=9)	H (N=5)	L (N=2)	H (N=1)	L (N=9)	H (N=14)	L (N=17)	H (N=6)	L (N=9)	H (N=14)
Duration on study drug (Days)	n	6	9	5	2	1	9	14	17	6	9	14
	Mean	1.5	21.3	2.2	2	1	2.2	14.3	12.1	2	2.2	14.3
	SD	0.55	59.88	1.79	1.41	NA	1.09	45.98	43.54	1.67	1.09	45.98
	Median	1.5	1	1	2	1	2	2	1	1	2	2
	Minimum	1	1	1	1	1	1	1	1	1	1	1
	Maximum	2	181	5	3	1	4	174	181	5	4	174
Total study drug consumed [a]	n	6	9	5	2	1	9	14	17	6	9	14
	Mean	1.81	48.84	9.6	7.75	2.72	4.33	18.71	27.41	8.45	4.33	18.71
	SD	0.686	138.066	10.301	2.553	NA	2.345	44.674	100.42	9.632	2.345	44.674
	Median	2	1.69	4.09	7.75	2.72	4	6	2.1	3.61	4	6
	Minimum	0.6	1	2.9	5.9	2.7	1	1	0.6	2.7	1	1
	Maximum	2.5	417	27.1	9.6	2.7	8	173	417	27.1	8	173
Compliance (%) [b]	n	6	9	5	2	1	9	14	17	6	9	14
	Mean	91.5	107.33	103.62	123.07	108.8	100	102.19	103.59	104.49	100	102.19
	SD	31.887	9.875	23.183	6.032	NA	0	6.778	21.883	20.843	0	6.778
	Median	103.5	107.33	104.33	123.07	108.8	100	100	107.33	106.37	100	100
	Minimum	47.5	92.1	71.7	118.8	108.8	100	99.4	47.5	71.7	100	99.4
	Maximum	124.5	126.8	136.3	127.3	108.8	100	125	127.3	136.3	100	125
Compliance categories [b]												
<80%	n (%)	2 (33.3)	0	1 (20.0)	0	0	0	0	2 (11.8)	1 (16.7)	0	0
80% - 100%	n (%)	0	2 (22.2)	1 (20.0)	0	0	9 (100)	12 (85.7)	2 (11.8)	1 (16.7)	9 (100)	12 (85.7)
100% - 125%	n (%)	4 (66.7)	6 (66.7)	2 (40.0)	1 (50.0)	1 (100)	0	2 (14.3)	11 (64.7)	3 (50.0)	0	2 (14.3)
>125%	n (%)	0	1 (11.1)	1 (20.0)	1 (50.0)	0	0	0	2 (11.8)	1 (16.7)	0	0

H=high-dose; IP=investigational product; L=low-dose; M=months; NA=not applicable; SD=standard deviation; Y=years.
[a] Total IP consumed was calculated differently depending on the formulation:
For tablets: (total number of study drug tablets dispensed – total number of study drug tablets returned)
For solution (g): (total weight of study drug liquid dispensed (g) – total weight of study drug liquid returned [g])
[b] IP compliance (%) was calculated differently depending on the formulation:
For tablets: (total IP consumed/total number of expected study drug tablets)
For solution: (total IP consumed [g]/total weight of expected study drug liquid [g])
Total expected product consumed was calculated differently depending on the formulation:
For tablets: (planned study drug daily number of tablets x overall treatment duration)
For solution (g): (planned study drug daily dose (mg) x overall treatment duration/1000)
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Safety Analysis Set.
Source: Table 14.3.1.1.

Overdose Report

One subject in the high-dose group in the age group ≥12 years to <18 years was overdosed during the study due to weighing error. The subject was overdosed on Study Day 1 with a total dose of 25 mg and overdosing was not associated with AE.

Adverse Events

Brief Summary of Adverse Events

A summary of AE data, including pre-treatment AEs, treatment-emergent AEs (TEAEs) relating to study therapy, TEAEs with severe intensity, other treatment-emergent significant AEs (OAEs), treatment-emergent SAEs, TEAEs leading to discontinuation, and deaths for the safety population is provided in Table 15.

Overall, among all subjects, 21 (80.8%) subjects in the low-dose group and 14 (70.0%) subjects in the high-dose group reported any AEs. Of these, 7 (26.9%) subjects in the low-dose group and 9 (45.0%) subjects in the high-dose group reported any pre-treatment AEs.

Overall, among all subjects, 19 (73.1%) subjects in the low-dose group and 13 (65.0%) subjects in the high-dose group reported any TEAEs. Of these, a total of 7 (26.9%) subjects in the low-dose group and 2 (10.0%) subjects in the high-dose group reported TEAEs related to the study drug. One subject each, in the low-dose group (3.8%) and high-dose group (5.0%), reported TEAEs that were severe in intensity. One (5.0%) subject, in the high-dose group, reported a TEAE leading to study discontinuation; and 1 (3.8%) subject, in the low-dose group reported any SAEs during the study.

Table 15. Overview of Adverse Events (Safety Analysis Set)

	Number (%) of subjects						
	Age group/Dose group						
	≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
Adverse event category	L (N=6)	L (N=9)	H (N=5)	L (N=11)	H (N=15)	L (N=26)	H (N=20)
Any AE	4 (66.7)	6 (66.7)	4 (80.0)	11 (100)	10 (66.7)	21 (80.8)	14 (70.0)
Any pre-treatment AE	2 (33.3)	2 (22.2)	3 (60.0)	3 (27.3)	6 (40.0)	7 (26.9)	9 (45.0)
Any TEAE	3 (50.0)	5 (55.6)	4 (80.0)	11 (100)	9 (60.0)	19 (73.1)	13 (65.0)
Any TEAE related to study therapy	1 (16.7)	0	0	6 (54.5)	2 (13.3)	7 (26.9)	2 (10.0)
Any TEAE with severe intensity	1 (16.7)	0	1 (20.0)	0	0	1 (3.8)	1 (5.0)
Any TEAE leading to discontinuation of study therapy	0	0	0	0	1 (6.7)	0	1 (5.0)
Any treatment-emergent SAE (including events with outcome = death)	1 (16.7)	0	0	0	0	1 (3.8)	0
Any AE with outcome = death	0	0	0	0	0	0	0
Any OAE	0	0	0	0	0	0	0

AE=adverse event; H=high-dose; IP=investigational product; L=low-dose; M=months; OAE=other treatment-emergent significant adverse event; SAE=serious adverse event; SAP=Statistical Analysis Plan; TEAE=treatment-emergent adverse event; Y=years.
Note: Any AE includes pre-treatment AEs, pre-treatment AEs were defined as events occurring prior to first dose of study medication.
Note: Treatment-emergence is defined in SAP Section 4.8.2.
Note: Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Safety Analysis Set.
Source: Table 14.3.2.1.

Analysis of Treatment-emergent Adverse Events

Treatment-emergent Adverse Events by System Organ Class and Preferred Term

The most frequent TEAEs (≥2% of all subjects) by SOC and preferred term (PT) in the safety population are provided in Table 16.

Note: Days since last dose is derived as the number of days since the first dose of either tablet or liquid formulation at the time of onset of the adverse event, as only first and final doses of IP were collected.

The most commonly reported TEAEs by SOC among all subjects were gastrointestinal disorder (9 [34.6%] subjects in low-dose and 10 [50%] subjects in high-dose), followed by general disorder and administration site conditions (3 [11.5%] subjects in low-dose and 5 [25.0%] subjects in high-dose), and investigations (5 [19.2%] subjects in low-dose and 3 [15.0%] subjects in high-dose).

The most frequently reported TEAEs by PT among all subjects were nausea (5 [19.2%] subjects in low-dose and 5 [25.0%] subjects in high-dose), followed by vomiting (5 [19.2%] subjects in low-dose and 3 [15.0%] subjects in high-dose), and constipation (3 [11.5%] subjects in low-dose and 4 [20.0%] subjects in high-dose).

Table 16. Summary of the Most Common (Reported in ≥2% of All Subjects) Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

	Number (%) of subjects						
	Age group/Dose group						
	≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
System organ class/ Preferred term	L (N=6)	L (N=9)	H (N=5)	L (N=11)	H (N=15)	L (N=26)	H (N=20)
Subjects with any TEAE	3 (50.0)	5 (55.6)	4 (80.0)	11 (100)	9 (60.0)	19 (73.1)	13 (65.0)
Blood and lymphatic system disorder	0	0	2 (18.2)	1 (6.7)	2 (7.7)	2 (10.0)	1 (20.0)
Anaemia	0	0	2 (18.2)	1 (6.7)	2 (7.7)	2 (10.0)	1 (20.0)
Gastrointestinal disorder	1 (16.7)	3 (33.3)	2 (40.0)	5 (45.5)	8 (53.3)	9 (34.6)	10 (50.0)
Nausea	0	2 (22.2)	1 (20.0)	3 (27.3)	4 (26.7)	5 (19.2)	5 (25.0)
Vomiting	1 (16.7)	1 (11.1)	0	4 (36.4)	3 (20.0)	5 (19.2)	3 (15.0)
Constipation	1 (16.7)	0	1 (20.0)	2 (18.2)	3 (20.0)	3 (11.5)	4 (20.0)
Abdominal pain	0	1 (11.1)	0	1 (9.1)	2 (13.3)	2 (7.7)	2 (10.0)
General disorders and administration site conditions	1 (16.7)	1 (11.1)	0	1 (9.1)	5 (33.3)	3 (11.5)	5 (25.0)
Infection and Infestations	0	1 (11.1)	0	1 (9.1)	0	2 (7.7)	0
Injury, poisoning and procedural complications	1 (16.7)	0	1 (20.0)	1 (9.1)	2 (13.3)	2 (7.7)	3 (15.0)
Procedural pain	1 (16.7)	0	1 (20.0)	0	1 (6.7)	1 (3.8)	2 (10.0)
Investigations	0	1 (11.1)	1 (20.0)	4 (36.4)	2 (13.3)	5 (19.2)	3 (15.0)
Aspartate aminotransferase increased	0	1 (11.1)	1 (20.0)	2 (18.2)	0	3 (11.5)	1 (5.0)
Musculoskeletal and connective tissue disorders	0	1 (11.1)	0	0	2 (13.3)	1 (3.8)	2 (10.0)
Nervous system disorders	0	1 (11.1)	1 (20.0)	2 (18.2)	2 (13.3)	3 (11.5)	3 (15.0)
Dizziness	0	1 (11.1)	0	1 (9.1)	1 (6.7)	2 (7.7)	1 (5.0)
Psychiatric disorders	1 (16.7)	1 (11.1)	1 (20.0)	1 (9.1)	0	3 (11.5)	1 (5.0)
Renal and urinary disorders	0	0	1 (20.0)	0	1 (6.7)	0	2 (10.0)
Respiratory, thoracic and mediastinal disorders	2 (33.3)	1 (11.1)	0	1 (9.1)	1 (6.7)	4 (15.4)	1 (5.0)
Skin and subcutaneous tissue disorders	0	1 (11.1)	1 (20.0)	2 (18.2)	2 (13.3)	3 (11.5)	3 (15.0)
Erythema	0	0	1 (20.0)	1 (9.1)	1 (6.7)	1 (3.8)	2 (10.0)

H=high-dose; IP=investigational product; L=low-dose; M=months; MedDRA=Medical Dictionary for Regulatory Activities; SAP=Statistical Analysis Plan; TEAE=treatment-emergent adverse event; Y=years.
Note: Treatment-emergence is defined in SAP Section 4.8.2.
Note: A subject can have one or more events with the same system organ class, and one or more preferred terms reported under a given system organ class.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Safety Analysis Set.
Note: MedDRA Version 19.1.
Source: Table 14.3.2.2.

Treatment-emergent Adverse Events by Investigator's Causality

The most frequent TEAEs (≥2% of all subjects) by investigator's causality and PT in the safety population are provided in Table 17.

A total of 7 (26.9%) subjects in the low-dose group and 2 (10.0%) subjects in the high-dose group reported TEAEs related to the study drug among all subjects.

The most frequently reported as causal TEAEs by PT term among all subjects were nausea (3 [11.5%] subjects in low-dose and 1 [5.0%] subject in the high-dose), followed by vomiting (3 [11.5%] subjects in low-dose and 1 [5.0%] subject in the high-dose), and aspartate aminotransferase increased (2 [7.7%] subjects in low-dose).

Table 17. Summary of the Most Common (Reported in ≥2% of All Subjects) Treatment-emergent Adverse Events by Preferred Term and Investigator's Causality Assessment (Safety Analysis Set)

	Number (%) of subjects						
	Age group/Dose group						
	≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
Preferred term/ Assessed causality	L (N=6)	L (N=9)	H (N=5)	L (N=11)	H (N=15)	L (N=26)	H (N=20)
Subjects with any TEAE	3 (50.0)	5 (55.6)	4 (80.0)	11 (100)	9 (60.0)	19 (73.1)	13 (65.0)
Constipation							
Causal	0	0	0	0	0	0	0
Noncausal	1 (16.7)	0	1 (20.0)	2 (18.2)	3 (20.0)	3 (11.5)	4 (20.0)
Nausea							
Causal	0	0	0	3 (27.3)	1 (6.7)	3 (11.5)	1 (5.0)
Noncausal	0	2 (22.2)	1 (20.0)	0	3 (20.0)	2 (7.7)	4 (20.0)
Vomiting							
Causal	0	0	0	3 (27.3)	1 (6.7)	3 (11.5)	1 (5.0)
Noncausal	0	1 (11.1)	0	2 (18.2)	2 (13.3)	3 (11.5)	2 (10.0)
Anaemia							
Causal	0	0	0	0	0	0	0
Noncausal	0	0	1 (20.0)	2 (18.2)	1 (6.7)	2 (7.7)	2 (10.0)
Abdominal pain							
Causal	0	0	0	1 (9.1)	0	1 (3.8)	0
Noncausal	0	1 (11.1)	0	0	2 (13.3)	1 (3.8)	2 (10.0)
Erythema							
Causal	0	0	0	0	0	0	0
Noncausal	0	0	1 (20.0)	1 (9.1)	1 (6.7)	1 (3.8)	2 (10.0)
Procedural pain							
Causal	0	0	0	0	0	0	0
Noncausal	1 (16.7)	0	1 (20.0)	0	1 (6.7)	1 (3.8)	2 (10.0)
Aspartate aminotransferase increased							
Causal	0	0	0	2 (18.2)	0	2 (7.7)	0
Noncausal	0	1 (11.1)	1 (20.0)	0	0	1 (3.8)	1 (5.0)

H=high-dose; IP=investigational product; L=low-dose; M=months; MedDRA=Medical Dictionary for Regulatory Activities; SAP=Statistical Analysis Plan; TEAE=treatment-emergent adverse event; Y=years.
Note: Treatment-emergence is defined in SAP Section 4.8.2.
Note: A subject can have one or more events with the same preferred term, and one or more causality statuses reported under a given preferred term.
Note; All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Safety Analysis Set.
Note: MedDRA Version 19.1.
Source: Table 14.3.2.3

Treatment-emergent Adverse Events by Severity

The most frequent TEAEs (≥2% of all subjects) by maximum reported intensity, SOC, and PT in the safety population are provided in Table 18.

Most of the TEAEs reported were mild or moderate in intensity. One subject each in the low-dose and high-dose groups reported any TEAEs with severe intensity.

The most frequently reported TEAEs by SOC and maximum reported intensity among all subjects were gastrointestinal disorders of mild intensity (8 [30.8%] subjects in low-dose and 9 [45.0%] subjects in high-dose) followed by general disorders and administration site conditions of mild intensity (2 [7.7%] subjects in the low-dose and 4 [20.0%] subjects in high-dose).

The most frequently reported TEAEs by PT term and maximum reported intensity among all subjects were nausea of mild intensity (5 [19.2%] subjects in the low-dose and 5 [25.0%] subjects in the high-dose), followed by vomiting of mild intensity (5 [19.2%] subjects in the low-dose and 3 [15.0%] subjects in the high-dose), and aspartate aminotransferase increased of mild intensity (3 [11.5%] subjects in the low-dose).

One subject in the low-dose group had severe TEAEs with SOC of psychiatric disorders and respiratory thoracic and mediastinal disorders; PT of laryngeal obstruction, psychiatric disorders; and PT of withdrawal symptoms.

One subject in the high-dose group had severe TEAEs of SOC Investigations for PT alanine aminotransferase increased and aspartate aminotransferase increased.

Table 18. Summary of the Most Common (Reported in ≥2% of All Subjects) Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Reported Intensity (Safety Analysis Set)

		Number (%) of subjects						
		Age group/Dose group						
		≥6M to <6Y	≥6Y to <12Y		≥12Y to <18Y		All subjects	
System organ class/ Preferred term	Maximum reported intensity	L (N=6)	L (N=9)	H (N=5)	L (N=11)	H (N=15)	L (N=26)	H (N=20)
Subjects with any TEAE	Severe	1 (16.7)	0	1 (20.0)	0	0	1 (3.8)	1 (5.0)
	Moderate	2 (33.3)	0	0	1 (9.1)	4 (26.7)	3 (11.5)	4 (20.0)
	Mild	0	5 (55.6)	3 (60.0)	10 (90.9)	5 (33.3)	15 (57.7)	8 (40.0)
Blood and lymphatic system disorders	Severe	0	0	0	0	0	0	0
	Moderate	0	0	0	0	1 (6.7)	0	1 (5.0)
	Mild	0	0	1 (20.0)	2 (18.2)	0	2 (7.7)	1 (5.0)
Anaemia	Severe	0	0	0	0	0	0	0
	Moderate	0	0	0	0	1 (6.7)	0	1 (5.0)
	Mild	0	0	1 (20.0)	2 (18.2)	0	2 (7.7)	1 (5.0)
Gastrointestinal disorders	Severe	0	0	0	0	0	0	0
	Moderate	1 (16.7)	0	0	0	1 (6.7)	1 (3.8)	1 (5.0)
	Mild	0	3 (33.3)	2 (40.0)	5 (45.5)	7 (46.7)	8 (30.8)	9 (45.0)
Abdominal pain	Severe	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0
	Mild	0	1 (11.1)	0	1 (9.1)	2 (13.3)	2 (7.7)	2 (10.0)
Constipation	Severe	0	0	0	0	0	0	0
	Moderate	0	0	0	0	1 (6.7)	1 (3.8)	1 (5.0)
	Mild	0	0	1 (20.0)	2 (18.2)	2 (13.3)	2 (7.7)	3 (15.0)
Nausea	Severe	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0
	Mild	0	2 (22.2)	1 (20.0)	3 (27.3)	4 (26.7)	5 (19.2)	5 (25.0)
Vomiting	Severe	0	0	0	0	0	0	0
	Moderate	0	0	0	0	0	0	0
	Mild	0	1 (11.1)	0	4 (36.4)	3 (20.0)	5 (19.2)	3 (15.0)
General disorders and administration site conditions	Severe	0	0	0	0	0	0	0
	Moderate	1 (16.7)	0	0	0	1 (6.7)	1 (3.8)	1 (5.0)
	Mild	0	1 (11.1)	0	1 (9.1)	4 (26.7)	2 (7.7)	4 (20.0)
Investigations	Severe	0	0	1 (20.0)	0	0	0	1 (5.0)
	Moderate	0	0	0	0	2 (13.3)	0	2 (10.0)

	Mild	0	1 (11.1)	0	4 (36.4)	0	5 (19.2)	0
Aspartate aminotransferase increased	Severe	0	0	1 (20.0)	0	0	0	1 (5.0)
	Moderate	0	0	0	0	0	0	0
	Mild	0	1 (11.1)	0	2 (18.2)	0	3 (11.5)	0
Alanine aminotransferase increased	Severe	0	0	1 (20.0)	0	0	0	1 (5.0)
	Moderate	0	0	0	0	0	0	0
	Mild	0	0	0	1 (9.1)	0	1 (3.8)	0
Respiratory, thoracic and mediastinal disorders	Severe	1 (16.7)	0	0	0	0	1 (3.8)	0
	Moderate	1 (16.7)	0	0	0	0	1 (3.8)	0
	Mild	0	1 (11.1)	0	1 (9.1)	1 (6.7)	2 (7.7)	1 (5.0)
Laryngeal obstruction	Severe	1 (16.7)	0	0	0	0	1 (3.8)	0
	Moderate	0	0	0	0	0	0	0
	Mild	0	0	0	0	0	0	0
Psychiatric disorders	Severe	1 (16.7)	0	0	0	0	1 (3.8)	0
	Moderate	0	0	0	1 (9.1)	0	1 (3.8)	0
	Mild	0	1 (11.1)	1 (20.0)	0	0	1 (3.8)	1 (5.0)
Withdrawal syndrome	Severe	1 (16.7)	0	0	0	0	1 (3.8)	0
	Moderate	0	0	0	0	0	0	0
	Mild	0	0	0	0	0	0	0

H=high-dose; IP=investigational product; L=low-dose; M=months; MedDRA=Medical Dictionary for Regulatory Activities; SAP=Statistical Analysis Plan; TEAE=treatment-emergent adverse event; Y=years.
Note: Treatment-emergence is defined in SAP Section 4.8.2.
Note: For each system organ class and preferred term, subjects are included only once, at the maximum intensity.
Note: All subjects 'low' is the total number of subjects who received a low-dose of the IP. All subjects 'high' is the total number of subjects who received a high-dose of the IP.
Note: Percentages were calculated out of the number of subjects in the Safety Analysis Set.
Note: MedDRA Version 19.1.
Source: Table 14.3.2.4.

Deaths

There were no deaths reported during this study.

Treatment-emergent Serious Adverse Events

During the study, SAEs were reported in 1 (3.8%) subject, in the low-dose group in the age group ≥6 months to <6 years. This subject had 2 SAEs: withdrawal syndrome and laryngeal obstruction.

Withdrawal syndrome: On Day 8, following prolonged analgosedation, the subject experienced withdrawal syndrome (severe), which was considered an SAE. The event was considered to have been caused by the following medications: fentanyl, remifentanil, propofol, midazolam, sevoflurane, dexmedetomidine, and ketamine. The event was considered serious for the following reasons: requires or prolongs hospitalization. The event ended on Day 20 with an outcome of recovered/resolved; the subject was discharged from hospital on the same day.

Laryngeal obstruction: On Day 4, the subject experienced laryngeal obstruction (severe), which was considered an SAE. The event was considered serious for the following reasons: life-threatening. The investigator considered the event of laryngeal obstruction to be not related to study medication. The event ended on Day 8 with an outcome of recovered/resolved.

Discontinuations Due to Treatment-emergent Adverse Events

The only TEAE that led to discontinuation of IP during the study was liver function increased reported in 1 (5.0%) subject in the high-dose in the age group ≥12 years to <18 years.

Liver function increased: On Day 4, the subject experienced liver function test increased [increased LFTs] (moderate) which was considered a discontinuation of IP due to AE. The investigator considered the AE to be related to study medication. The event ended on Day 21 with an outcome of recovered/resolved.

Safety Results Summary

• Overall, among all subjects, 21 (80.8%) subjects in the low-dose group and 14 (70.0%) subjects in the high-dose group reported any AEs. Overall, among all subjects, 19 (73.1%) subjects in the low-dose group and 13 (65.0%) subjects in the high-dose group reported any TEAEs.

• Overall, among all subjects, a total of 7 (26.9%) subjects in the low-dose group and 2 (10.0%) subjects in the high-dose group reported TEAEs related to the study drug.

• One subject each, in the low-dose group (3.8%) and high-dose group (5.0%) reported TEAEs that were severe in intensity. One (5.0%) subject in high-dose group, reported TEAEs leading to study discontinuation; and 1 (3.8%) subject in the low-dose group reported SAEs during the study.

• The most frequently reported TEAE by PT among all subjects was nausea (5 [19.2%] subjects in the low-dose and 5 [25.0%] subjects in the high-dose groups), followed by vomiting (5 [19.2%] subjects in the low-dose and 3 [15.0%] subjects in the high-dose groups), and constipation (3 [11.5%] subjects in the low-dose and 4 [20.0%] subjects in the high-dose groups).

• A total of 7 (26.9%) subjects in the low-dose group and 2 (10.0%) subjects in the high-dose group reported TEAEs related to the study drug among all subjects.

• Most of the TEAEs reported were mild or moderate in intensity.

• One subject each in the low-dose and high-dose groups reported any TEAEs with severe intensity.

· Only 1 subject reported any SAE in the low-dose group in the age group ≥6 months to <6 years.

2.3.3. Discussion and overall conclusions on clinical aspects

Discussion

The study was an open-label, multicenter, Phase 1 study to assess the PK and safety of naloxegol in pediatric patients aged ≥6 months to <18 years receiving treatment with opioids.

A total of 57 subjects were enrolled and assigned treatment; of which, 46 subjects received treatment. Overall 33 subjects were female and 13 subjects were male in the Safety Analysis Set. The mean age was 2.8 years in the age group ≥6 months to <6 years; 9.6 years in the age group ≥6 years to <12 years; and 14.6 years in the age group ≥12 years to <18 years. The primary and secondary efficacy objectives were single- and multiple-dose PK results. However, no multiple-dosing analysis was performed due to a low number of subjects.

Single-dose PK analysis was performed with the objective to evaluate the naloxegol exposures of adult equivalent 12.5 and 25 mg doses in pediatric subjects receiving opioids from ≥6 months to <18 years of age. Naloxegol AUC and Cmax values for subjects from ≥6 years to <18 years of age were derived by NCA. A PPK model was developed to derive the AUC and Cmax values for pediatric subjects ≥6 months to <18 years of age. The noncompartmental PK analysis of the 12.5 and 25 mg adult equivalent doses in adolescent subjects (≥12 years to <18 years of age) revealed comparable naloxegol exposures compared to that of adult subjects.

The AUC values for pediatric subjects ≥6 years to <12 years of age were approximately 45% lower for the 12.5 mg (46.1 hr*ng/mL) and approximately 60% lower for the 25 mg (65.4 hr*ng/mL) adult equivalent exposures. These findings were expected, because body weight was not identified as a significant covariate in the PPK analysis, and the dose adjustment by body weight was not needed in pediatric subjects. Body weight of the subjects in this analysis ranged from 8.0 to 133.9 kg. However, CL/F and V1/F of naloxegol were found to be independent on body weight in this analysis. Based on this, it would suggest that allometric scaling of CL/F and V1/F is not needed to extrapolate the exposure of naloxegol pediatric subject ≥6 years to <18 years of age. Although subgroup analysis

indicated exposure to naloxegol in subjects with mild/moderate hepatic impairment was 41% higher than that in subjects with normal hepatic function; impaired hepatic function was not found to be a significant factor on CL/F or V1/F of naloxegol. The BSV of CL/F and V1/F of naloxegol in the base model was 54.5% and 66.3%, respectively. After covariate model building, the BSV of CL/F and V1/F of naloxegol in the final model was 50.7% and 63.7%, respectively. This suggested the covariate factors described approximately 4% of the variability. The BSV at this level could result in difficulty to detect significance and thus not identify impaired hepatic function, and body weight on CL/F or V1/F of naloxegol. Strong CYP3A4 inducer, moderate CYP3A4 inhibitor, P-gp inhibitor and P-gp inducer were found to be significant factors on the CL/F of naloxegol in the previous PPK analysis of naloxegol in volunteer adult subjects and OIC adult patients (Al-Huniti et al 2015). These factors were not available in the pediatric patients and were not investigated in this PPK analysis. However, the estimated BSV of CL/F of naloxegol was 48% in the previous PPK analysis, which is only 3% less than the estimate in this PPK analysis.

Employing the final PPK model of naloxegol oral dose, AUC0-∞ and Cmax of naloxegol in the three pediatric age groups, OIC adults and healthy adults were determined from Monte Carlo simulation of PK profiles after a single oral dose of 25 mg naloxegol. Model-predicted naloxegol AUC0-∞ of the three pediatric age groups was 106%, 112%, and 119% of the AUC0-∞ in OIC adults, respectively.

The other secondary analyses performed were palatability, acceptability, and clinical outcome results. For naloxegol liquid oral solution, at Visit 2, in the low-dose group, mean palatability score was reported as 59.6 for 5 of 9 subjects in the age group ≥6 years to <12 years, and 50.0 in the high-dose group in the age group ≥12 years to <18 years. At Visit 3, results were available only for 1 subject who scored 100 in the age group ≥6 years to <12 years in low-dose group. Regarding acceptability, all subjects in the age group ≥12 years to <18 years 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 (who were also able to swallow tablets). The number of subjects with the ability to swallow the oral solution was too small to draw conclusions (1 [16.7%] subject).

The median time (95% CI) to first BMs was 16 hours in the low-dose group in the ≥6 months to <6 years age group, 63 hours for both low-dose and high-dose groups in the ≥6 years to <12 years age group, and 110 hours and 103 hours for low-dose and high-dose groups, respectively, in the ≥12 years to <18 years age group. The mean number of days with a BM per week was 5 days for subjects in the age group ≥6 months to <6 years, 4.12 days for subjects in the low-dose group and 5.31 days in the high-dose group in the age group ≥6 years to <12 years, and 2.18 days for subjects in the low-dose groups and 1.81 days in the high-dose group in the age group ≥12 years to <18 years. The mean number of days with laxative use per week was 0.71 days for subjects in the low-dose group and 2.8 days in the high-dose group in the age group ≥6 years to <12 years, and 3.87 days for subjects in the low-dose group and 2.49 days in the high-dose group in the age group ≥12 years to <18 years. No subjects in the age group ≥6 months to <6 years (low-dose group) used any laxative.

Thirty-two subjects experienced TEAEs, and the most commonly reported TEAE was nausea. Overall, among all subjects, 19 (73.1%) subjects in the low-dose group and 13 (65.0%) subjects in the high-dose group reported any TEAEs. Of these, a total of 7 (26.9%) subjects in the low-dose group and 2 (10.0%) subjects in the high-dose group reported TEAEs related to the study drug. One subject each, in the low-dose group (3.8%) and high-dose group (5.0%) reported TEAEs that were severe in intensity. One (5.0%) subject in the high-dose group, reported a TEAE leading to study discontinuation; and 1 (3.8%) subject in the low-dose group reported SAEs during the study.

Overall Conclusions

- Naloxegol exhibits dose-linear PK using both NCA and PPK over the dose range of 5 to 25 mg.

- The NCA- and PPK-derived naloxegol drug exposures in pediatrics subjects ≥6 years to <12 years of age that received either the 12.5 or 25 mg adult equivalent dose were lower than the OIC adult exposures. It is unclear why the observation of lower exposure with the 12.5 mg dose was not taken into account when the 25 mg equivalent dose was determined.
- The PPK model-derived naloxegol drug exposures in pediatric subjects 6 months to < 6 years of age that received the adult 12.5 mg equivalent dose were lower than the adult exposures.
- Naloxegol NCA- and PPK-derived drug exposures that were normalized to a fixed dose in the 2 pediatric age groups (≥6 years to <12 years, and ≥12 years to <18 years of age) were consistent to adults exposures. This conclusion is less clear based on PK parameters calculated by NCA.
- Monte Carlo simulations of the PPK model predicted that following administration of naloxegol 25 mg in pediatric subjects 6 months to < 6 years of age naloxegol exposures would be comparable to those following administration of naloxegol 25 mg to adults.
- The palatability and acceptability data were insufficient to draw any conclusions.
- No fatal events were reported. Naloxegol was well-tolerated, and no new safety findings were observed.

3. Rapporteur's overall conclusion and recommendation

The PK parameters of naloxegol in pediatrics were derived by NCA (subjects ≥6 years to <18 years) and popPK analysis (subjects ≥6 months to <18 years). For subjects 6 months to < 12 years that received the 12.5 mg adult equivalent dose, drug exposure was lower compared to that of adults. It should be clarified why the exposure observed in the lower dose cohort was not taken into account when determining the 25 mg equivalent dose.

Conclusions on comparable naloxegol exposure in the three pediatric age groups, OIC adults and healthy adults following administration of a fixed 25 mg naloxegol dose are based on Monte Carlo simulations of the popPK model. An in-depth assessment of the model building, evaluation and simulations performed will be conducted at the time of submission of the planned type II variation. At present, no modifications to the SmPC are proposed.

The palatability and acceptability data were insufficient to draw relevant conclusions. Safety data are in line with current clinical experience with Moventig in adults (refer to Moventig SmPC). A clarification on the low number of patients in the lowest age group that actually received naloxegol treatment is requested (refer to the RfSI).

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarifications as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

*Although 12 patients have been recruited in the age group ≥6 months to <6 years, only 50% of them received the actual treatment resulting in 6 patients receiving low dose treatment in cohort 1. The MAH

is requested to discuss the reasons why such a high percentage of patients in this age group eventually did not receive the assigned treatment.

*According to the protocol, the 12.5 mg equivalent doses in the various age groups were based on PBPK modeling and projected to provide similar exposure to that achieved in adults at 12.5mg. For the ≥6 years to <12 year pediatric age group, however, lower naloxegol exposure was observed compared to adults. The protocol further defines that for the higher dose (25 mg equivalent), the exposure observed in the previous (lower) dose will be taken into account. However, it seem like this was not the case as exposure for the ≥6 years to <12 year pediatric age group receiving the 25 mg equivalent dose is even lower (39% of AUC in adults). The MAH is asked to clarify.

MAH responses to Request for supplementary information

Question 1

Although 12 patients have been recruited in the age group ≥6 months to <6 years, only 50% of them received the actual treatment resulting in 6 patients receiving low dose treatment in cohort 1. The MAH is requested to discuss the reasons why such a high percentage of patients in this age group eventually did not receive the assigned treatment.

Summary of the Applicant's Response

Study D3820C00016 was an open-label, phase I, multicentre study to assess the PK and safety of naloxegol in paediatric patients aged ≥6 months to <18 years receiving treatment with opioids and presenting with opioid-induced constipation (OIC) or at risk of OIC. The study comprised 3 different age groups proceeding sequentially from the oldest to the youngest age group, and each age group comprised 2 cohorts.

Per protocol, cohort 5 was to enrol at least 4 patients in the age group ≥6 months to <6 years who were administered a dose of naloxegol equivalent to 12.5 mg of the adult dose.

Twelve patients were recruited in Cohort 5; however, six patients discontinued prior to receiving naloxegol treatment for the reasons summarised in the Table below:

Table: Cohort 5 Discontinued Subjects

Subject ID	Age/Sex/Race	Date of Discontinuation	Treatment Received	Main Reason for Discontinuation
[redacted]	4Y/F/White	16/Nov/2017	No	Withdrawal by parent/guardian and subject decision
[redacted]	3Y/M/White	08/Feb/2019	No	Withdrawn from study due to severe non-compliance to protocol*
[redacted]	-/F/-	04/Sep/2018	No	Other: Unable to draw blood
[redacted]	2Y/M/White	23/Oct/2020	No	Withdrawn from study due to subject decision
[redacted]	9M/F/Other	17/Dec/2020	No	Study specific withdrawal criteria: not able to perform ECG
[redacted]	13M/M/White	26/Jan/2021	No	Eligibility criteria not met: concomitant use of methadone

*Visit 1/Enrolment/Screening, date 07/Feb/2019: ECG: Test not performed, patient was non-compliant with test (3 attempts were made)

As illustrated above, the main reasons for patients' discontinuation in this cohort were either parent/guardian's decision (2 patients) or protocol non-compliance (4 patients). It should be noted that cohort 5 enrolled patients in the youngest age group. In addition, patients were assigned a study number and treatment allocation on screening; however, if important protocol-required pre-study activities were not performed or if the parent/guardian decided to withdraw consent between screening and randomisation, patients were discontinued from the study prior to receiving treatment, in line with Section 3.6 of the study protocol.

The MAH believes the high percentage of patients discontinuing prior to receiving the assigned naloxegol treatment in this cohort was incidental.

Assessment of the Applicant's Response

In the youngest age group, half of the 12 patients recruited eventually did not receive the assigned treatment because of parent/guardian's decision or protocol non-compliance. The MAH considers the high number of patients discontinuing early to be incidental. As the total number of patients recruited, 12, is low, the high discontinuation rate indeed might very well be a chance event, and does not appear to be related to the foreseen treatment.

Conclusion

Issue resolved.

Question 2

According to the protocol, the 12.5 mg equivalent doses in the various age groups were based on PBPK modeling and projected to provide similar exposure to that achieved in adults at 12.5mg. For the ≥6 years to <12 year pediatric age group, however, lower naloxegol exposure was observed compared to adults. The protocol further defines that for the higher dose (25 mg equivalent), the exposure observed in the previous (lower) dose will be taken into account. However, it seem like this was not the case as exposure for the ≥6 years to <12 year pediatric age group receiving the 25 mg equivalent dose is even lower (39% of AUC in adults). The MAH is asked to clarify.

Summary of the Applicant's Response

It is the MAH's position that the protocol-specified processes for determining the adult equivalent 25 mg naloxegol for the ≥ 6 to < 12 years of age group (cohort 4), were followed. The D3820C00016 protocol specified that the first cohort in each age group would receive naloxegol doses targeted to achieve similar exposures to adults dosed at 12.5 mg, based on physiological based pharmacokinetic (PK) modelling and allometric scaling. The second cohort in each age group would receive a naloxegol dose targeted to achieve similar exposure to the adult equivalent 25 mg dose based on the (PK) results from the naloxegol adult equivalent 12.5 mg cohort. The naloxegol dose regimens for cohorts receiving the adult equivalent 25 mg dose were determined upon review of the PK and safety data by the Safety and Pharmacokinetic Review Committee (SPRC). The minutes from the SPRC meeting that reviewed the safety and PK results from ≥ 6 to < 12 years of age cohort (cohort 3), receiving the adult equivalent 12.5 mg dose of naloxegol are attached. Pharmacokinetic data from 9 subjects enrolled in cohort 3 and cohorts 1 and 2 (≥ 12 to < 18 years of age receiving the adult equivalent 12.5 and 25 mg dose of naloxegol, respectively), were summarized in the PK Summary Document (attached) that was provided to the SPRC. The SPRC minutes state that the committee unanimously approved enrolling into the ≥ 6 to < 12 years of age cohort targeted to receive the adult equivalent 25 mg dose of naloxegol (cohort 4). The SPRC also agreed that based on review of the PK data of cohorts 1, 2 and cohort 3, the naloxegol dose for cohort 4 (≥6 to <12 year of age) should be double the ≥ 6 to < 12 year cohort receiving the adult equivalent 12.5 mg as follows:

>35 kg = 12.5 mg

25-35 kg= 7.5 mg

<25 kg= 5 mg

The MAH therefore believes that all protocol-specified processes were followed.

Assessment of the Applicant's Response

The Applicant submitted the SPRC meeting minutes in which it is documented that the committee agreed, based on the PK data, that the starting dose for the high dose group (adult equivalent 25 mg dose) should be double the dose used in the low group (adult equivalent 12.5 mg dose). Even though it is not fully understood why no alternative dose adaptations were considered, given the markedly lower exposure in the ≥ 6 to < 12 years age cohort compared to adults for the low dose group, the review and acceptance of the proposed dose is ultimately the responsibility of the SPRC as stated in the protocol.

Conclusion

Issue resolved.

5. Rapporteur's revised overall conclusion and recommendation

☒ **Fulfilled:**

The applicant has presented study D3820C00016 (SAFARI) completed. This study was part of the agreed PIP (EMEA-001146-PIP01-11). A request for supplementary information was brought forward, to enable a full assessment of the context of the post approval measure. In general, the PK findings in the paediatric population were expected. Safety data are in line with current clinical experience with Moventig in adults. An in-depth assessment of the model building, evaluation and simulations performed will be conducted at the time of submission of the planned type II variation.
No changes proposed to be made to the PI was agreed by the CHMP. The MAH intends to submit a variation application to include the data from the SAFARI study to the relevant sections of the SmPC after approval of a type II variation submitted in October 2022.

Annex. Line listing of all the studies included in the program development

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Moventig Active substance: naloxegol

Study title	Study number	Date of completion	Date of submission of final study report
Phase 1, Open-label, Multicenter Study to Assess the Pharmacokinetics and Safety of Naloxegol in Pediatric Patients Ages ≥6 Months to <18 Years Receiving Treatment with Opioids	D3820C00016	December 2021	05-07-2022