A Phase I Open-Label Multicentre Study to Assess the Pharmacokinetics and Safety of Naloxegol in Paediatric Patients Ages >= 6 Months to < 18 Years Receiving Treatment with Opioids

Published: 13-03-2014
Last updated: 20-04-2024

To assess the pharmacokinetics and safety of naloxegol in paediatric patients ages > 6 months to < 18 years receiving treatment with opioids.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON44584

Source
ToetsingOnline

Brief title
KODIAK

Condition

- Gastrointestinal conditions NEC

Synonym
Constipation, obstipation

Research involving
Human

Sponsors and support

Primary sponsor: Kyowa Kirin Pharmaceutical Develpment Ltd.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Children, Naloxegol, Opioids, Pharmacokinetics

Outcome measures

Primary outcome

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

To assess the safety and tolerability of naloxegol in paediatric OIC patients

Secondary outcome

To characterize the PK of naloxegol after multiple, once-daily, oral dosing in paediatric OIC patients who continue participation beyond Day 1. A minimum of 3 days of dosing is required for multiple-dose PK analysis.

To evaluate the acceptability of the study medication in paediatric OIC patients through assessment of: 1) palatability of liquid formulation and, 2) the ability of the patient to swallow the tablet.

Study description

Background summary

A well-tolerated and efficacious orally administered treatment option for

constipation due to treatment with opioids remains a major unmet medical need. Opioids have many physiological effects on the gastrointestinal (GI) system, including decreased gastric motility and gastric emptying, diminished intestinal secretions, and decreased peristalsis in the colon. Often these effects can result in constipation. Estimates of the incidence of constipation within the population of adult patients taking opioids vary widely (15% to 90%). Current treatments for opioid induced constipation (OIC) are sub-optimal, with up to 46% of adult patients not achieving the desired treatment outcome.

KKI is developing naloxegol (previously known as NKTR-118), a peripherally acting mu-opioid antagonist, for the treatment of OIC in patients receiving opioid therapy for pain.

Currently there are no approved medicines for treatment of OIC in children and there are no well controlled prospective data demonstrating safety and efficacy of peripherally-acting mu opioid receptor antagonists (PAMORA) in a paediatric population.

Study objective

To assess the pharmacokinetics and safety of naloxegol in paediatric patients ages > 6 months to < 18 years receiving treatment with opioids.

Study design

Phase 1, open-label study.

Patients are subdivided into 3 different age groups:
Age group: 12 years through 17 years
Age group: 6 years through 11 years
Age group: 6 months through 5 years

Within the different age groups patients are treated with two different dosings (2 cohorts)

the study starts in the highest age group. 8 patients will receive doses targeted to achieve similar exposure to adults dosed at 12,5 mg based on physiological based pharmacokinetic modelling. Then 8 new patients within this age group will de dosed with a higher dose of naloxegol. This dose will be determined by the "Independent Safety and PK review Committee". This committee reviewes the PK and safety data and will make decisions regarding the dosing and opening of cohorts.

Patients will be administrered with naloxegol once daily (tablets or oral formulation)

Intervention

Patients will be administrered with a certain dose of naloxegol once daily (tablets or oral formulation).

Study burden and risks

On several days during the study, patients will undergo the following assessments:
- anamnesis (at screening also medical history)
- physical examination
- vital signs (blood pressure, pulse, temperature)
- length
- weight
- ECG
- blood and urine assessments
- questionnaires (palatability of naloxegol, opioid withdrawal symptoms assessment, pain assessment, assessment of bowel movement (diary)
- pregnancy test (if applicable)

Adverse events of naloxegol:
Safety and efficacy of naloxegol have not been established in paediatric patients.
Adverse events considered causally related to the use of NGL include the following: abdominal pain, diarrhea, nausea, headache, vomiting, nasopharyngitis, hyperhidrosis and flatulence.

Other adverse events also reported in clinical trials of naloxegol to date, but not determined to be causally related to the use of the drug, include the following:
• Back pain
• Extremity pain
• Fatigue
• Sinusitis
• Increased BP
• Syncope
• Opioid Withdrawal (OWD)
• FDA has recently expressed concerns, based on findings of drugs within the class, that there may be the potential for increased cardiovascular risk with the use of peripherally acting opioid antagonists, of which naloxegol is a member of the class. The nature of this risk, if any, is not fully understood.

Female patients cannot become pregnant during this study. Male patients should make sure that their partners do not become pregnant during this study.

Contacts

Public
Kyowa Kirin Pharmaceutical Develpment Ltd.

Galabank Business Park, Queen street 3
Galashiels TD1 1QH
GB
Scientific
Kyowa Kirin Pharmaceutical Develpment Ltd.

Galabank Business Park, Queen street 3
Galashiels TD1 1QH
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion 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 and be able to return at 24 hours for PK sampling.
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

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 (eg, 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 (eg, Hirschsprung's disease, malrotation, volvulus, pseudo-obstruction syndromes).
7. Currently active medical conditions or ongoing treatments (eg, 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 LFTs 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 (See Section 7.7.2 for list of excluded concomitant medications)
17. Patients with clinically significant BBB disruptions (eg, active multiple sclerosis, recent brain injury)
18. Patients with known hypersensitivity to other opioid antagonists

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Naloxegol

Ethics review

Approved WMO

Date:	13-03-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	24-02-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-04-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-05-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-10-2016

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-11-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-12-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-003935-32-NL
ClinicalTrials.gov	NCTnr02099591
CCMO	NL47983.000.14

Study results

Results posted: 06-07-2022

Summary results
Trial never started

First publication
27-05-2022