Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).

COORDINATING INVESTIGATORS: Dr Andrew Davies, UK
Dr Jan Tack, Belgium

PROTOCOL CODE: NACASY

SPONSOR: Kyowa Kirin International plc.

Previous versions of the protocol and amendments (number and date):

- Version 1.0, dated on 06/Feb/2018

Current version (number and date):

- Version 2.0, dated on 06/Apr/2018

ACCEPTANCE OF THE PROTOCOL BY THE SPONSOR AND COORDINATING INVESTIGATOR

Title of the clinical trial: Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).

Protocol code: NACASY
Version (number and date): Version: 2.0 dated on 06/Apr/2018

Coordinating investigator's signature	Date of signature (DD-MMM-YYYY)
Investigator's name (in capital letters):	
Sponsor's signature	Date of signature (DD-MMM-YYYY)
Name and position (in block capitals)	

ACCEPTANCE OF THE PROTOCOL BY THE INVESTIGATOR AT THE SITE

Title of the clinical trial: Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).

Protocol code: NACASY
Version (number and date): Version: 2.0 dated on 06/Apr/2018

Investigator's signature	Date of signature (DD-MMM-YYYY)

Investigator's name (in capital letters):

A. Protocol descriptive title and version.

Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).

Version: 2.0 dated on 06/Apr/2018

B. Study director

Dr Ana Fernández Velasco
International Medical Affairs Director
Kyowa Kirin International plc.
Avda. de Burgos 17, 1st floor
28036 Madrid, Spain
Phone: +34 91 534 37 10
Fax: +34 91 535 21 97
e-mail: ana.fernandez@kyowakirin.com

C. Sponsor

Kyowa Kirin International plc.

D. Summary:

1. Name of sponsor and address.

Kyowa Kirin International plc.
Avda. de Burgos 17, 1st floor
28036 Madrid, Spain
Phone: +34 91 534 37 10
Fax: +34 91 535 21 97
e-mail: ana.fernandez@kyowakirin.com

2. Title of the study.

Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).

3. Protocol code.

NACASY

4. Name and address of principal investigator.

Dr Jan Tack, MD, PhD

Professor of Medicine, Translational Research Centre for Gastrointestinal Disorders (TARGID), University of Leuven

Department of Clinical and Experimental Medicine, University of Leuven

Head of Clinic, University Hospital Gasthuisberg, Department of Gastroenterology

Herestraat 49, 3000 Leuven, Belgium

Tel: +32 16 34 42 25

jan.tack@med.kuleuven.be

Dr Andrew Davies FRCP

Consultant in Palliative Medicine

Department of Supportive & Palliative Care

Royal Surrey County Hospital / St. Luke's Cancer Centre

Egerton Rd, Guildford GU2 7XX, United Kingdom

Tel: +44 1483 464885

adavies12@nhs.net

5. CRO

APICES

Av. Antonío López, 16 – 1ª

28320 – Madrid (Spain)

Tel: +34 91 8166804

Fax: +34 918169172

e-mail: ana.moreno@apices.es

6. Type of sites where the study will be conducted.

The study will be conducted in pain units, oncology departments and palliative units of 32 European Hospitals.

7. IEC evaluating the study.

The study will be evaluated by local IEC according to local regulations.

8. Rationale and background

Opioids have been the cornerstone of analgesic treatment for severe chronic pain. OIC is the most commonly reported adverse effect associated with opioids, and compromises patient satisfaction with analgesic treatment, adherence to analgesic treatment regimens and quality of life. Guidelines recommend laxatives for the management of OIC in patients with cancer. In patients who do not respond to standard laxatives, peripherally acting mu-opioids receptor antagonists (PAMORAs) are a valid option. Naloxegol is an oral PAMORA indicated for the treatment of OIC in adult patients who have had an inadequate response to standard laxatives.

No study results evaluating the use of Naloxegol in cancer patients according to routine clinical practice outside of controlled clinical trials are yet available. This study aims to evaluate the safety and efficacy of Naloxegol in a real-world treatment study in patients with cancer pain diagnosed with OIC.

9. Primary objective.

The objective of this study is to assess the safety and efficacy of Naloxegol in a real world setting in cancer patients.

- The primary safety end point is the incidence of adverse events leading to study discontinuation.
- The primary efficacy end point is response rate during the 4 weeks treatment period. Response is defined as three or more bowel movements (without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more bowel movements over baseline.

10. Design.

This is a single-arm, open label, multinational, multicentre, prospective, real world observational study of Naloxegol in adult subjects with Opioid Induced Constipation (OIC) in patients receiving Naloxegol in routine clinical practice. Subjects who are receiving Naloxegol (prescribed by their physician according to the SmPC, which recommends that all currently used maintenance laxative therapy should be halted) during the enrolment period may be eligible for enrolment into the study.

11. Disease or disorder under study.

Opioid Induced Constipation with inadequate laxative response.

OIC is defined as documented <3 Spontaneous Bowel Movements (SBMs)/week on average in the previous 2 weeks before diagnosis. In addition patients must report ≥2 of the following symptoms in at least 25% of the BMs during this period: lumpy or hard stools (Bristol Stool Scale - BSS) stool type 1 or 2); straining; sensation of incomplete BM; sensation of anorectal obstruction / blockage; manual manoeuvres to facilitate BM. Finally, loose stools are rarely present without the use of laxatives.

12. Details of the study drugs.

Naloxegol is a peripherally acting, μ-opioid receptor antagonists (PAMORA) that specifically targets the opioid receptor mechanisms responsible for OIC. Naloxegol is indicated for the treatment of OIC in adult patients who have had an inadequate response to laxatives.

13. Study population and total number of subjects.

This study will involve 315 patients (out-patients or in-patients) with OIC from 32 European hospitals.

D.13.1. Inclusion criteria

- Patient ≥ 18 years old
- Patient with cancer pain
- Patient who is receiving treatment with opioids for at least 4 weeks, and is expected to remain on opioids for duration of study
- Patient with opioid-induced constipation
- Patient in whom the clinician plans treatment with Naloxegol according to routine clinical practice (Naloxegol SmPC recommends that all currently used maintenance laxative therapy should be halted)
- Signing of the informed consent

D.13.2. Exclusion criteria

- Patients with colorectal cancer

14. Variables

Primary variables

Primary safety variable is the adverse events leading to study discontinuation.

Primary efficacy variable is response rate during the 4 weeks treatment period.

The following variables will be collected during the study:

- demographic data, cancer and pain clinical characteristics and treatments,
- opioid induced constipation: symptoms, laxative treatments, bowel movements
- Naloxegol treatment: dose, adverse events,
- rescue medication,
- study questionnaires:
    - Bowel function index (BFI)
    - Bristol stool scale
    - Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL)
- Patient satisfaction

15. Data source

Data to be recorded on the CRF should be taken from clinical records collected in the course of normal clinical practice and the mentioned questionnaires. This study will not alter the clinical management of subjects. No procedures other than those connected with routine standard of care and the questionnaires will be performed.

16. Study size

Sample size has been calculated based on the primary safety objective of this study: to evaluate the incidence of adverse events leading to study discontinuation.

Previous studies shown that the incidence of adverse events leading to study discontinuation is about 10% when the follow-up is 12 weeks. We expect than the incidence of adverse events leading to study

discontinuation in our study will be about 2%, since the follow-up will only be 4 weeks. With an overall sample size of 315 patients, it is possible to detect this 2% of discontinuations due to adverse events with a 95% confidence interval and a precision of ± 1.5%.

17. Data analysis

The primary safety end point is the incidence of adverse events leading to study discontinuation. Number and percentage of patients who present an adverse event leading to study discontinuation and 95% CI will be provided.

The primary efficacy end point is response rate during the 4 weeks treatment period. Response is defined as three or more bowel movements (without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more bowel movements over baseline. Response rate will be provided as frequency and 95% CI will also be presented.

Analysis of secondary variables is detailed in section 8.

Exploratory and descriptive methods will be used to describe every study variable. Continuous variables will be described by mean, median, standard deviation, minimum and maximum. Categorical variables will be shown as distribution of frequencies and percentage.

18. Schedule.

The study is expected to be conducted in 24 months:

6 months for preparation (Health Authorities (HA) & IEC authorisation, formalisation of contract with healthcare service providers, if needed per local regulations)

9 months for patient recruitment

6 months for patient follow-up & data entry

3 months for data analysis

The study is expected to start (inclusion of first patient) in July 2018.

Milestones

- Start of data collection: July 2018
- End of data collection: July 2019
- Final report: December 2019

19. Source of financing.

Kyowa Kirin International plc., the sponsor, will provide financial support to conduct the study.

Kyowa Kirin International plc. agrees to finance the study according to the guidelines of this protocol. This financing includes the cost of the study's submission for evaluation by IEC/HA of participating countries according to local regulations, payments to investigators, the design, maintenance and management of the clinical database, the statistical analysis and the statistical report.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Full terminology
AE	Adverse Event
BFI	Bowel function index
CRF	Case report form
CI	Confidence interval
CRA	Contract Research associate
CRO	Contract Research Organization
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
EOS	End of Study
GCP	Good Clinical Practice
HA	Health Authority
IEC	Independent ethic committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
OIC	Opioid Induced Constipation
PAC-QOL	Patient Assessment of Constipation – Quality of Life Questionnaire
PGI-I	Patient Global Impression of Improvement
QC	Quality control
SAE	Serious Adverse Event
SBM	Spontaneous bowel movements
SOP	Standard operating procedure
SmPC	Summary of Product Characteristics

E. Work plan.

The study sponsor will send the protocol to IEC/HA according local regulations in each participating country. When the study has been approved and all other administrative procedures have been completed, the study will start in the participating sites/countries.

The participating investigators shall be responsible for screening patients who meet the screening criteria established in the protocol. Each patient invited to take part in the study will be duly informed by the investigator or an authorised member of his or her team. He or she will also be given a document with the most important information related to the study; this document is called a "patient information sheet". No patient will be included in the study until he or she has been duly informed by the investigator and has granted his/her informed consent in writing.

The study is conducted by completing a Case Report Form that will contain the information available in the medical records. Data will be recorded on an electronic case report form from clinical records collected in the normal course of clinical practice. Data will be collected (where available and where the procedure conducted per routine clinical practice) as follows:

Visit 1, Baseline, Start of treatment

- Selection criteria
- Informed consent
- Physical examination
- Bowel function index (BFI)
- Bristol stool scale
- Previous treatments for OIC
- Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL)
- Analgesic treatment
- Frequency of bowel movements per week
- Naloxegol dose
- Patient's diary is given to patient

Visit 2, week 2

- Adverse events
- Patient bowel diary
- Analgesic treatment
- Naloxegol treatment interruptions/dose adjustments
- Frequency of bowel movements per week
- Other laxative use

Visit 3, week 4 (End of Study - EOS)

- Adverse events
- Bowel function index (BFI)
- Patient bowel diary
- Bristol stool scale
- Patient Assessment of Constipation – Quality of Life Questionnaire
- Analgesic treatment interruptions/dose adjustments
- Naloxegol treatment interruptions/dose adjustments
- Frequency of bowel movements per week
- Other laxative use
- Patient satisfaction (PGI-I)

The investigator will only collect the data available in the patients' medical records and the questionnaires detailed above; said patients will have been followed up according to regular clinical practice and received treatment according to the investigator's clinical judgement. In no case shall a patient's inclusion in the study affect regular clinical practice.

Data will be obtained from routine clinical records and transcribed onto an anonymous case report form (CRF) which will be in three parts:

I. Baseline information / Visit 1

II. Visit 2 – week 2

III. Visit 3 – week 4, End of study (EOS) – at 4 weeks after Naloxegol initiation (unless preceded by subject death, loss to follow up or withdrawal of consent)

The study will end when the last subject remaining on the study completes the 4 weeks observation period, dies, withdraws informed consent, or is lost to follow-up, whichever occurs first.

F. General and specific objectives.

Primary objective / outcome

The objective of this study is to assess the safety and efficacy of Naloxegol in a real world setting in cancer patients.

- The primary safety end point is the incidence of adverse events leading to study discontinuation.
- The primary efficacy end point is response rate during the 4 weeks treatment period. Response is defined as three or more bowel movements (without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more bowel movements over baseline.

Secondary objectives / outcomes

- Proportion of patients that have a BFI score change of ≥12 points at the end of the study treatment (4 weeks).
- Proportion of patients that have a BFI score <30 at the end of the study (patients adequately treated).
- Time to the first post-dose bowel movement.
- Change in stool consistency (Bristol stool scale).
- Change in Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL).
- Incidence of overall adverse events, including SAEs.
- Analgesic treatment interruptions/dose adjustments.
- Naloxegol treatment interruptions/dose adjustments.
- Patient satisfaction (PGI-I).

G. Critical review of the literature.

Pain occurs in 30% of all cancer patients and 59% of patients receiving anti-cancer treatment experience pain, as has been observed in several studies [1]. The prevalence is even higher (64% to 87%) in patients with advanced cancer [1-2].

Opioids have been the cornerstone of analgesic treatment for severe chronic pain. Patients with a wide variety of pain conditions, such as pain from degenerative joint diseases, other musculoskeletal pain, neuropathic pain and also cancer pain receive treatment with opioids. Following pain management guidelines, opioids can provide adequate pain relief in 75% to 90% of patients with cancer pain [2-3].

The use of opioid analgesics requires careful selection and monitoring of patients to achieve an optimal balance between the benefits and risks of these agents [4-8]. Opioids, in addition to the analgesic effect, produce a wide variety of undesirable effects, including alterations in gastrointestinal function, sedation [4], hormonal [4,6] and cognitive [4,5] changes, pruritus [4], sweating [6], bladder dysfunction [6], respiratory depression [6], among others. However, despite these limitations, opioid analgesics remain a treatment option for patients with chronic pain due to its efficacy and the wide variety of options available regarding drugs and formulations to individualize the treatment [7-8].

Constipation is one of the most frequent and debilitating side effects of opioids, occurring in about 40% to 70% of patients being treated for chronic pain. Over 64% of cancer patients experience OIC, which is highly problematic in this population due to the debilitation effects of the disease itself [9]. Opioids are effective for alleviating pain via their actions at opioid receptors in the central nervous system (CNS) and the peripheral nervous system [10]. In addition, opioid actions on μ-receptors throughout the gastrointestinal tract often lead to impairment of motility and a variety of symptoms, including constipation, which taken together is called opioid-induced constipation (OIC).

OIC has been defined by a multidisciplinary working group as a change when initiating opioid therapy from baseline bowel habits that is characterised by any

of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation and harder stool consistency [11].

As mentioned before, among the patients receiving opioids, constipation is the most commonly reported adverse effect [12]. Opioid-induced constipation compromises patient satisfaction with analgesic treatment, adherence to analgesic treatment regimens and also affects patient quality of life [13]. Dietary modifications, lifestyle changes, and laxatives are used to treat opioid-induced constipation, but their efficacy is limited.

Guidelines from the European Association for Palliative Care (EAPC) recommend laxatives for the prophylaxis or management of OIC in patients with cancer [14], but there is no single laxative of choice. The main options would be stool softeners, laxatives that increase GI contractility or that induce fluid secretion. There are no randomized controlled trials to support the use of laxatives in the treatment of OIC.

Although generally well-tolerated, side-effects of laxatives include bloating, cramps, abdominal pain, nausea, diarrhoea, dehydration, and electrolyte imbalances [15].

Naloxegol is a PEGylated derivative of the μ-opioid receptor antagonist naloxone. PEGylation reduces Naloxegol's passive permeability and also renders the compound a substrate for the P-glycoprotein transporter. Due to poorer permeability and increased efflux of Naloxegol across the blood-brain barrier, related to P-gp substrate properties, the CNS penetration of Naloxegol is minimal. Naloxegol acts by binding to μ-opioid receptors in the GI tract targeting the underlying causes of OIC (i.e. reduced GI motility, hypertonicity and increased fluid absorption). Naloxegol functions as a peripherally-acting μ-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system. Naloxegol has been approved for the treatment of OIC in adult patients who have had an inadequate response to laxatives.

The efficacy of Naloxegol in patients with OIC was demonstrated in two double-blind, randomised, placebo-controlled phase 3 trials [16]. In both studies, Naloxegol 25 mg was associated with statistically significant improvements in stool frequency and numerical improvements in OIC symptoms compared with placebo, as assessed by response rate in the overall population over 12 weeks and in a subgroup of patients with inadequate response to laxatives. Furthermore, Naloxegol 25 mg significantly improved time to first post-dose spontaneous bowel movement (SBM), and days per week with an SBM [16].

However, information regarding the use of Naloxegol in cancer patients outside of controlled clinical trials is not yet available.

This study aims to evaluate the safety and efficacy of Naloxegol in a real-world treatment study in patients with cancer pain diagnosed with OIC.

H. Methods:

1. Design and rationale.

This is a single arm, open label, multinational, multicentre, prospective, real world observational study of Naloxegol in adult subjects with Opioid Induced Constipation and inadequate laxative response. Subjects who are receiving Naloxegol (prescribed by their physician according to the SmPC, which recommends that all currently used maintenance laxative therapy should be halted) during the enrolment period may be eligible for enrolment into the study.

Data will be obtained from routine clinical records and transcribed onto the CRF in three visits:

I. Baseline visit

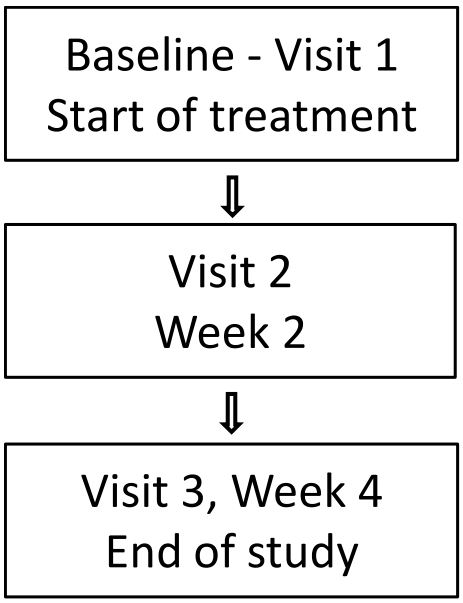
II. Visit 2 – week 2

III. Visit 3 – week 4, End of study (EOS)

EOS visit will take place 4 weeks after Naloxegol initiation (unless preceded by subject death, loss to follow up or withdrawal of consent)

The study will end when the last subject remaining on the study completes the 4 weeks observation period, dies, withdraws informed consent, or is lost to follow-up, whichever occurs first.

Figure 1: Study design



Subjects who are receiving Naloxegol (prescribed by their physician) during the enrolment period may be eligible for enrolment into the study. Each subject will have their data collected for a period of 4 weeks from their first dose of Naloxegol regardless of the duration of their Naloxegol treatment.

This observational study will not impose any additional procedures or changes to the routine management of subjects. Data for the study will be obtained from clinical practice records and transcribed in to an anonymous CRF.

This study is will not alter the clinical management of subjects. No additional visits other than those routinely scheduled will be required, and no procedures other than those connected with routine standard of care and the mentioned questionnaires will be performed. Data to be recorded on the CRF should be taken from clinical records collected in the course of normal clinical practice.

This study design will enable us to gather information of Naloxegol safety and efficacy in clinical practice for subjects with OIC in Europe. It will also inform us of Naloxegol utilisation as it occurs in routine clinical practice, which may differ from utilisation in the controlled environment of a clinical

study, and of the nature of the population for which it is being used. This study will provide additional information on the incidence of adverse drug reactions.

It is planned that each participating site includes 10 patients in the study.

Justification

Opioids have been the cornerstone of analgesic treatment for severe chronic pain. OIC is the most commonly reported adverse effect associated with opioids, and compromises patient satisfaction with analgesic treatment, adherence to analgesic treatment regimens and quality of life. Guidelines recommend laxatives for the management of OIC in patients with cancer. In patients who do not respond to standard laxatives, peripherally acting mu-opioids receptor antagonists (PAMORAs) are a valid option. Naloxegol is an oral PAMORA indicated for the treatment of OIC in adult patients who have had an inadequate response to standard laxatives.

No study results evaluating the use of Naloxegol in cancer patients according to routine clinical practice outside of controlled clinical trials are yet available. This study aims to evaluate the safety and efficacy of Naloxegol in a real-world treatment study in patients with cancer pain diagnosed with OIC.

2. Study population.

This study will involve approximately 315 patients (out-patients or in-patients) with OIC in European hospitals.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study.

H.2.1. Inclusion criteria

- Patient ≥ 18 years old
- Patient with cancer pain
- Patient who is receiving treatment with opioids for at least 4 weeks, and is expected to remain on opioids for duration of study
- Patient with opioid induced constipation (OIC)

- Patient in whom the clinician plans treatment with Naloxegol according to routine clinical practice (Naloxegol SmPC recommends that all currently used maintenance laxative therapy should be halted)
- Signing of the informed consent

H.2.2. Exclusion criteria

- Patients with colorectal cancer

OIC is defined as documented <3 SBMs/week on average in the previous 2 weeks before diagnosis. In addition patients must report ≥2 of the following symptoms in at least 25% of the BMs during this period: lumpy or hard stools (Bristol Stool Scale (BSS) stool type 1 or 2); straining; sensation of incomplete BM; sensation of anorectal obstruction / blockage; manual manoeuvres to facilitate BM. Finally, loose stools are rarely present without the use of laxatives.

Withdrawal and replacement of subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution.

Withdrawal of consent for a study means that the subject does not wish to or is unable to continue further study participation. If a subject withdraws full consent, no further data will be collected.

Enrolled subjects who subsequently are identified as meeting one or more exclusion criteria will be removed from the study.

Subjects who leave the study for any reason before the end of the observational period or are lost to follow-up will not be replaced.

3. Source of information.

This study will not alter the clinical management of subjects. No additional visits other than those routinely scheduled will be required, and no procedures other than those connected with routine standard of care and the mentioned questionnaires will be performed. Data to be recorded on the

CRF should be taken from clinical records collected in the course of normal clinical practice and the mentioned questionnaires.

The investigator at each site is responsible for ensuring that all required data (as listed below and where performed as routine clinical practice) is recorded.

4. Operational definition of outcome, exposure and other measures.

After a subject has been enrolled, baseline (pre-Naloxegol) data from that subject's medical records will be completed onto the eCRF by the investigator, or designee. Baseline values will be considered as those obtained most recently prior to initiation of Naloxegol. Data obtained after the initiation of Naloxegol and subsequently during the remainder of the 4 weeks observational period will similarly be completed onto the eCRF. This data will include the following, when available as standard clinical practice:

Visit 1 - Baseline - Start of treatment

- **ICF signature**
- **Selection criteria**
- **Demographics**
  - Age
  - Gender
  - Race
  - Height
  - Weight
- **Cancer characteristics**
  - Primary tumour site
  - Stage
  - Metastatic locations
- **Current cancer treatment**
  - Chemotherapy, yes/no
  - Radiotherapy, yes/no; specify location
- **Pain**
  - Pain location
  - Current pain treatment
    - Patient has been on opioids > 1 month, yes/no
    - Analgesic treatment, type (dose)
    - Other treatments
- **Opioid Induced Constipation**

  - Symptoms: straining, sensation of incomplete evacuation, stool consistency
  - Previous laxative treatments
    - Bulking agents, yes/no, end date/ongoing
    - Osmotic laxatives, yes/no, end date/ongoing
    - Stimulant laxatives, yes/no, end date/ongoing
    - Stool softeners, yes/no, end date/ongoing
    - Prucalopride, yes/no, end date/ongoing
    - Linaclotide, yes/no, end date/ongoing
    - Lubiprostone, yes/no, end date/ongoing
    - Other (please specify), end date/ongoing
  - Naloxegol start date
  - Straining
  - Complete/incomplete evacuation
  - Pain level (NRS), average and worst pain level that occurred during the previous 24 hours
- **Study questionnaires**
  - Bowel function index (BFI)
  - Bristol stool scale
  - Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL)

Visit 2: week 2

- **Pain**
  - Pain location
  - Current pain treatment
    - Analgesic treatment, type (dose)
    - Other treatments
- **Opioid Induced Constipation**
  - Symptoms: straining, sensation of incomplete evacuation, stool consistency
  - Naloxegol treatment interruptions/adjustments
  - Naloxegol related adverse events
  - Combination with other OIC treatments?, yes/no
    - Bulking agents, yes/no
    - Osmotic laxatives, yes/no
    - Stimulant laxatives, yes/no
    - Stool softeners, yes/no
    - Prucalopride, yes/no
    - Linaclotide, yes/no
    - Lubiprostone, yes/no
    - Other (please specify)

- **Patient diary**
  - Date and time of BM (recorded at the time of each BM)
  - Stool consistency (BSS) (recorded at the time of each BM)
  - Straining (recorded at the time of each BM)
  - Complete/incomplete evacuation (recorded at the time of each BM)
  - Pain level (NRS) recorded each evening for the average and worst pain level that occurred during the previous 24 hours
  - Date and time of use of laxative rescue medication recorded at the time the medication is taken
- **Study questionnaires**
  - Bowel function index (BFI)
  - Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL)

Visit 3: week 4

- **Pain**
  - Pain location
  - Current pain treatment
    - Analgesic treatment , type (dose)
    - Other treatments
- **Opioid Induced Constipation**
  - Symptoms: straining, sensation of incomplete evacuation, stool consistency
  - Naloxegol treatment interruptions/adjustments
  - Naloxegol related adverse events
  - Combination with other OIC treatments?, yes/no
    - Bulking agents, yes/no
    - Osmotic laxatives, yes/no
    - Stimulant laxatives, yes/no
    - Stool softeners, yes/no
    - Prucalopride, yes/no
    - Linaclotide, yes/no
    - Lubiprostone, yes/no
    - Other (please specify)
- **Patient diary**
  - Date and time of BM (recorded at the time of each BM)
  - Stool consistency (BSS) (recorded at the time of each BM)
  - Straining (recorded at the time of each BM)
  - Complete/incomplete evacuation (recorded at the time of each BM)

- Pain level (NRS) recorded each evening for the average and worst pain level that occurred during the previous 24 hours
- Date and time of use of laxative rescue medication recorded at the time the medication is taken

- **Study questionnaires**
  - Bowel function index (BFI)
  - Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL)
  - Patient satisfaction (PGI-I)

5. Planned sample size and rationale.

Sample size has been calculated based on the primary safety objective of this study: to evaluate the incidence of adverse events leading to study discontinuation.

Previous studies shown that the incidence of adverse events leading to study discontinuation is about 10% when the follow-up is 12 weeks. We expect than the incidence of adverse events leading to study discontinuation in our study will be about 2%, since the follow-up will only be 4 weeks. With an overall sample size of 315 patients, it is possible to detect this 2% of discontinuations due to adverse events with a 95% confidence interval and a precision of ± 1.5%.

6. Methods for obtaining data.

This study proposes a prospective collection of data during a 4 week follow-up period. Given the observational nature of the present study, the data will be obtained from the patients' and / or the patients' clinical history and the questionnaires.

The burden of constipation on patients' everyday functioning and well-being will be evaluated by Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL).

H.6.1. PAC-QOL

The PAC-QOL scale [17] is a 28-item self-report instrument designed to evaluate the burden of constipation on patients' everyday functioning and well-being in the 2 weeks (14 days) prior to assessment. Each item is rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely). The

scale will take approximately 5 minutes to answer. The patients need to be able to read and to be fluent in the local language. The instrument can be used to generate an overall score, but is also reported to assess 4 specific constipation-related domains including: 1) Worries and concerns (11 items), 2) Physical discomfort (4 items), 3) Psychosocial discomfort (8 items), and 4) Satisfaction (5 items). The PAC-QOL will be administered to patients at Visit 1 (start of treatment) and visit 3 (week 4, EOS).

The PAC-QOL questionnaire will be completed by patients at the study centre. Study staff will provide initial training on how to fill out the questionnaire. Patients are to fill out the questionnaire in a quiet area, without any help from family, friends, or study staff.

H.6.2. Patient diary

The patient diary will be completed each day from the evening of Visit 1 to the morning of Visit 3. The diary will include the following daily recordings:

- Date and time of BM (recorded at the time of each BM)
- Stool consistency (BSS) (recorded at the time of each BM)
- Straining (recorded at the time of each BM)
- Complete/incomplete evacuation
- Use of laxative rescue medication
    - Bulking agents, yes/no
    - Osmotic laxatives, yes/no
    - Stimulant laxatives, yes/no
    - Stool softeners, yes/no
    - Prucalopride, yes/no
    - Linaclotide, yes/no
    - Lubiprostone, yes/no
    - Other (please specify)

H.6.3. Stool consistency (Bristol Stool Scale)

Patients will rate stool consistency through completion of the BSS after each BM. The BSS is a medical aid designed to classify the form of human faeces into 7 categories [18]. The form of the stool depends on the time it spends in the colon. The 7 stool types are:

1. Separate hard lumps, like nuts (hard to pass)

2. Sausage-shaped, but lumpy

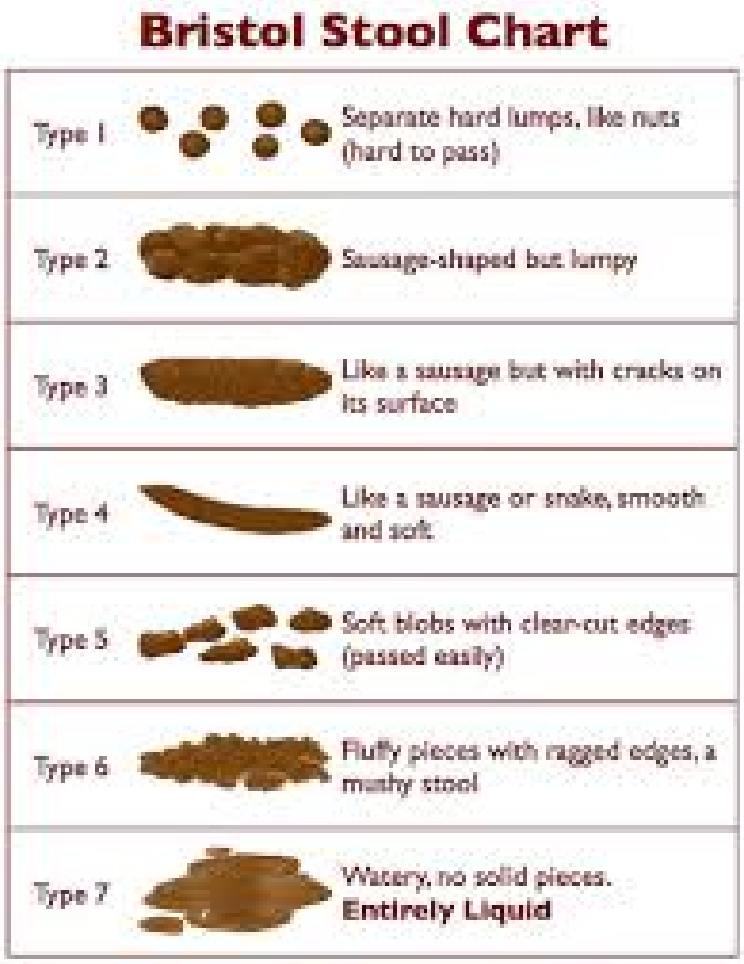
3. Like sausage, but with cracks on its surface

4. Like a sausage or snake, smooth and soft

5. Soft blobs with clear cut edges (passed easily)

6. Fluffy pieces with ragged edges, a mushy stool

7. Watery, no solid pieces.



Types 1 and 2 indicate constipation, types 3 and 4 represent “ideal stools,” and Types 5 to 7 are tending towards diarrhoea or urgency.

H.6.4. Straining

The degree of straining with each BM will be recorded at the time of the BM. A single-item straining question will be asked in the patient diary. The question is:

"How much did you strain during your bowel movement?"

Patients will be asked to respond on a 5 point Likert scale choosing one of the following options:

1 = Not at all

2 = A little bit

3 = A moderate amount

4 = A great deal

5 = An extreme amount.

H.6.5. Complete/incomplete evacuation

Patients will record the completeness of evacuation at the time of each BM and after the straining question. A single question on the completeness of evacuation will be asked in the patient diary. The question is:

"Did you feel like your bowels were completely empty after the bowel movement?"

Patients will provide a yes or a no response to the complete/incomplete evacuation question.

7. Data management.

All subjects must personally sign and date the consent form before enrolment. All subjects who are to be enrolled on the study must be entered onto the Interactive Web Response System (IWRS) by authorised site personnel. A subject is considered to be enrolled upon completion of this step.

All subjects who enter into the study will be allocated a unique subject identification number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study.

In order to guarantee the confidentiality of the study data, only the following persons and entities will have access thereto: the investigator and his/her staff, the sponsor or a person designated by the sponsor, the IEC, the

relevant healthcare authorities and the persons responsible for analysing the data.

The content of the CRFs, as well as the documents generated during the study, will be protected against non-permitted use by persons not involved in the investigation and will be considered strictly confidential and will not be revealed to third parties.

The investigator must make sure to maintain patients' anonymity and protect their identity from unauthorised parties. Patients will not be identified by name on the CRFs, but by an identification code. The investigator must keep a record of patient recruitment, including the codes assigned for participation in the study.

The investigator will organise the safekeeping of the study documentation until the end of the study. He/she must also comply with the local standards/recommendations regarding the safekeeping of patients' records.

The processing of the personal data required in this study is governed by the European General Data Protection Regulation and local regulation.

8. Data analysis.

Statistical considerations

This section describes only the most relevant parts of the statistical analyses planned for this study. All statistical methodology that is to be applied to this trial will be described in detail in a Statistical Analysis Plan (SAP) which will be finalised prior to database lock. The statistical analysis will be performed by the statistical department of the CRO.

Exploratory and descriptive methods will be used to describe every study variable. Continuous variables will be described by mean, median, standard deviation, minimum and maximum. Categorical variables will be shown as distribution of frequencies and percentage. Also a 95% CI will be presented if this information is considered relevant to describe a variable.

Description of analysis sets

The safety analysis set will be the Safety population, defined as all patients who meet all selection criteria and received at least 1 dose of study drug.

The efficacy analysis set will be the efficacy population, defined as all patients who meet all selection criteria, received at least 1 dose of study drug and have at least one post-baseline efficacy assessment.

Analysis of primary outcomes

The primary safety end point is the incidence of adverse events leading to study discontinuation. Number and percentage of patients who present an adverse event leading to study discontinuation and 95% CI will be provided.

The primary efficacy end point is response rate during the 4 weeks treatment period. Response is defined as three or more bowel movements (without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more bowel movements over baseline. Response rate will be provided as frequency and 95% CI will also be presented.

Analysis of secondary outcomes

Number and percentage of patients that have a BFI score change ≥12 points and BFI score <30 (patients adequately treated) at the end of the study treatment (4 weeks) will be provided.

Time to the first post-dose bowel movement will be described using mean, median, standard deviation and range.

The mean daily Bristol stool scale (BSS) score for an interval will be calculated as the sum of daily values for the interval divided by the number of days in which the data were collected. Change from baseline in the mean BSS score will be calculated for weeks 2 and 4 as the post-baseline value minus the baseline value, where baseline is the mean daily BSS score recorded during the baseline visit. Positive changes from baseline indicate improvement.

For the PAC-QOL, each of the 28 items is scored from 0 to 4. For items 18, 25, 26, 27, and 28, higher scores represent better outcomes. The scores for these items will be reversed (reversed score=4-original score), so that higher scores represent worse outcomes for all items. The 28-item PAC-QOL is divided into 4 subscales:

- Physical discomfort (items 1 to 4)
- Psychosocial discomfort (items 5 to 12)
- Worries/concerns (items 13 to 23)
- Satisfaction (items 24 to 28).

For each visit, individual subscale scores will be calculated as the mean of the non-missing items for that subscale. The total score will be calculated as the mean of all non-missing items. If more than 50% of values for a subscale score or the total score are missing for a visit, the values for that score will be set to missing. Change from baseline in the PAC-QOL subscale and total scores will be calculated for weeks 2 and 4 as the post-baseline value minus the baseline value, where baseline is the value collected into the baseline visit. Negative changes from baseline indicate improvement.

Analgesic and Naloxegol treatment interruptions will be described by frequency and percentage of patients. Details of Naloxegol treatment interruptions will be provided.

To evaluate the global improvement Patient Global Impression of Improvement (PGI-I) will be used. Number and percentage of patients for each category of response in the scale will be provided.

AEs will be coded according MedDRA preferred terms and the severity will be graded using the following 3 points scale:

- Mild (asymptomatic)
- Moderate (symptomatic, but does not interfere significantly with function)
- Severe (interferes significantly with function)

A table detailing adverse events taking into account the severity, with number and percentage of patients with each event/severity, will also be provided.

9. Quality control.

All the data will be obtained from the patients' medical records and the patients' questionnaire at each study visit. The study data will be recorded in

an eCRF. The data will be stored guaranteeing their confidentiality, security and authenticity.

A data management plan will be prepared for the study, defining all aspects of data management and processing. Said data management plan will include the following in detail:

- Validation processes.
- Query resolution processes.
- Structure and basic parts of the application for study data collection.
- General considerations regarding the data, including validation rules and normal ranges used in the different parameters recorded in the study.

The data will be stored in a relational database in a MySQL server. The application will be duly protected by an SSL security certificate for correct encoding of transferred data.

10. Limitations of the design, information source and analytical methods.

The limitations of the study are those stemming from its non-interventional design. Although data will be collected from the medical records, it cannot be guaranteed that all the information to be collected is available in all the participating sites.

The source of information will be the medical records of the patients, which will be reviewed to confirm that the patients included in the study meet the screening criteria described in the protocol before they are invited to participate, and to collect the required study follow-up information.

I. Ethical considerations/protection for the research participants:

The study will be conducted according to the requirements expressed in the Declaration of Helsinki (Fortaleza revision, October 2013) and Good Epidemiological Practices, and current European regulations relative to the conduct of observational studies.

The processing, reporting and transfer of personal data from all the research participants will be in compliance with the provisions of the European General Data Protection Regulation and local regulation.

As general considerations, all the parties involved in this study, the sponsor, investigators and others accept national and international ethical standards regarding research.

The protocol shall be submitted to an IEC for evaluation prior to the start of patient enrolment, as needed per local regulations. Any information required by the protocol may be subject to audits by the sponsor, independent organisations and/or competent authorities, but data confidentiality will be a basic condition, and the data shall be used solely for the purposes specified in the protocol and reported to the authorities.

1. Risk–benefit analysis for research subjects.

Given its observational, non-interventional nature based solely on the collection of data from patients' medical records and the questionnaires, this study does not present a risk for the study subjects, as it does not involve a change in the patients' treatment or follow-up by the investigator. The patient will be followed up and treated according to the regular practice of the participating doctor. This study will obtain information related to the use of Naloxegol in regular clinical practice.

2. Considerations regarding patient information and informed consent.

Before a subjects' participation in the study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits of this observational study in a language that he/she can understand.

The investigator must inform the patient as fully as possible, using a language and terms that he/she can understand, about the voluntary nature of his/her participation that will enable the retrospective collection of data from medical records, without involving any change in the treatment or medical care that would be provided without participating. He will answer

his/her questions and, pursuant to current legislation, obtain the subject's consent, which must be signed personally and dated, or signed and dated by an impartial witness or by his/her legal representative, orally confirming consent before witnesses. The patient will receive a signed and dated hard copy of the informed consent form. The acquisition of informed consent should be documented in the subject's medical records.

The subject may revoke his or her consent to the use of his/her data in the analysis at any time, without having to provide a reason and without liability or prejudice of any kind.

3. Data confidentiality.

The processing of the personal data required in this study is governed by the European General Data Protection Regulation and local regulation. When the personal data of investigators and/or patients are stored and processed, the necessary action will be taken to protect them and prevent access by unauthorised third parties.

Only the investigator, his or her team and the technical personnel participating in the study will have access to patient data, in order to ensure their confidentiality. Access will also be available for the sponsor or a person designated by the sponsor, the IEC and the relevant health authorities.

The investigator must ensure that the subject's confidentiality is maintained:

- On the case report forms or other study documents, subjects should be identified by a subject study number only.
- On Serious Adverse Drug Reaction forms, subjects should be identified by their subject study number only.
- Other study documents (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC direct access to review the subject's original medical records for verification of data (unless not permitted by local law). Direct access includes examining, analysing, verifying, and

reproducing any records and reports that are important to the evaluation of the study.

4. Interference with the physician's prescription habits.

This study is an observational study, that is, a study where the medicinal products are prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the subject to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the subject in the study. No additional diagnostic or monitoring procedures shall be applied to the subjects and epidemiological methods shall be used for the analysis of collected data.

This study does not interfere with the doctor's prescription habits or regular clinical practice, as it is limited to collecting data and does not involve diagnostic or therapeutic procedures other than those involved in regular clinical practice.

For this reason, each physician will have to select those individuals eligible to participate in the study from among the population he/she treats. If the investigator decides or not to start or change treatment, this will be independent from the study and he may do so freely according to regular clinical practice irrespective of the patient's participation.

J. Management and reporting of adverse reactions.

Proper notification and analysis of safety information of observational post-authorisation studies are essential for the protection of patients, investigators and the sponsor, and are required by the health authorities. This observational post-authorisation study conducted by Kyowa Kirin International plc. will be carried out following the legal requirements to ensure adequate notification of the safety information.

1. Definitions

Adverse event

Any undesired medical event that the patient could present during treatment with a drug, but which is not necessarily causally related to said drug.

Adverse drug reaction

Adverse drug reaction can be defined as a harmful response to a drug that occurs with doses normally used in humans for the prophylaxis, diagnosis or treatment of diseases or to change a physiological function.

A reaction, unlike an event, is characterised by a suspected causal relationship between the drug and the episode; in other words, it is deemed possible by the healthcare professional who reviews the case.

Serious adverse reaction

As described in ICH-E2A, a serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The characteristics/consequences should be considered at the time of the reaction to determine the seriousness. For example, life-threatening refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered serious.

2. Record of adverse events

Each investigator will be responsible for assessing the adverse events (either spontaneously reported by the patient or detected by the investigator) detected during the study period and for recording them in the Case Report Form (CRF), establishing:

- ⇨ Onset date,
- ⇨ Duration,
- ⇨ Intensity: Evaluated using the following classification:

- Mild: a generally transient adverse reaction that does not interfere with the patient's normal activities.
- Moderate: an adverse reaction that limits but does not prevent the patient's normal activities.
- Severe: adverse reaction in which discomfort or unbearable pain prevents the patient's normal activities.

⇨ Causality (definite, probable, possible, not related, unknown, not applicable).

- Definite: a clinical event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.
- Probable: a clinical event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
- Possible: a clinical event with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
- Not related: a clinical event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- Unknown: a clinical event that cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

⇨ Seriousness (serious, not serious).

⇨ Action taken by the doctor (e.g. none, dose increase, dose decrease, permanent discontinuation).

⇨ Outcome (e.g. fatal, recovered, recovered with sequelae, recovering, not recovered).

⇨ Suspected drug(s), if any.

All adverse events and special situations (ie. overdose, exposure to a product by breastfeeding, abuse, misuse, accidental exposure, medication error, etc.) following exposure to a Kyowa Kirin product must be systematically recorded on the CRF and in the patient's source documents, regardless of their severity or causality (ie, regardless of whether or not they have a relationship with any of the treatments that the patient is receiving). The collection of adverse events should start from the beginning of the treatment, and be carried out with all adverse events, whatever their severity, occurring within 30 days after the last use by the patient. The participating physician must assess all adverse events that occurred to record the relationship of the event with the product under investigation; the causal relationship of the adverse event must be recorded in the CRF. An adverse event will be considered an adverse reaction if there is at least one reasonable possibility (ie, a causal relationship is possible, probable or definite). If necessary, the sponsor (and / or the participating physician, when appropriate) will notify the adverse reaction to the local health authorities following the regulation in force.

All adverse events should be followed according to clinical practice, whatever their severity. This follow-up should be recorded in the patient's source documents (and documented following the sponsor's instructions).

All adverse events collected during the study will be summarised in the final study report.

3. Serious adverse event reporting procedures

The participating investigator must notify the serious adverse events to the Kyowa Kirin Local Safety Office PV mailbox, with the serious adverse event notification form immediately, in 24 hours after its knowledge.

Updated information relating to a previously reported SAE must be notified also in the adverse event notification form to Kyowa Kirin within 24 hours of receipt of the additional information. The investigator may be asked to provide follow-up information.

In case of adverse reactions following exposure to a non- Kyowa Kirin product, the participating investigator must notify the MAH or the competent authority according to local regulations.

Any event that requires hospitalisation, defined as an in-patient admission, regardless of length of stay (or prolongation of hospitalisation), occurred during the study must be reported as a serious adverse event, except for hospitalisations for the following reasons:

- Hospitalisations not intended to treat an acute illness or adverse event (e.g. for social reasons such as the expected admission in a long-term care centre).
- Surgical interventions or other procedures scheduled before entry into the study.

The investigator should immediately inform Kyowa Kirin Local Safety Office of any safety issues (overdose, abuse, medication error, etc.) associated with a Kyowa Kirin product with the serious adverse event notification form.

The sponsor assumes the responsibility of duly notifying the health authorities of the adverse events related to any drug of Kyowa Kirin, as established in the current legislation, as well as safety concerns associated with any drug of Kyowa Kirin.

Any confirmed pregnancy (of either a female patient or the partner of male patient) should be reported to Kyowa Kirin. Information should be provided using the pregnancy notification form and must be reported within 24 hours of the Investigator's knowledge. Follow-up information on the pregnancy outcome should be communicated by the investigator to Kyowa Kirin Local Safety Office as soon as available.

Kyowa Kirin Local Safety Offices:

Denmark: infose@kyowakirin.com T: +46 (0)70 620 17 74 Fax: Not available	**Finland:** infose@kyowakirin.com T: +46 (0)70 620 17 74 Fax: Not available

France: pvfrance@kyowakirin.com T: +33 1 55 39 14 30 Fax: +33 1 55 39 14 31	**Germany:** KyowaKirin-PhV@spm2-safety.com T: +49 (0)6201 846 40 66 Fax: +49 (0) 6201 570 59 71
Italy: pharmacovigilance@direnzo.biz T: +39 0677209020 Fax: +39 0670474067	**Netherlands:** pv-nl@kyowakirin.com T: +31 (0) 900-1231236 Fax: Not available
Norway: infose@kyowakirin.com T: +46 (0)70 620 17 74 Fax: Not available	**Spain:** farmacovigilanciaes@kyowakirin.com T: +34 91 534 37 10 / +34 660 88 33 22 Fax: +34 91 535 21 97
Sweden: infose@kyowakirin.com T: +46 (0)70 620 17 74 Fax: Not available	**UK:** medinfo@kyowakirin.com T: +44 (0)1896 664000 Fax: +44 (0)1896 664001

K. Plans for dissemination of results.

All the information related to the study is considered confidential and the property of the sponsor until its publication; it may not be revealed to others without the prior written consent of the sponsor and may not be used other than for the conduct of this study.

Only the sponsor or its representatives may report the information obtained in this study to physicians and regulatory agencies, except if required by law.

The results of this study may be published in scientific journals and/or presented at congresses.

The final decision to publish a manuscript/abstract/presentation will be made by the sponsor.

L. Resources for conducting the study and assigning tasks. Supply method for the medicinal product. Funding.

Kyowa Kirin International plc., the sponsor, will provide appropriate financial support to conduct the study.

Kyowa Kirin International plc. agrees to finance the study according to the guidelines of this protocol. This financing includes the cost of the studys' submission for evaluation by IEC/HA of participating countries according to local regulations, payments to investigators, the design, maintenance and management of the database, the statistical analysis and the statistical report.

M. References.

1. Van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, et al. Prevalence of pain in patients with cancer: A systematic review of the past 40 years. Ann Oncol 2007;18(9):1437-1449.
2. Peng WL, Wu GJ, Sun WZ, et al. Multidisciplinary management of cancer pain: A longitudinal retrospective study on a cohort of end-stage cancer patients. J Pain Symptom Manage 2006; 32(5): 444-452.
3. Zech DF, Grond S. Lynch J, et al. Validation of World Health Organization Guidelines for cancer pain relief: A 10-year prospective study. Pain 1995;63(1):65-76.
4. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009; 10:113–30. [PubMed: 19187889]
5. Jamison RN, Edwards RR. Risk factor assessment for problematic use of opioids for chronic pain. Clin Neuro-psychol. 2013; 27:60–80.
6. Warner EA. Opioids for the treatment of chronic noncancer pain. Am J Med. 2012; 125:1155–61. [PubMed: 22944349]
7. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. Mayo Clin Proc. 2009; 84:602–12. [PubMed: 19567714]
8. Fine PG, Mahajan G, McPherson ML. Long-acting opioids and short-acting opioids: appropriate use in chronic pain management. Pain Med. 2009; 10(Suppl 2):S79–88. [PubMed: 19691687]
9. Panchal SJ, Muller-Scwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract 2007;61(7):1181-1187.
10. Luo M, Li L, Lu CZ, Cao WK. Clinical efficacy and safety of lactulose for minimal hepatic encephalopathy: a meta-analysis. Eur J Gastroenterol Hepatol. 2011; 23:1250–7. [PubMed: 21971378]
11. Camilleri, M, Drossman, DA, Becker, G. Emerging treatments in neurogastroenterology: A multidisciplinary working group consensus statement on opioid-induced constipation. Neurogastroenterol Motil 2014; 26: 1386–1395.

12. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain. 2004; 112:372–80.
13. Hjalte F, Berggren AC, Bergendahl H, Hjortsberg C. The direct and indirect costs of opioid-induced constipation. J Pain Symptom Manage. 2010; 40:696–703.
14. Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol. 2012; 13:e58–68.
15. Pappagallo M. Incidence, prevalence and management of opioid bowel dysfunction. Am J of Surgery 2001;182:11s-8s.
16. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med 2014; 370: 2387–2396.
17. Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the Patient Assessment of Constipation Quality of Life questionnaire. Scand J Gastroenterol. 2005 May;40(5):540-51
18. Lewis SJ, Heaton KW. Stool form as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920-924.

N. Changes to the protocol.

All changes made to the protocol must be described in a written amendment that shall be signed by the investigator and the sponsor's representative and filed together with the protocol.

Protocol amendments must be made only with the prior approval of Kyowa Kirin. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. Where applicable, IEC must be informed of all amendments and give its approval.

Any changes made to this protocol shall be reported to the IEC that performed its review. In the case of substantial amendments, those that affect the objectives, methods or ethical considerations shall be subject to a new evaluation by the IEC that gave a favourable opinion on the protocol, and administrative authorisation shall be sought for the amendment. In amendments not affecting these points, the IEC will be notified, explaining why they are not classified as substantial.

Ñ. Practical considerations:

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC for written approval, where required by local law.

Before the start of the study, it must be approved by an accredited IEC. The start-up of the study will be carried out in accordance with the local legislation in each of the participating countries.

For administrative procedures, a document that specifies the responsibilities delegated by the sponsor in the person or company acting on its behalf will be submitted, if the sponsor does not submit the documentation.

Once the respective authorisations are obtained, the sponsor will have to inform the persons responsible for the healthcare providers where the study is conducted, providing them with a copy of the protocol and the documents that accredit IEC approval before contract signature, if applicable, according to local procedures and regulations.

The documentation related to the post-authorisation study comprises its master file and consists of the essential documents that enable evaluation of the conduct of the post-authorisation study and the quality of the data obtained. The study master file provides the basis for possible audits conducted by the sponsor through independent auditors and for inspections by the competent authorities.

The sponsor and the investigator will keep the essential documents and materials of each study for at least five years after its completion, or for longer if so specified in other applicable requirements.

The sponsor may decide to discontinue or terminate the study at any time and for any reason. This decision will be reported to the investigators in writing. Likewise, an investigator will have to immediately inform the sponsor in writing if he/she decides to withdraw from the study. In both cases, this decision must be documented and the IEC and the competent authorities, if applicable, must be informed according to local regulations.

1. Follow-up and final reports.

The sponsor will inform the Health Authorities of the start of the study, if applicable.

The definitive closure of this study will occur once all the data of the last patient included in the study has been collected. The statistical analysis will be performed after the closure of the clinical database and a report will be submitted, to be reviewed and approved by the study sponsor.

A copy of the final report will be sent to the IEC that authorised the conduct of the study, and to the Health Authorities, if applicable, according to local regulations.

2. Dissemination of results.

All the information related to the study is considered confidential and the property of the sponsor until its publication; it may not be revealed to others without the prior written consent of the sponsor and may not be used other than for the conduct of this study.

The results of this study may be published in scientific journals and/or presented at congresses.

The final decision to publish a manuscript/abstract/presentation will be made by the sponsor.

The sponsor may delay publication or communication for a limited time to protect the confidentiality or registered nature of any information contained therein.

To coordinate dissemination of data from this study, the sponsor encourages the formation of a publication committee consisting of several principal investigators and appropriate sponsor staff. The committee is expected to solicit input and assistance from other investigators and sponsor staff as appropriate. Membership on the committee does not guarantee authorship.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet all conditions.
- When a large, multi-centre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to the sponsor for corporate review.

O. Annexes:

1. Annex 1: Case Report Form.

Attached in a separate document.

2. Annex 2: Coordinating investigator's commitment.

Dr _____

Hospital _____

Hereby declares:

That he has evaluated the study protocol entitled: "Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).", version 2.0 dated on April, 06, 2018, with study code NACASY, and undertakes:

- To sign the protocol and any amendment thereto with the sponsor.
- To take joint responsibility with the sponsor for the production of the follow-up and final reports.
- To contribute to the dissemination of the study results in collaboration with the sponsor
- To sign an agreement in which he is recognised as the study investigator and confirms that he is conversant with the protocol and any amendments to same, and agrees with it in all its terms.
- To provide information to the study subjects and obtain their consent.
- To undertake to correctly collect, record and report the data, and be liable for their updating and quality before the auditors involved.
- To report adverse events to the sponsor as established in the protocol.
- To respect the confidentiality of the data of the patients participating in the study.
- To facilitate monitoring visits, sponsor audits and health authority inspections.
- To be capable of answering the questions of the scientific and professional community with regard to the study's objectives, basic methodology and the significance of the results.

Investigator's signature: _____ Date: _____/_____/_____
Day Month Year

3. Annex 3: IEC Approval.

Attached in a separate document.

4. Annex 4: Summary of Product Characteristics for the study medication.

Attached in a separate document.

5. Annex 5: Patient Information Sheet.

Attached in a separate document.

6. Annex 6: Informed Consent Form.

Attached in a separate document.

7. Annex 7: Financial summary.

Attached in a separate document.

8. Annex 8: Investigator's commitment.

Dr _____

Department: _____

Hospital: _____

Hereby declares:

That he has evaluated the study protocol entitled: “Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosed with Opioid Induced Constipation (OIC).”, version 2.0 dated on April, 06, 2018, with study code NACASY, and undertakes:

- To sign an agreement in which he is recognised as the study investigator and confirms that he is conversant with the protocol and any amendment to same, and agrees with it in all its terms.
- To provide information to the study subjects and obtain their consent.
- To undertake to correctly collect, record and report the data, and be liable for their updating and quality before the auditors involved.
- To report adverse events to the sponsor as established in the protocol.
- To respect the confidentiality of the data of the patients participating in the study.
- To facilitate monitoring visits, sponsor audits and health authority inspections.
- To be capable of answering the questions of the scientific and professional community with regard to the study's objectives, basic methodology and the significance of the results.

Investigator's signature: _____ Date: _____/_____/_____
Day Month Year