PASS Information

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Joint PASS	No
Research question and objectives	This study is designed to describe the characteristics of patients prescribed naloxegol at time of first prescription, including the use of naloxegol in non-indicated populations, and treatment patterns of naloxegol in follow-up
Country(-ies) of study	United Kingdom, Germany, Norway, and Sweden
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1. Abstract

Title

An Observational Post-Authorisation Safety Study (PASS) Study of MOVENTIG® (Naloxegol) Drug Utilisation in Selected European Populations

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Keywords

naloxegol, drug utilisation, Europe, opioid-induced constipation, laxative

Rationale and Background

AstraZeneca (AZ), the original market authorisation holder (MAH) for naloxegol, committed to conducting this post-authorisation observational safety study (PASS). The study is an obligation under the terms of the risk management plan (RMP). After acquiring naloxegol, Kyowa Kirin International (KKI) have taken over the requirements for the market authorisation (including this PASS) from AZ. This PASS is to determine the characteristics of patients prescribed naloxegol at time of first prescription and treatment patterns of naloxegol in the follow-up period in the United Kingdom (UK), Norway, Sweden, and Germany (added Q2, 2016).

Research Question and Objectives

The overall research questions for this study are: 1) What are the demographic, clinical, and treatment characteristics (including dose) at baseline of patients prescribed naloxegol in real-world practice (including the use of naloxegol in non-indicated populations)? and 2) What are the treatment patterns of naloxegol utilisation during follow-up (including dosing and the use of naloxegol in non-indicated populations and in vulnerable/special populations)?

Primary objectives:

- To describe the characteristics of patients prescribed naloxegol at time of first prescription (demographics, targeted co-morbidities, targeted co-medications, provider characteristics, and indication characteristics).
- To describe any of the following treatment patterns:

- Discontinuation of naloxegol (permanently during the observation period)
- Switching from naloxegol to other drug(s) potentially used by patients with opioid-induced constipation (OIC)
- Prescription of other drug(s) potentially used by patients with OIC in the same period when naloxegol is prescribed (augmentation)
- Restart in the prescription of naloxegol (after temporary discontinuation or treatment holiday)
- Continuous treatment with naloxegol during the study period
- Change in dosing

Exploratory objective: To identify predictors of length of naloxegol use

Study Design

This is a drug utilisation, retrospective cohort study using observational data from multiple countries: the UK, Germany (added in Q2, 2016), Norway, and Sweden.

Setting

The study period started on the date of naloxegol launch, or the first naloxegol prescription in the database in each of the countries, and ended at the time point when the target sample size of 3,000 exposed patients across databases was reached. The target sample size was reached in 2019, with data from Norway and Sweden up to 2018; therefore, no further datacut was requested in Norway and Sweden. In the UK and Germany, the most recent datacuts by the time of extraction were used for this study.

- UK: 1 October 2015 to 30 September 2019 (the most recent data available)
- Norway: 1 December 2015 to 31 December 2018 (target sample size reached in 2018)
- Sweden: 7 October 2015 to 31 December 2018 (target sample size reached in 2018)
- Germany: 1 August 2015 to 31 January 2020 (the most recent data available)

Subjects and Study Size, including Dropouts

Patients who were newly prescribed naloxegol were identified from the selected data sources in the targeted countries. Patients analysed in this study were those who have at least 12 months of continuous data available prior to first prescription.

Variables

Variables in this drug utilisation study include demographic, targeted co-morbidities, targeted co-medications, medical history, health provider characteristics, and naloxegol exposure and treatment outcomes (discontinuation, switching, augmentation, restart of naloxegol after temporary discontinuation and continuous treatment with naloxegol).

Data Sources

The data sources targeted for this study include The Health Improvement Network (THIN) in the UK, the IMS® Longitudinal Prescription Database in Germany, the Norwegian Prescription Database, and the Swedish Prescribed Drug Register. Selected data sources in the UK and Germany are expected to be a representative sample of patients who are naloxegol exposed in those countries (naloxegol prescribers in THIN were all general practitioners). Selected data sources in Norway and Sweden cover the countries' entire populations.

Results

In total, 17,254 patients with less than 12 months of data prior to index date were included in the analyses (13,949 [80.9%], 1,717 [10.0%], 1,324 [7.7%] and 264 [1.5%] from the four selected databases in Germany, Sweden, Norway and the UK, respectively). Mean age for naloxegol users was 57.1 years (SD: 17.3), 63.9 years (16.5), 63.9 years (16.5) and 68.8 years (14.8) in UK, Norway, Sweden and Germany, respectively. The majority of patients had prior use of opioids (ranging from 91.9% to 99.6 %) and laxative (ranging from 69.9% to 92.7%). The most frequently used opioid class across four countries was 'other' opioid (e.g., tramadol, opioids in combination with antispasmodics or opioids in combination with non-opioid analgesics) with prevalence use ranging from 51.6% in Germany to 91.3% in the UK, followed by natural opioid alkaloids, with prevalence use ranging from 67.1% in Germany to 90.3% in Sweden. The median amount of prior opioid use per day was highest in Sweden (59.6 morphine milligram equivalent [MME] per day), followed by Norway (57.8 MME), the UK (45.0 MME) and Germany (41.7 MME). The most common co-morbidities across all countries was pain conditions (ranged from 85.3% to 93.2%). Gastrointestinal (GI) conditions were also common (ranging from 49.9% to 84%). Cancer presented in 28.8% of all patients in the UK, 23.1% in Germany, 55.4% in Sweden.

The median naloxegol treatment duration (time until the discontinuation) was longest in Norway, followed by the UK, Sweden and Germany (Norway: 90 days [IQR: 30–180 days], UK: 61 days [30–224 days], Sweden: 40 days [30–120 days] and Germany: 30 days [IQR: 30–90 days]). Dose of the first naloxegol prescription was 25 mg per day in most patients across countries (95.3%, 74.4%, 70.1%, and 64.6%, UK, Norway, Sweden, UK and Germany, respectively). Dose increase during follow-up was not frequent, ranging from 1.2% in Norway to

7.2% in the UK. Dose decrease ranged from 0.8% in Norway to 2.7% in the UK and Sweden. Treatment discontinuation was the most common in Germany (90.9%) and the least common in Norway (55.1%). Treatment switch was the most common in Sweden (29.4%) and the least common in Germany (14.4%). Treatment augmentation was the most common in the UK (31.1%) and the least common in Germany (9.5%). Among those who discontinued, naloxegol restart was the most common in the UK (15.5%) and the least common in Norway (12.5%).

Subgroup analyses show that the use of naloxegol was common in patients aged ≥65 years old (33.3% to 63.5%), patients with CV diseases (35.6% to 79.5%). With regards to potential off-label use, 8.5% (Norway) to 24.9% (Germany) of all naloxegol users had no history of current, regular opioid use, and 16.5% (Sweden) to 42.3% (Norway) had no record of laxative use within 180 days. The subgroup with concurrent use of CYP3A inhibitors, inducers or Pgp modulators (strong, moderate or weak) was large in Norway and Sweden (Sweden: 54.9%, Norway: 54.0%, Germany: 35.8%, UK: 24.2%). By potency, concurrent use with strong CYP3A inhibitors was high in Norway (12.4%), concurrent use with strong CYP3A inducers was high in Germany (23.6%).

In the meta-analyses, no factors were associated with more than 15% increase of discontinuation risk. Prior use of laxative was associated with 16% decrease of naloxegol discontinuation risk (HR: 0.84 [0.76, 0.93]). Concurrent use of non-opioid analgesics was associated with 29% increase of risk of switching (HR: 1.29 [1.20, 1.40]); naloxegol users in the 35-54 years old age class (compared with ≥75 years old) were 15% less likely to switch (HR: 0.85 [0.75, 0.97]). Concurrent use of CYP3A inducers, concurrent use of non-opioid analgesics, and history of cancer was associated with 19%, 33% and 35% higher risk of augmentation (HR: 1.19 [1.08, 1.30]), 1.33 [1.21, 1.45]) and 1.35 [1.02, 1.81], respectively); no factor was significantly associated with a decreased risk of augmentation.

Discussion

Overall, naloxegol was used in short to medium term in the four selected countries. The use of naloxegol was common in vulnerable populations, such as patients with CV diseases, the elderly and patients with cancer. More robust data on naloxegol safety in these vulnerable populationsare needed. Concurrent use with strong CYP3A inhibitors in Norway and CYP3A inducers in Germany was common. Physicians should carefully consider when and how to prescribe strong CYP3A inhibitors or inducers simultaneously with naloxegol. Off-label use in patients with no regular opioid use or prior laxative use should be avoided. The results from this study can be generalised to the UK primary care setting, Norwegian and Swedish primary and secondary care settings, and outpatient care in Germany.