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An observational post-authorization safety study (PASS) of naloxegol drug utilization in four European countries

Gunnvald Kvarstein[1,2] | Anna MS Kindlundh-Högberg[3] | Mounir Ould Setti[4,5] | Rafik Namane[3] | Ruvimbo Muzwidzwa[6] | Hartmut Richter[7] | Katja M. Hakkarainen[8,9]

[1]Institute for Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[2]Department of Pain Management and Research, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway

[3]Kyowa Kirin International plc, Galabank Business Park, Galashiels, UK

[4]Global Database Studies, Real World Solutions, IQVIA, Espoo, Finland

[5]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

[6]RWE DBS Epidemiology, IQVIA, London, UK

[7]Epidemiology, Real World Solutions, IQVIA, Frankfurt/Main, Germany

[8]Global Database Studies, Real World Solutions, IQVIA, Mölndal, Sweden

[9]Epidemiology & Real-World Science, RWE Scientific Affairs, Parexel International, Gothenburg, Sweden

Correspondence
Katja M. Hakkarainen, Epidemiology & Real-World Science, RWE Scientific Affairs, Parexel International, Gothenburg, Sweden.
Email: research@kmhakkarainen.com

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Kyowa Kirin Pharmaceutical Development

Abstract

Purpose: Naloxegol has been shown to be an efficient alternative to treat opioid-induced constipation (OIC). This study aimed at describing the characteristics of naloxegol users and assessing patterns of naloxegol use and associated factors.

Methods: This drug utilization cohort study used observational registry data on patients newly prescribed naloxegol in four European countries. Patient characteristics and patterns of naloxegol use and associated factors were described.

Results: A total of 17 254 naloxegol users were identified across the countries. Their median age was 56–71 years, and each country had a majority of women (ranging 57.5%–62.9%). Multiple comorbidities, including cancer, were common. Natural opium alkaloids and osmotically acting laxatives (excluding saline) were the most frequently used opioids and laxatives. Overall prior use of opioids ranged from 91.9% to 99.6% and overall prior use of laxatives ranged from 69.9% to 92.4%. Up to 77.7% had prior use of medications with interaction potential, and up to 44.5% used them concurrently with naloxegol. Naloxegol was discontinued by 55.1%–90.9% of users, typically during the first 30 days. Approximately 10%–30% switched to or augmented the treatment with another constipation medication or restarted naloxegol after discontinuation. Augmentation with another constipation medication was relatively common, suggesting that naloxegol was used for multifactorial constipation.

Conclusion: The present study reflects real-world clinical use of naloxegol, including in vulnerable patient groups. Some naloxegol users lacked laxative or regular opioid use within six months before index date or used naloxegol concomitantly with medications presenting an interaction potential.

KEYWORDS
discontinuation, drug utilization, laxative, Moventig®, Naloxegol, opioid-induced constipation, PAMORA

Key Points

- Naloxegol was typically used by older adults, women, and patients with multiple comorbidities, including conditions with precaution of naloxegol use.

- Natural opium alkaloids and osmotically acting laxatives (excluding saline) were the most frequently used opioids and laxatives, respectively.
- Overall prior use of opioids was 98.3%–99.6% in Sweden, Norway, and the UK, but 91.9% in Germany. Overall prior use of laxatives was 92.7% and 92.4% in Sweden and the UK, but 69.9% and 71.1% in Germany and Norway.
- Up to three quarters used medications with interaction potential prior to naloxegol use and up to 44% used them concomitantly with naloxegol. Many of these patients had cancer.
- A third to a half of naloxegol discontinuations occurred during the first 30 days. The proportion of patients who discontinued declined after 3 months.

Plain Language Summary

Opioid use is typically accompanied by constipation that is often resistant to common laxative treatments. Naloxegol has been shown to be an efficient option to treat opioid-induced constipation, and this study aims at describing the characteristics of naloxegol users and their patterns of utilization in four European countries: Germany, Norway, Sweden, and the United Kingdom. Our study found that naloxegol was used mostly by older adults (aged 56–71 years), women (about 60% of total users), and patients with multiple comorbidities, including conditions with precaution of naloxegol use. A number of participants used naloxegol in concomitance with medications with interaction potential (44%). However, use of medication with interaction potential was more frequent prior to naloxegol initiation (78%). Also, prior laxative and prior high-dose opioid use decreased the likelihood of discontinuation. Naloxegol discontinuation occurred typically within the first month of treatment, and treatment augmentation with another constipation medication was also common.

1 | INTRODUCTION

Chronic pain is a major public health challenge globally and in Europe.[1–3] Patients with chronic pain are frequently treated with opioids.[4–6] Around 80% of these patients report one or more side effects,[7,8] notably opioid-induced constipation (OIC), which is reported in 51%–87% of chronic cancer-related pain patients and in 41%–57% of chronic non-cancer pain patients.[7,9–11] Laxatives are considered the first line therapeutic option for OIC,[12,13] but estimates suggest that more than half of patients with OIC fail to respond adequately to laxatives.[14,15] Peripherally acting μ-opioid receptor antagonists (PAMORAs) have been shown to be an efficient alternative to laxatives in the treatment of OIC.[16] At present, four PAMORAs approved by the United States' Food and Drug Administration (FDA) are available for treating OIC orally: methylnaltrexone, alvimopan, naldemedine, and naloxegol.[17,18]

Chemically derived from naloxone by the addition of PEGylated (polyethylene glycol modified) chain,[19] naloxegol (Moventig®) was the first oral PAMORA to receive approval from both the FDA (September 2014) and the European Medicines Agency (EMA) (December 2014) for treating OIC.[20,21] Naloxegol is indicated for the treatment of OIC in adult patients who have had an inadequate response to laxative(s), that is, concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days. In the current summary of product characteristics (SmPC), naloxegol is contraindicated in patients with an increased risk of gastrointestinal (GI) obstruction or perforation and in patients concomitantly using strong CYP3A4 (cytochrome P450, family 3A4) inhibitors. Naloxegol is not recommended in patients with severe hepatic impairment, concomitant use of CYP3A4 inducers, age < 18 years, pregnancy, or breastfeeding.[22] In clinical trials,[23–26] naloxegol was associated with improved outcomes compared to placebo: higher responder rates amongst patients who had responded inadequately to laxative treatment, shorter time to first spontaneous bowel movement, and better patient assessment of constipation symptoms. Naloxegol was generally well-tolerated both short- and long-term, with no mean difference from placebo or usual care in average pain intensity, daily opioid dose, or in opioid withdrawal scores.

To further understand the safety and utilization of naloxegol in adults treated for OIC in real-world settings, an observational post-authorization safety study (PASS) was conducted in Europe, as requested by the EMA.[27] This study was an obligation under the terms of the risk management plan, and its specific objectives were to describe the characteristics of naloxegol users and to assess patterns of naloxegol use and associated factors.

2 | METHODS

2.1 | Design, settings, and participants

This is a retrospective drug utilization cohort study (EUPAS12598) that used observational registry data on patients newly prescribed naloxegol in four European countries: Germany (IQVIA Longitudinal Prescription Database, covering 60% of all reimbursed prescriptions in Germany)[28] (from 1 August 2015 to 31 January 2020), Norway

(multiple national registries, all drug prescriptions in Norway)[29–31] (from 1 December 2015 to 31 December 2018), Sweden (multiple national registries, all drug prescriptions in Sweden)[32,33] (from 7 October 2015 to 31 December 2018), and the UK (the Health Improvement Network database, covering 6% of the UK population)[34,35] (from 1 October 2015 to 30 September 2019). A more detailed description of the data sources is provided in Data S1. This is a descriptive drug utilization study focusing exclusively on reporting the patterns of drug utilization among naloxegol users. Therefore, the study does not include a comparator group of patients treated with other alternatives.

As the inclusion criterion, naloxegol users identified during the study period, starting on the day of marketing authorization of naloxegol in each of the study countries, were included, representing all naloxegol users in real-world settings. Therefore, all study participants were, by design, new users of naloxegol. The term naloxegol "use" is applied, although it could not be established whether the prescribed/dispensed drugs were actually used by the patients. As the exclusion criterion, patients were excluded if lacking a minimum 12-month of available data before the first prescription of naloxegol (index date). Data were collected from the index date until the end of follow-up, defined as either the end of the study period, disenrollment from the database, or death, whichever happened first.

2.2 | Study variables

Data collected on patient characteristics covered demographics, comorbidities (including pain conditions and targeted comorbidities, namely cancer and cardiovascular [CV], pulmonary, neurological, gastrointestinal, and other conditions), and prior and concomitant medications (including patterns of opioid use), among other characteristics.

Variables on naloxegol use patterns included supply duration of prescribed/dispensed naloxegol, dose of first naloxegol prescription, and dose increase/decrease. Further, indicated by the prescribed drug dose and prescribed or dispensed quantity (package size; number of packages), patterns of naloxegol use determined treatment discontinuation (hereafter, discontinuation), switching to another constipation medication (switching), naloxegol augmentation with another constipation medication (augmentation), and treatment restart (restart) (Data S2).

In addition, a selection of variables was considered to define subpopulations of interest for subgroup analyses with regards to 1. *Use of naloxegol by patients*: age <18 years; no regular (for at least one month) opioid use within 6 months before index date; no laxative use within 6 months before index date; and 2. *Special populations and populations with precautions or contraindications for naloxegol use*: age ≥65 years; pregnancy; concurrent use of naloxegol with medications presenting a drug–drug interaction potential, including a CYP3A4 inhibitor, a CYP3A4 inducer, or a P-gp (permeability glycoprotein) modulator; concurrent use of naloxegol with methadone; prior hepatic impairment; prior renal impairment; and history of cardiovascular disease. The subgroups of interest reflected patients with possible deviation from the SmPC and vulnerable populations represented as special populations and populations with precautions or contraindications for naloxegol use, according to the SmPC.[22]

2.3 | Statistical analysis

First, characteristics of study participants and their patterns of naloxegol use were described by country, with summary statistics and proportions.

Second, subgroup analyses were performed through descriptive statistics of the characteristics and patterns of naloxegol use for each of the subpopulations of interest, in each study country.

Third, for each country, using Cox proportional hazards regression, naloxegol users' characteristics were assessed in terms of hazard ratios (HRs), for their association with each of the following variables as dependent variables: discontinuation, switching, augmentation, and restart. In the models assessing discontinuation, switching, or augmentation, the analyzed population included all naloxegol users, and the period from index date to event occurrence or end of follow-up was set as the period at risk. The analysis of restart concerned only participants who discontinued naloxegol use during the study period, with the period at risk defined from discontinuation to restart or end of follow-up. To identify factors associated with the patterns of naloxegol use, a stepwise approach for variable selection was used in the Cox regression models, testing different sets of patient characteristics, as independent variables with the minimum Akaike Information Criteria.

Fourth, a common set of factors associated with the patterns of naloxegol use, relevant across study countries, was selected based on the previously described variable selection process and the clinical importance. This common set of variables was used to fit Cox proportional hazards regression models for each country, assessing the outcomes of discontinuation, switching, augmentation, and restart, as in the second step of the analyses. The resulting HRs from each country were combined through a random-effects model meta-analysis. Heterogeneity between countries was assessed using I^2 statistic and was presented along with overall estimates.

Statistical analyses were carried out using SAS® software v9.4, Stata software v11, and R programming language 2.15.2.

3 | RESULTS

3.1 | Characteristics of naloxegol users

Among a total of 24 807 new naloxegol users identified during the study period, 17 254 were included in the study: 13949 (80.9%) from Germany, 1324 (7.7%) from Norway, 1717 (10.0%) from Sweden, and 264 (1.5%) from the UK. Study participants were mostly women (59.2% in Germany, 57.5% in Norway, 58.9% in Sweden, and 62.9% in the UK) and had a median age (interquartile range [IQR]) of 71 (59–80) years in Germany, 66 (51.75–76) in Norway, 64 (50–74) in Sweden, and 56 (45–70) in the UK. Most naloxegol users reported prior use of

TABLE 1 Selected characteristics of naloxegol users and patterns of naloxegol use.

Characteristics		Germany[a] (*n* = 13 949)	Norway (*n* = 1324)	Sweden (*n* = 1717)	UK (*n* = 264)
Selected characteristics of naloxegol users					
Median age at index date, years (IQR)		71 (59–80)	66 (51.75–76)	64 (50–74)	56 (45–70)
Female gender, *n* (%)		7454 (59.2%)[b]	761 (57.5%)	1011 (58.9%)	166 (62.9%)
Overall prior opioid use, *n* (%)		12 825 (91.9%)	1311 (99.0%)	1688 (98.3%)	263 (99.6%)
Overall prior laxative use, *n* (%)		9747 (69.9%)	941 (71.1%)	1592 (92.7%)	244 (92.4%)
Overall daily dosage of prior opioid use[d], *n* (%)		12 208 (87.5%)	1270 (95.9%)	1620 (94.4%)	102 (38.6%)
Prior constipation, *n* (%)		NA	426 (32.2%)	481 (28.0%)	147 (55.7%)
Comorbidities, *n* (%)	CV disease conditions	11 090 (79.5%)	579 (43.7%)	868 (50.6%)	134 (50.8%)
	Neurologic conditions	7354 (52.7%)	292 (22.1%)	332 (19.3%)	75 (28.4%)
	GI disease conditions	11 720 (84.0%)	744 (56.2%)	856 (49.9%)	206 (78.0%)
	Psychiatric conditions	10 011 (71.8%)	490 (37.0%)	661 (38.5%)	187 (70.8%)
	Renal disease	172 (1.2%)	411 (31.0%)	461 (26.8%)	115 (43.6%)
	Hepatic disease	984 (7.1%)	254 (19.2%)	317 (18.5%)	23 (8.7%)
	Cancer	3224 (23.1%)	781 (59.0%)	951 (55.4%)	76 (28.8%)
	Pain conditions	12 996 (93.2%)	1052 (79.5%)	1464 (85.3%)	239 (90.5%)
History of GI surgery, *n* (%)		NA	627 (47.4%)	701 (40.8%)	72 (27.3%)
Prior medications, *n* (%)	CV disease/risk factor	11 151 (79.9%)	946 (71.5%)	1246 (72.6%)	195 (73.9%)
	Psychiatric	9837 (70.5%)	1197 (90.4%)	1532 (89.2%)	243 (92.0%)
	Neurologic[e]	7292 (52.3%)	817 (61.7%)	1093 (63.7%)	193 (73.1%)
	Musculoskeletal	10 805 (77.5%)	1175 (88.7%)	1515 (88.2%)	224 (84.8%)
	Alimentary tract and metabolism[c]	13 349 (95.7%)	1246 (94.1%)	1634 (95.2%)	253 (95.8%)
	Anti-infectives for systemic use	10 272 (73.6%)	1282 (96.8%)	1623 (94.5%)	260 (98.5%)
	Non-opioid analgesics	12 207 (87.5%)	1190 (89.9%)	1613 (93.9%)	227 (86.0%)
	CYP3A4 inducer	6998 (50.2%)	955 (72.1%)	1210 (70.5%)	178 (67.4%)
	CYP3A4 inhibitor	5731 (41.1%)	998 (75.4%)	1125 (65.5%)	205 (77.7%)
	P-gp modulator	3575 (25.6%)	736 (55.6%)	577 (33.6%)	200 (75.8%)
Concomitant medications, *n* (%)	CV disease/risk factors	8870 (63.6%)	674 (50.9%)	882 (51.4%)	119 (45.1%)
	Psychiatric	7318 (52.5%)	958 (72.4%)	1272 (74.1%)	150 (56.8%)
	Neurologic[e]	4734 (33.9%)	487 (36.8%)	741 (43.2%)	74 (28.0%)
	Musculoskeletal	4807 (34.5%)	456 (34.4%)	649 (37.8%)	34 (12.9%)
	Alimentary tract and metabolism[c]	11 875 (85.1%)	1060 (80.1%)	1385 (80.7%)	176 (66.7%)
	Anti-infectives for systemic use	4057 (29.1%)	513 (38.7%)	550 (32.0%)	60 (22.7%)
	Opioids	11 947 (85.6%)	1292 (97.6%)	1641 (95.6%)	240 (90.9%)
	Non-opioid analgesics	6647 (47.7%)	892 (67.4%)	1211 (70.5%)	110 (41.7%)
	CYP3A4 inducer	3451 (24.7%)	560 (42.3%)	764 (44.5%)	43 (16.3%)
	CYP3A4 inhibitor	1679 (12.0%)	271 (20.5%)	317 (18.5%)	12 (4.5%)
	P-gp modulator	1202 (8.6%)	138 (10.4%)	175 (10.2%)	29 (11.0%)
Patterns of naloxegol use					
Median supply duration of prescribed/dispensed naloxegol, days (IQR)		30 (30–90)	90 (30–180)	40 (30–120)	61 (30–224)
Dose of first naloxegol prescription	12.5 mg per day, *n* (%)	4935 (35.4%)	62 (4.7%)	440 (25.6%)	79 (29.9%)
	25 mg per day, *n* (%)	9014 (64.6%)	1262 (95.3%)	1277 (74.4%)	185 (70.1%)
Naloxegol dose increase, *n* (%)		843 (6.0%)	16 (1.2%)	67 (3.9%)	19 (7.2%)

TABLE 1 (Continued)

Characteristics		Germany[a] (*n* = 13 949)	Norway (*n* = 1324)	Sweden (*n* = 1717)	UK (*n* = 264)
Naloxegol dose decrease, *n* (%)		331 (2.4%)	11 (0.8%)	47 (2.7%)	7 (2.7%)
Discontinuation of naloxegol, *n* (%)	Temporary discontinuation	1754 (12.6%)	165 (12.5%)	231 (13.5%)	41 (15.5%)
	Permanent discontinuation[f]	10 922 (78.3%)	564 (42.6%)	795 (46.3%)	122 (46.2%)
	Overall discontinuation	12 676 (90.9%)	729 (55.1%)	1026 (59.8%)	163 (61.7%)
Discontinuation (overall) by timing of discontinuation, *n* (%)	Discontinuation of naloxegol at 1 month	7537 (54.0%)	419 (31.6%)	608 (35.4%)	88 (33.33%)
	Discontinuation of naloxegol at 3 months	10 178 (73.0%)	559 (42.2%)	785 (45.7%)	111 (42.05%)
	Discontinuation of naloxegol at 6 months	11 548 (82.8%)	647 (48.9%)	904 (52.6%)	140 (53.03%)
	Discontinuation of naloxegol at 12 months	12 275 (88.0%)	698 (52.7%)	989 (57.6%)	148 (56.06%)
Switching, *n* (%)		2004 (14.4%)	210 (15.9%)	504 (29.4%)	70 (26.5%)
Augmentation, *n* (%)		1323 (9.5%)	329 (24.8%)	490 (28.5%)	82 (31.1%)
Restart, *n* (%)[g]		1754 (13.8%)	165 (22.6%)	231 (22.5%)	41 (25.2%)
Continuous treatment, n (%)		1273 (9.1%)	595 (44.9%)	691 (40.2%)	101 (38.3%)

Abbreviations: CV, cardiovascular; CYP3A4, cytochrome P450, family 3A4; GI, gastrointestinal; IQR, interquartile range; *n*, number of patients; NA, not available; P-gp, permeability glycoprotein; UK, United Kingdom.

[a]Data on age and gender are not available for 14 (0.1%) and 1355 (9.7%) patients in Germany.

[b]This proportion was calculated excluding, from the denominator, patients with missing information on gender.

[c]Not including laxatives.

[d]Data on daily dosage amount of prior opioid 'missing' for 161 (61%) patients in the UK.

[e]Concerns discontinuations of naloxegol which were not followed by a subsequent prescription or dispensation of naloxegol.

[f]Not including opioids.

[g]Concerns naloxegol users who have discontinued naloxegol.

opioids (from 91.9% in Germany to 99.6% in the UK) and prior use of laxatives (from 69.9% in Germany to 92.7% in Sweden) (Table 1).

Among classes of opioids, natural opium alkaloids were the most frequently used (73.0% in Germany, 79.6% in Norway, 91.9% in Sweden, and 83.3% in the UK), and among classes of laxatives, osmotically acting laxatives (excluding saline) were the most frequently used (87.0%, 79.0%, 93.8%, and 95.9%, in the respective study countries). The median (IQR) dosage of prior opioid use per day was the highest in Sweden (59.64 MME [morphine milligram equivalent]/day [18.7–164.2]), followed by Norway (57.75 MME/day [16.7–183.0]), UK (45 MME/day [30.0–100.0]), and Germany (41.7 MME/day [22.8–75.0]). The proportion of patients prescribed >100 MME per day (last opioid prescription within the 6 months prior to the index date), among those with prior opioid prescriptions, was the highest in Norway (38.0%) and Sweden (37.0%) (24.5% in the UK and 14.5% in Germany) (Data S3).

Most but not all naloxegol users had a pain condition (93.2% in Germany, 90.5% in the UK, 85.3% in Sweden, and 79.5% in Norway). German and British users had a high prevalence of GI disorders (84.0% and 78.0%, respectively) and psychiatric conditions (71.8% and 70.8%, respectively). Also, CV conditions were observed in 79.5% of the patients in Germany, but in only 43.7%–50.8% of the patients in the other countries. On the other hand, the proportion of patients with cancer appeared markedly higher in Norway (59.0%) and Sweden (55.4%) than in the UK (28.8%) and Germany (23.1%). The majority of patients across all four countries had prior or concomitant medication to naloxegol. Use of medication presenting a potential of interaction with naloxegol varied between 25.6% and 77.7% prior to naloxegol use and between 4.5% and 44.5% in concomitance with naloxegol (Table 1).

3.2 | Patterns of naloxegol use

Naloxegol was typically prescribed for three months in Norway (median, 90; IQR, 30–180), two in the UK (61, 30–224), and about one month in Sweden (40, 30–120) and in Germany (30, 30–90). Most study participants were prescribed 25 mg of naloxegol per day on their first prescription (from 64.6% of users in Germany to 95.3% of users in Norway). Only a small proportion of users increased (1.2%–7.2% across countries) or decreased (0.8%–2.7%) their naloxegol dosage during follow-up, while a considerable proportion of patients discontinued naloxegol during the study period (90.9% in Germany, and 55.1%–61.7% in the other study countries) (Table 1).

Median time until naloxegol discontinuation was 30 days in each country in the main cohort (Data S3). Most discontinuations seemed to occur within 1 month after naloxegol initiation (from 31.6% of all users in Norway to 54.0% in Germany). The proportions of those who discontinued in each country did not seem to increase significantly after 3 months (Table 1 and Data S3). The proportions of those switching naloxegol to another constipation medication (i.e., laxatives, lubiprostone, linaclotide, or prokinetics), augmenting naloxegol with another constipation medication, or restarting naloxegol after discontinuation ranged from about 10% to 30% of the participants in each country (Table 1).

3.3 | Subgroup analyses

The proportion of naloxegol users aged ≤18 years was less than 1.1% in each of the study countries. Users with no history of current or regular opioid use, within 6 months before index date, represented a quarter of the patients in Germany (24.9%), and less than 14.4% in the other countries. The proportions of naloxegol use, with regards to the absence of history of laxative use within 6 months before index date, were 35.7% in Germany, 42.3% in Norway, 16.5% in Sweden, and 17.4% in the UK. However, figures in relation to naloxegol discontinuation, switching, augmentation, and restart in the subpopulations with patients aged <18 years, no regular opioid use within 6 months before index date, or no laxative use within 6 months before index date presented a roughly similar pattern to those in the main cohort (Data S4).

In terms of special populations and populations with precautions or contraindications for naloxegol use, the proportion of users aged ≥65 years was nearly two-thirds of the users in Germany (63.5%), half of the users in Norway (52.9%) and in Sweden (48.2%), and a third of the users in the UK (33.3%). These naloxegol users seemed to have higher proportions of CV conditions, but lower proportions of psychiatric conditions than those in the main cohort. Pregnancy could not be assessed in Germany, but it was reported in very low proportions in the other countries (0.2% in Norway, 0.3% in Sweden, and 0.0% in the UK). Concurrent use of naloxegol with a CYP3A4 inhibitor, a CYP3A4 inducer, or a P-gp modulator was reported among a third of the users in Germany, half of the users in Norway and in Sweden, and less than a quarter of the users in the UK. Naloxegol users concurrently using these drugs seemed to have higher proportions of cancer than the main cohort. Concurrent use of naloxegol with methadone and history of addiction concerned mainly patients from Sweden and Norway and presented with a younger median age and slightly higher proportions of males than the main cohort. The proportions of patients with a history of renal impairment varied across countries without exceeding 20% and showed higher proportions of patients who started naloxegol at 12.5 mg per day than in the main cohort. On the other hand, the proportions of naloxegol users with a history of a CV disease varied widely, ranging from 35.6% in the UK to 79.5% in Germany. This last subgroup appeared slightly older than the main cohort across countries. Overall, patterns of naloxegol discontinuation, switching, augmentation, and restart across subgroups of special populations and populations with precautions or contraindications for naloxegol use appeared relatively comparable to the proportions in the main cohort (Data S4).

3.4 | Factors associated with the patterns of naloxegol use

In the meta-analyses of factors associated with the patterns of naloxegol use (Table 2, more details in Data S5), prior opioid use with a daily dose higher than 50 MME was associated with a decrease in discontinuation, with a very low heterogeneity across the countries (I^2, 0.0%). Prior laxative use was also found associated with a decrease in discontinuation (HR, 0.84; 95% CI, 0.76–0.93; I^2, 38.0%). On the other hand, no use of opioids 6 months before index date was found associated with a decrease in restart (0.63; 0.50–0.80; 0.0%). Concurrent use of non-opioid analgesics and history of cancer were found associated with a higher risk of switching and augmentation, while concurrent use of CYP3A4 inducers were associated with an increased risk of augmentation (Table 2). The results of the Cox regression analyses assessing factors associated with the patterns of naloxegol use in the four study countries, and used in the meta-analyses, are presented in Data S6.

4 | DISCUSSION

To the best of our knowledge, this is the first multi-country study to analyze the real-world patterns of naloxegol use. The study reveals important aspects of the use of naloxegol. The users were mainly older adults, patients with multiple comorbidities, and patients with precautions of naloxegol use. Overall prior use of opioids was 98%–99.6% in Sweden, Norway, and UK, but 92% in Germany. Overall prior use of laxatives was 93% and 92% in Sweden and UK, but 70% and 71% in Germany and Norway. Also, up to 44.5%% of the users had a concurrent medication with interaction potential.

In accordance with a large real-world study from Spain (KYONAL),[36] naloxegol users were older than those who took part in the related clinical trials.[37] Naloxegol was also expectedly more used by women in real-world settings, reflecting gender differences in healthcare utilization and prevalence of chronic pain.[38] A portion of the patients had no record of laxative (up to 42.3%) or regular opioid use (up to 24.9%) within 6 months before index date. However, these figures might be overestimated as our data poorly capture over-the-counter use of laxatives and hospital- and institution-dispensed opioids.[29,39] While cancer patients have not been included in clinical trials,[37] we observed that about a quarter of the patients in Germany and in the UK and over half of the patients in Sweden and Norway had a history of cancer, in accordance with real-world data from France[40] and in agreement with the experts from the Delphi consensus who unanimously endorsed PAMORAs as alternative treatments of OIC in patients with cancer.[41] For instance, previous real-world

TABLE 2 Meta-analyses of factors associated with the patterns of naloxegol use.

Common set of factors associated with the patterns of naloxegol use	Discontinuation		Switching		Augmentation		Restart	
	HR (95% CI)	I^2	HR (95% CI)	I^2	HR (95% CI)	I^2	HR (95% CI)	I^2
Age class 18–34 years (vs. ≥75 years)	1.17 (0.99, 1.37)	39.30%	0.99 (0.80, 1.23)	0.00%	1.00 (0.79, 1.27)	0.00%	0.97 (0.74, 1.25)	0.00%
Age class 35–54 years (vs. ≥75 years)	1.04 (0.88, 1.23)	72.70%	0.85 (0.75, 0.97)*	6.90%	0.91 (0.81, 1.04)	0.00%	1.26 (0.99, 1.59)	39.40%
Age class 55–74 years (vs. ≥75 years)	1.02 (0.98, 1.06)	0.00%	0.95 (0.88, 1.04)	0.00%	0.96 (0.82, 1.13)	45.80%	1.04 (0.77, 1.41)	61.50%
Sex (male vs. female)	0.95 (0.86, 1.05)	57.70%	0.91 (0.81, 1.01)	20.60%	1.12 (0.98, 1.28)	42.80%	1.02 (0.93, 1.12)	0.00%
Index year 2016 and earlier (vs. 2018 and later)	1.19 (0.96, 1.46)	81.60%	1.04 (0.76, 1.44)	77.70%	0.83 (0.64, 1.07)	70.70%	0.96 (0.85, 1.07)	0.00%
Index year 2017 (vs. 2018 and later)	1.05 (1.01, 1.09)*	0.00%	1.08 (0.91, 1.28)	36.20%	1.01 (0.81, 1.26)	67.00%	1.05 (0.94, 1.16)	0.00%
History of any cancer within 12 months before index date	0.89 (0.66, 1.22)	94.80%	1.17 (0.87, 1.58)	84.60%	1.35 (1.02, 1.81)*	83.10%	1.05 (0.93, 1.18)	0.00%
Last use of opioid beyond 3 months vs. within 3 months	1.29 (0.87, 1.93)	80.40%	0.89 (0.74, 1.08)	0.00%	0.80 (0.64, 1.01)	0.00%	1.14 (0.96, 1.36)	0.00%
No use of opioid within 6 months before index date (vs. ≤50 MME daily)	1.11 (0.74, 1.67)	68.60%	1.24 (0.98, 1.55)	0.00%	1.29 (0.90, 1.86)	11.70%	0.63 (0.50, 0.80)***	0.00%
Previous daily dose of opioid >100 MME within 6 months before index date (vs. ≤50 MME daily)	0.92 (0.88, 0.97)**	0.00%	0.93 (0.84, 1.04)	0.00%	0.97 (0.86, 1.09)	0.00%	1.21 (1.02, 1.44)*	23.90%
Previous daily dose of opioid 51–100 MME within 6 months before index date (vs. ≤50 MME daily)	0.89 (0.85, 0.93)***	0.00%	0.91 (0.83, 1.01)	0.00%	1.03 (0.90, 1.17)	13.20%	1.12 (0.87, 1.45)	44.20%
Laxative use within 12 months before index date	0.84 (0.76, 0.93)**	38.00%	1.72 (0.69, 4.25)	95.20%	1.54 (0.72, 3.30)	94.60%	1.26 (0.94, 1.70)	54.60%
Concurrent use of CYP3A4 inducers	0.84 (0.62, 1.12)	94.40%	0.87 (0.64, 1.16)	85.20%	1.19 (1.08, 1.30)***	0.00%	1.12 (0.96, 1.32)	27.10%
Concurrent use of non-opioid analgesics	0.98 (0.87, 1.11)	68.50%	1.29 (1.20, 1.40)***	0.00%	1.33 (1.21, 1.45)***	0.00%	0.95 (0.87, 1.04)	0.00%
Concurrent use of P-gp modulators	1.09 (0.89, 1.34)	79.30%	1.13 (0.98, 1.30)	9.80%	1.07 (0.93, 1.23)	0.00%	1.03 (0.90, 1.18)	0.00%

Abbreviations: CI, confidence interval; CYP3A4, cytochrome P450, family 3A4; HR, hazard ratio, adjusted for the other factors associated with the patterns of naloxegol use; I^2, heterogeneity statistic; mg, milligram; MME, morphine milligram equivalent; P-gp, permeability glycoprotein; UK, United Kingdom.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

studies supported the effectiveness and tolerability of naloxegol in patients with advanced cancer.[40,42] Evidence from the large Spanish real-world study (KYONAL), the first long-term real-world study specifically focusing on cancer patients, revealed that 77.8% of individuals with OIC responded favorably to naloxegol treatment at the 12-month mark.[36] Further supporting these results, a recent multinational Naloxegol Cancer Study (NACASY), carried out across 26 centers in ten European countries, reinforced the observed improvements in constipation and quality of life in patients dealing with cancer-related pain and OIC and confirmed the established safety profile of the drug.[43] However, considering the risk of perforation, physicians should be highly cautious using naloxegol in patients with cancer of the GI tract, peritoneum, or the ovaries.[44]

We observed that naloxegol was largely prescribed to patients with CV conditions and variably prescribed to patients with hepatic impairment and renal disease. Although use of CYP3A4 inducers, CYP3A4 inhibitors, and Pgp modulators prior to naloxegol was common, their concomitant use with naloxegol was markedly more limited, possibly indicating prescribers' awareness of the drugs' potential of interaction. High proportions of cancer were observed among patients who concomitantly used naloxegol with drugs with potential interaction, possibly explaining the need of using these drugs despite the risk of interaction.

Apart from patients in Norway, a quarter to a third of the study participants initiated naloxegol treatment with a dose of 12.5 mg per day, in accordance with the observation that a significant proportion of naloxegol users had precautions of use, for which a low naloxegol starting dose is recommended.[22] For instance, we reported higher proportions of patients who started naloxegol at 12.5 mg per day in the renal impairment subpopulation. As in the previously mentioned Spanish real-world study,[36] dose changes during naloxegol treatment were infrequent in our study.

While discontinuations were frequent within the first month of naloxegol use, the proportion of patients who discontinued declined after 3 months. This observed decline may be indicative of a period of adaptation to naloxegol, where initial side effects diminish or patients begin to experience positive effects. Consequently, an approach to patient education emphasizing patience and adherence in the early stages of treatment could promote better compliance, thus improving the therapeutic outcomes. Also, patients with prior laxative use or a higher dose of prior opioid use had lower odds of discontinuing naloxegol, indicating usage of naloxegol as a second line treatment of OIC. Prior laxative use also increased the likelihood of switching naloxegol for another constipation medication, possibly back to the one priorly used. Although data on the safety and effectiveness of combining naloxegol with another laxative is limited, considerable proportions of patients augmented naloxegol treatment with another constipation medication during follow-up. This augmentation seemed favored by a history of cancer, in line with the recommendation to prescribe PAMORAs with laxatives in patients with multifactorial constipation, especially in cancer.[41] The observed pattern of augmentation indicates a need for research into the long-term safety and efficacy of combining naloxegol with other constipation medications.

In addition to a lack of pooling of the descriptive analyses of the included databases,[45] the generalizability of the study might be limited by a possible selection bias in the UK and Germany where the used databases cover only a portion of the countries' populations, unlike the Swedish and Norwegian databases. Also, comorbidities in Germany were indirectly identified using medications. Further, drugs dispensed outside of community pharmacy settings or administered in hospitals or nursing homes are poorly captured, underestimating opioid use. Further, the results shall be interpreted considering that the findings on naloxegol "use" were based on prescription/dispensing data, and thereby may not fully reflect actual intake of naloxegol. Finally, the results on the factors associated with patterns of naloxegol use should be interpreted cautiously, as the list of factors considered for the analysis is not comprehensive and the proportional hazards assumption for the Cox proportional hazards models was not formally tested.

In conclusion, this real-world study has found that naloxegol was typically used by older adults, women, and patients with multiple comorbidities, including cancer. Patients with prior laxative use or a higher dose of prior opioid use had lower odds of discontinuing naloxegol. Natural opium alkaloids and osmotically acting laxatives (excluding saline) were the most frequently used opioid and laxative classes, respectively. Some naloxegol users had no regular opioid use within 6 months before index date, no laxative use within 6 months before index date, and have used naloxegol concomitantly with medications presenting an interaction potential. Naloxegol discontinuation occurred typically within a month of treatment start. The result that augmentation with another constipation medication was relatively common suggests that naloxegol was used for multifactorial constipation. The present registry study reflects real-world clinical use of naloxegol, including in vulnerable patient groups.

AUTHOR CONTRIBUTIONS

Gunnvald Kvarstein and Katja M Hakkarainen were jointly involved in conceiving the research study, its design and also in interpretation of results. Mounir Ould Setti wrote the manuscript. Gunnvald Kvarstein, Ruvimbo Muzwidzwa, Hartmut Richter and Katja M Hakkarainen are accountable for data analysis and results from their respective country sites (Norway, United Kingdom, Germany and Sweden). Anna MS Kindlundh-Högberg and Rafik Namane critically reviewed the manuscript. All the authors have reviewed the draft and the final results of the study and were able to request additional analyses and information as needed. All of the authors have reviewed/provided feedback on the manuscript and have approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work. All authors made substantial contributions to design, data analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Gunnvald Kvarstein was paid by the research company 'EPID Research' now termed IQVIA for his consultant Principal Investigator role for Norway. Mounir Ould Setti, Ruvimbo Muzwidzwa, Hartmut Richter and Katja M Hakkarainen were consultants through their employment at IQVIA at the time of the study. Anna MS Kindlundh-Högberg and Rafik Namane are employees of Kyowa Kirin. The authors report no other conflict of interest in this work.

ETHICS STATEMENT

The study included aggregated human data from secondary data sources and was approved by the Local Ethics Review Board in Germany, Norway, Sweden, and United Kingdom. Data protection, data privacy and storage of data for the study were governed by the standard policies of IQVIA.

ORCID

Mounir Ould Setti https://orcid.org/0000-0002-8298-110X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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