# Naloxegol Provides Clinically Meaningful Healthcare Related Quality of Life (HR-QOL) Improvement (PAC-QOL) in Patients with Opioid-Induced Constipation (OIC): A Pooled Analysis of Two Global Phase 3 Studies of Naloxegol

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## BACKGROUND

- The American Gastroenterological Association (AGA) reported that opioid-induced constipation (OIC) affects 40-80% of patients taking chronic opioid therapy.[1]
- OIC is the most common adverse event associated with opioids[2] and negatively impacts patients' healthcare related quality of life (HR-QOL).[3]
- Over 50% of patients with non-cancer pain reported modifying their opioid regimen due to constipation.[3]
- 25-86% of older patients receiving opioids for chronic pain experience opioid-induced constipation (OIC).[4] Older adults are particularly susceptible to OIC due to comorbidities, polypharmacy, and reduced physical activity.[5]
- Naloxegol (Movantik®) is a peripherally acting mu-opioid receptor antagonist (PAMORA) which targets the GI tract to decrease the constipating effects of opioids. It was shown to be effective in treating OIC in adult subjects with non-cancer related pain in two pivotal Phase 3 Studies (KODIAC 4 and 5: NCT01309841/NCT01323790).[6]

## OBJECTIVE

- This study evaluates the efficacy of naloxegol in providing clinically meaningful HR-QOL improvement in patients with OIC.

## METHODS

- This pooled analysis of two randomized, placebo-controlled trials (KODIAC 4 and 5) utilizes the validated Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) to evaluate the efficacy of naloxegol in providing clinically meaningful HR-QOL improvement in the overall patient population as well as patients aged ≥65 years.
- Patient-reported scores from the PAC-QOL questionnaire were collected during KODIAC 4 and 5 as supportive efficacy measures of OIC HR-QOL improvement.
- PAC-QOL scoring for each domain (Physical Discomfort, Worries/Concerns) was measured on the following scale: 0 (absence of symptoms) to 4 (very severe). The Satisfaction domain was measured on the scale of 0 (not at all) to 4 (extremely).
- Two Minimal Clinically Important Difference (MCID) thresholds were used to identify responders and non-responders. Minimal clinically important differences (MCID) are patient derived scores that reflect changes in a clinical intervention that are meaningful for the patient.
  - PAC-QOL MCID threshold of ≥0.5 is based on literature[7] and naloxegol real-world studies in cancer patients with OIC.[8,9]
  - PAC-QOL MCID threshold of ≥0.8 is based on anchor method analysis of naloxegol Phase 3 clinical trial data.[10]

## DEMOGRAPHICS AND BASELINE CLINICAL CHARACTERISTICS (ITT POPULATION)

- A total of 1337 subjects receiving naloxegol (12.5 mg, n=445; 25 mg, n=446) and placebo (n=446) were included in the ITT analysis of KODIAC 4 and 5 trials (Table 1).
- Key demographics included mean age (52 years), ≥65 years of age (11 %), female (62.4%), white (79%), and black (18.6%). The duration of opioid therapy in subjects averaged 3.6 years. The mean baseline opioid morphine equivalent daily dosage was 137.7 mg.
- The overall baseline values for PAC-QOL Total, Physical Discomfort, Psychosocial Discomfort, Worries/Concerns, and Satisfaction scores were similar across groups (Table 1).

**Table 1. Baseline Demographic and Clinical Characteristics of the Intent-to-Treat (ITT) Population**

| Baseline Characteristics | | | |
|---|---|---|---|
| **Characteristic** | **Pooled** (N = 1337) | **KODIAC-4** (n = 641) | **KODIAC-5** (n = 696) |
| **PAC-QOL** | | | |
| **Total score** | | | |
| Mean (SD) | 2.0 (0.8) | 2.0 (0.8) | 2.0 (0.8) |
| Range | 0.1-3.9 | 0.4-3.9 | 0.1-3.9 |
| **Physical discomfort** | | | |
| Mean (SD) | 2.1 (0.9) | 2.1 (0.9) | 2.0 (0.9) |
| Range | 0-4 | 0-4 | 0-4 |
| **Psychosocial discomfort** | | | |
| Mean (SD) | 1.3 (1.0) | 1.4 (0.9) | 1.3 (0.9) |
| Range | 0-3.9 | 0-3.9 | 0-3.9 |
| **Worries/concern** | | | |
| Mean (SD) | 2.0 (1.0) | 2.0 (1.0) | 1.9 (0.9) |
| Range | 0-4 | 0-4 | 0-4 |
| **Satisfaction** | | | |
| Mean (SD) | 3.3 (0.7) | 3.3 (0.6) | 3.3 (0.7) |
| Range | 0-4 | 0.6-4 | 0-4 |

## RESULTS

**Rapid and Sustained Improvement in Constipation Related Quality of Life**

- MCID Threshold ≥0.5
  - In the overall population, naloxegol 25 mg and 12.5 mg demonstrated a rapid, sustained, statistically significant, and clinically meaningful improvement in HR-QOL vs. PBO at both week 4 and week 12. (Figure 1, Table 2)
  - In older (≥65 years) adults, naloxegol 25 mg and 12.5 mg demonstrated a rapid, sustained, statically significant, and clinically meaningful improvement in HR-QOL vs. PBO at both 4 weeks and 12 weeks. (Table 2)
- MCID Threshold ≥0.8
  - In the overall population, naloxegol 25 mg and 12.5 mg demonstrated a rapid, statistically significant, and clinically meaningful improvement in HR-QOL vs. PBO at week 4. (Figure 1, Table 2)
  - At week 12, higher proportions of PAC-QOL responders were also observed for naloxegol 25 mg and 12.5 mg vs. PBO. (Figure 2, Table 2)
  - In older (≥65 years) adults, naloxegol 25 mg and 12.5 mg demonstrated a rapid, sustained, statically significant, and clinically meaningful improvement in HR-QOL vs. PBO at both 4 weeks and 12 weeks. (Table 2)
- Odds ratios (ORs) were generally consistent across both MCIDs ≥0.5 and ≥0.8
  - At 4 weeks for both MCID thresholds, patients receiving naloxegol 25 mg and 12.5 mg were 40-70% more likely to achieve clinically meaningful HR-QOL improvement than with PBO.
  - At 12 weeks for both MCID thresholds, patients receiving naloxegol 25 mg and 12.5 mg were 30-50% more likely to achieve clinically meaningful HR-QOL improvement than with PBO.
  - In older (≥65 years) adults at both MCID thresholds, patients receiving naloxegol 12.5 mg demonstrated a 2.6-3.5-fold higher likelihood of PAC-QOL response than with PBO at 4- and 12- weeks. Patients receiving naloxegol 25 mg demonstrated 2.5-4.4-fold higher likelihood of PAC-QOL response than with PBO at 4- and 12-weeks.

**Figure 1. Percentage of Subjects Achieving ≥0.5-point Decrease in PAC-QOL Total Score**

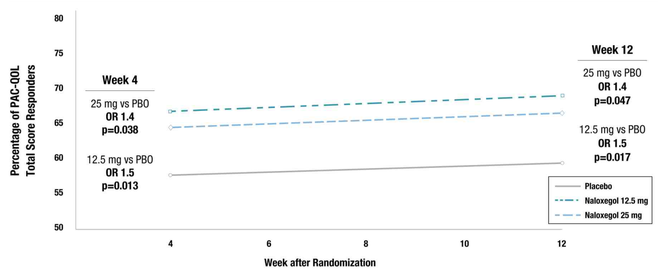



**Figure 2. Percentage of Subjects Achieving ≥0.8-point Decrease in PAC-QOL Total Score**

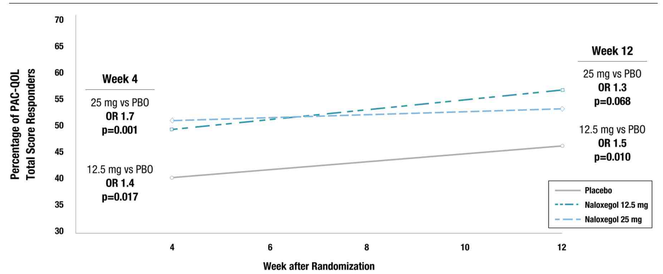



**Table 2. Proportion of Subjects Achieving Clinically Meaningful Improvement in PAC-QOL Total Score**

| | Time Point | Placebo | Naloxegol 12.5 mg | Naloxegol 25 mg | Comparison Odds Ratio Naloxegol 12.5 mg vs. Placebo | | Comparison Odds Ratio Naloxegol 25 mg vs. Placebo | |
|---|---|---|---|---|---|---|---|---|
| | | Responder n/N (%) | Responder n/N (%) | Responder n/N (%) | OR [95% CI] | p-value | OR [95% CI] | p-value |
| **PAC-QOL MCID Threshold ≥0.5** | | | | | | | | |
| Overall Population | Week 4 | 239/418 (57.2) | 274/414 (66.2) | 264/413 (63.9) | 1.5 [1.1 – 1.9] | 0.013 | 1.4 [1.0 – 1.9] | 0.038 |
| | Week 12 | 214/363 (58.9) | 241/352 (68.5) | 222/336 (66.1) | 1.5 [1.1 – 2.1] | 0.017 | 1.4 [1.0 – 1.9] | 0.047 |
| Patients ≥65 years old | Week 4 | 20/45 (44.4) | 32/41 (78.1) | 37/50 (74.0) | 3.5 [1.2 – 10.0] | 0.018 | 3.0 [1.2 – 7.7] | 0.023 |
| | Week 12 | 18/40 (45.0) | 26/38 (68.4) | 34/46 (73.9) | 2.8 [1.1 – 7.3] | 0.031 | 3.8 [1.3 – 11.2] | 0.017 |
| **PAC-QOL MCID Threshold ≥0.8** | | | | | | | | |
| Overall Population | Week 4 | 166/418 (39.7) | 202/414 (48.8) | 208/413 (50.4) | 1.4 [1.1 – 1.9] | 0.017 | 1.7 [1.2 – 2.2] | 0.001 |
| | Week 12 | 166/363 (45.7) | 198/352 (56.3) | 177/336 (52.7) | 1.5 [1.1 – 2.1] | 0.010 | 1.3 [0.9 – 1.9] | 0.068 |
| Patients ≥65 years old | Week 4 | 11/45 (24.4) | 21/41 (51.2) | 29/50 (58.0) | 3.3 [1.3 – 8.3] | 0.010 | 4.4 [1.8 – 10.9] | 0.001 |
| | Week 12 | 14/40 (35.0) | 22/38 (57.9) | 27/46 (58.7) | 2.6 [1.0 – 6.6] | 0.041 | 2.5 [1.0 – 6.2] | 0.030 |

**Improvement in PAC-QOL Subdomains**

- A significantly greater proportion of patients receiving naloxegol 25 mg and 12.5 mg vs. PBO achieved clinically meaningful improvement in the PAC-QOL Satisfaction subdomain for both MCID thresholds at 12 weeks ($p < 0.05$ for both doses). (Figures 3a-d)
- Other PAC-QOL subdomains also showed statistically significant and numerical improvement with naloxegol (25 mg, 12.5 mg) vs. PBO. (Figures 3a-d)

**Figures 3a-d. Likelihood of Achieving PAC-QOL MCID by Subdomain Scores at Wk 12: Naloxegol vs. Placebo (KODIAC 4 and 5; ITT Population)**

**Figure 3a. The Likelihood of Achieving PAC-QOL (MCID ≥0.5 Reduction) Improvement at Wk 12: Naloxegol 12.5 mg vs. PBO Odds Ratio (95% CI)**

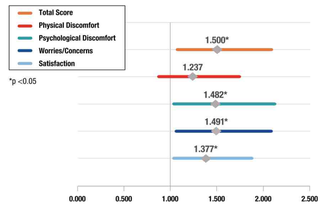



**Figure 3b. The Likelihood of Achieving PAC-QOL (MCID ≥0.5 Reduction) Improvement at Wk 12: Naloxegol 25 mg vs. PBO Odds Ratio (95% CI)**

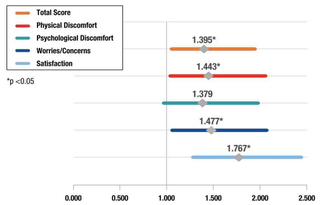



**Figure 3c. The Likelihood of Achieving PAC-QOL (MCID ≥0.8 Reduction) Improvement at Wk 12: Naloxegol 12.5 mg vs. PBO Odds Ratio (95% CI)**

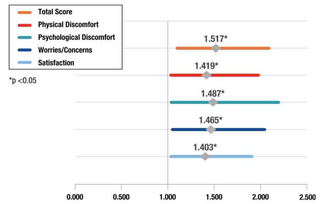
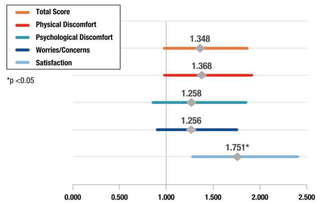



**Figure 3d. The Likelihood of Achieving PAC-QOL (MCID ≥0.8 Reduction) Improvement at Wk 12: Naloxegol 25 mg vs. PBO Odds Ratio (95% CI)**




## SAFETY

- The proportion of subjects with AEs leading to discontinuation across treatment groups were: naloxegol 25 mg (10.3%), naloxegol 12.5 mg (4.8%), and placebo (5.4%).
  - The most common GI-related AEs leading to discontinuation were abdominal pain (4%, 0.9%, 0.2%, respectively), diarrhea (3.1%, 0.9%, 0.7%, respectively), and nausea (1.1%, 1.1%, 0.2%, respectively).
- In older (≥65 years) adults, the proportion of subjects with treatment emergent adverse events (TEAEs) leading to discontinuation across treatment groups were: naloxegol 25 mg (7.5%), naloxegol 12.5 mg (6.7%), and placebo (10.0%).
  - The most common GI-related TEAEs leading to discontinuation in older (≥65 years) adults were abdominal pain (5.7%, 0.0%, 0.0%, respectively), diarrhea (3.8%, 0.0%, 2.0%, respectively), and nausea (1.9%, 0.0%, 2.0%, respectively).

## CONCLUSIONS

- **Naloxegol demonstrated rapid and clinically meaningful, constipation-related HR-QOL improvement in patients with OIC across both MCID thresholds ≥0.5 and ≥0.8 in the overall population.**
- **In older (≥65 years) adults with OIC, naloxegol maintained clinically meaningful, HR-QOL improvement. This improvement was generally dose dependent, with significant gains demonstrated for naloxegol doses at both MCID thresholds ≥0.5 and ≥0.8.**
- **Improvement in patient satisfaction was associated with improvement in HR-QOL. Such HR-QOL improvement may be an important clinical consideration in improving OIC management.**
- **Both naloxegol regimens were well-tolerated and demonstrated a favorable safety profile.**
- **These findings suggest naloxegol may enable clinicians to improve quality of life in patients with OIC.**

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