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

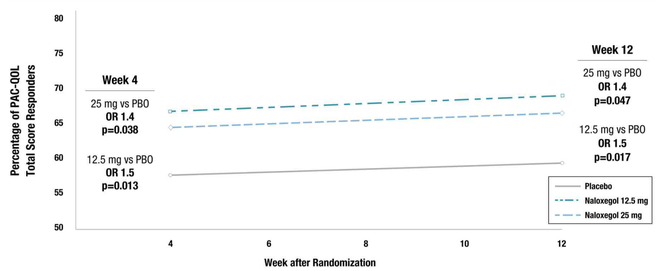


Figure 2. Percentage of Subjects Achieving ≥0.8-point Decrease in PAC-QOL Total Score

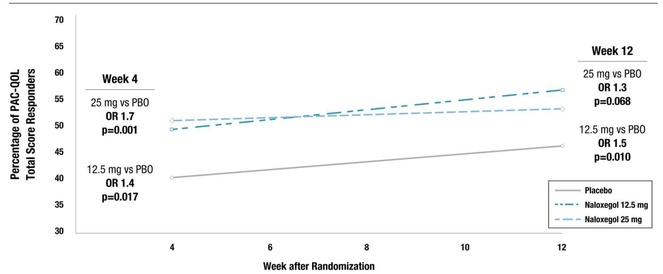


Table 2. Proportion of Subjects Achieving Clinically Meaningful Improvement in PAC-QOL Total Score

	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)

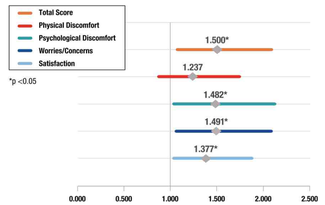


Figure 3b. The Likelihood of Achieving PAC-QOL (MCID ≥0.5 Reduction) Improvement at Wk 12: Naloxegol 25 mg vs. PBO Odds Ratio (95% CI)

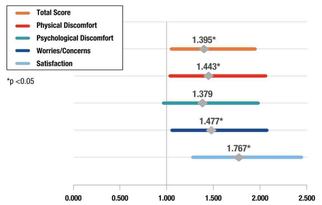


Figure 3c. The Likelihood of Achieving PAC-QOL (MCID ≥0.8 Reduction) Improvement at Wk 12: Naloxegol 12.5 mg vs. PBO Odds Ratio (95% CI)

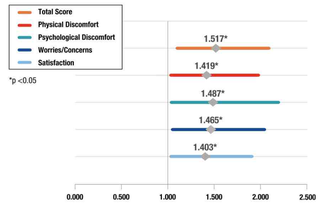
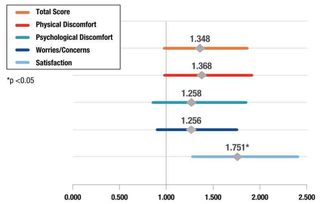


Figure 3d. The Likelihood of Achieving PAC-QOL (MCID ≥0.8 Reduction) Improvement at Wk 12: Naloxegol 25 mg vs. PBO Odds Ratio (95% CI)



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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