Naloxegol Provides Clinically Meaningful Symptom Improvement (PAC-SYM) 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]
- 58% of patients with OIC reported at least one severe or very severe constipation-related symptom.[2]
- 25-86% of older patients receiving opioids for chronic pain experience opioid-induced constipation (OIC).[3] Older adults are particularly susceptible to OIC due to comorbidities, polypharmacy, and reduced physical activity.[4]
- Naloxegol (Movantik®) is a peripherally acting mu-opioid receptor antagonist (PAMORA) which targets the GI tract to decrease the constipating effects of opioids. It has demonstrated a rapid and predictable response and relief of OIC symptoms in patients treated with opioids for non-cancer pain in two Phase 3 clinical trials (KODIAC 4 and 5: NCT01309841/ NCT01323790).[5,6]

OBJECTIVE

- This study evaluates the efficacy of naloxegol in providing clinically meaningful symptom 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 Symptoms questionnaire (PAC-SYM) to evaluate the efficacy of naloxegol in providing clinically meaningful symptom improvement in the overall patient population as well as patients aged ≥65 years.
- Data were pooled from the KODIAC 4 and 5 Intent-to-Treat (ITT) population. PAC-SYM scores were collected during KODIAC 4 and 5 as supportive efficacy measures.
- Scores range from 0 (absence of symptoms) to 4 (very severe) for each domain (abdominal, rectal, and stool symptoms).
- 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-SYM MCID threshold of ≥0.5 is based on literature[7,8] and naloxegol real-world studies in cancer patients with OIC.[9,10]
  - PAC-SYM MCID threshold of ≥0.8 is based on anchor method analysis of naloxegol Phase 3 clinical trial data.[11]

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 mean baseline values for PAC-SYM total, abdominal, rectal, and stool symptoms 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-SYM			
Total score			
Mean (SD)	1.8 (0.7)	1.8 (0.7)	1.8 (0.8)
Range	0-3.9	0-3.9	0-3.9
Abdominal symptoms			
Mean (SD)	1.7 (0.9)	1.7 (0.9)	1.7 (0.9)
Range	0-4	0-4	0-4
Rectal symptoms			
Mean (SD)	1.3 (0.9)	1.3 (0.9)	1.3 (0.9)
Range	0-4	0-4	0-4
Stool symptoms			
Mean (SD)	2.3 (0.9)	2.3 (0.8)	2.3 (0.9)
Range	0-4	0-4	0-4

RESULTS

- MCID Threshold ≥0.5
  - At week 4, treatment with naloxegol 25 mg demonstrated a rapid, statically significant, and clinically meaningful improvement in symptoms vs. PBO. A trend in the same direction was seen for the 12.5 mg dose. (Figure 1, Table 2)
  - At week 12, there was a significantly higher proportion of clinically meaningful PAC-SYM responders with both naloxegol doses vs. PBO. (Figure 1, Table 2)
  - In older (≥65 years) adults, treatment with naloxegol 12.5 mg and 25 mg demonstrated a rapid, statically significant, and clinically meaningful improvement in symptoms vs. PBO at both 4 weeks and 12 weeks. (Table 2)
- MCID Threshold ≥0.8
  - Treatment with naloxegol 25 mg was associated with rapid, sustained, and clinically meaningful improvement in symptoms vs. PBO at 4- and 12- weeks. (Figure 2, Table 2)
  - Numerical symptom improvement was seen with naloxegol 12.5 mg at both timepoints.
  - In older (≥65 years) adults, treatment with naloxegol 12.5 mg demonstrated a rapid, statically significant, and clinically meaningful improvement in symptoms vs. PBO at 4 weeks and numerical improvement at 12 weeks. Naloxegol 25 mg demonstrated significant and clinically meaningful improvement in symptoms vs. PBO at 12 weeks and numerical improvement at 4 weeks. (Table 2)
- ORs were generally consistent across both MCIDs ≥0.5 and ≥0.8
  - Patients receiving naloxegol 12.5 mg demonstrated a 20-50% higher likelihood of PAC-SYM response than with PBO at both time-points. Patients receiving naloxegol 25 mg demonstrated 40-80% higher likelihood of PAC-SYM response than with PBO at both time-points.
  - In older (≥65 years) adults, patients receiving naloxegol 12.5 mg demonstrated a 2.4-3.3-fold higher likelihood of PAC-SYM response than with PBO at both time-points. Patients receiving naloxegol 25 mg demonstrated 2.6-4.1-fold higher likelihood of PAC-SYM response than with PBO at both time-points.

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

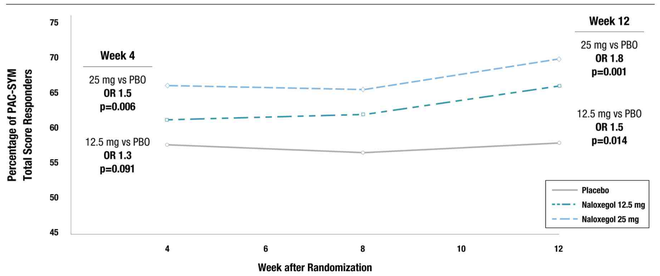


Figure 2. Percentage of Subjects Achieving ≥0.8-point Decrease in PAC-SYM Total Score

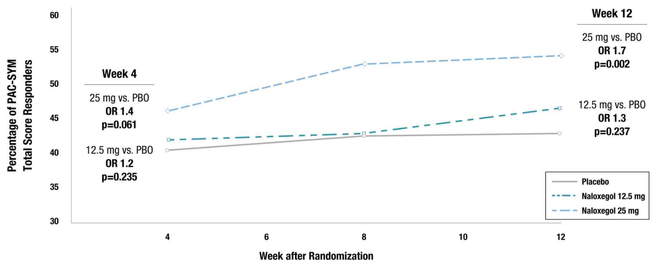


Table 2. Proportion of Subjects Achieving Clinically Meaningful Improvement in PAC-SYM Total Score

	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-SYM MCID Threshold ≥0.5								
Overall Population	Week 4	233/407 (57.3)	246/404 (60.9)	254/387 (65.6)	1.3 [0.9 – 1.8]	0.091	1.5 [1.1 – 2.1]	0.006
	Week 12	207/359 (57.7)	231/352 (65.6)	230/331 (69.5)	1.5 [1.1 – 2.1]	0.014	1.8 [1.3 – 2.5]	0.001
Patients ≥65 years old	Week 4	17/44 (38.6)	27/41 (65.9)	32/47 (68.1)	3.2 [1.2 – 8.7]	0.020	4.1 [1.5 – 11.1]	0.006
	Week 12	19/40 (47.5)	27/38 (71.1)	32/46 (69.6)	2.8 [1.0 – 7.6]	0.041	2.7 [1.0 – 7.4]	0.047
PAC-SYM MCID Threshold ≥0.8								
Overall Population	Week 4	162/407 (39.8)	168/404 (41.6)	176/387 (54.5)	1.2 [0.9 – 1.6]	0.235	1.4 [0.9 – 1.9]	0.061
	Week 12	152/359 (42.3)	161/352 (45.7)	177/331 (53.5)	1.3 [0.9 – 1.7]	0.237	1.7 [1.2 – 2.4]	0.002
Patients ≥65 years old	Week 4	11/44 (25.0)	20/41 (48.8)	21/47 (44.7)	3.3 [1.2 – 9.1]	0.024	2.6 [0.9 – 7.3]	0.080
	Week 12	11/40 (27.5)	18/38 (47.4)	22/46 (47.8)	2.4 [0.9 – 6.5]	0.093	3.2 [1.0 – 9.9]	0.043

Improvement in PAC-SYM Subdomains

- Subdomain analyses revealed dose-dependent responses.
- At week 12, significant and clinically meaningful improvement in PAC-SYM rectal (ORs: MCID ≥0.5=1.7;MCID ≥0.8=1.9) and stool symptoms (ORs: MCID ≥0.5=2.0; MCID ≥0.8=2.0) subdomains were achieved for naloxegol 25 mg vs. PBO ($p<0.05$) at both MCID thresholds. (Figures 3a-d)

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

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

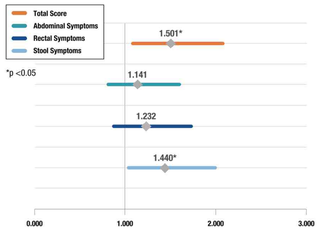


Figure 3b. The Likelihood of Achieving PAC-SYM (MCID ≥0.5 Reduction) Improvement at Wk 12: Naloxegol 25 mg vs. PBO Odds Ratio (95% CI)

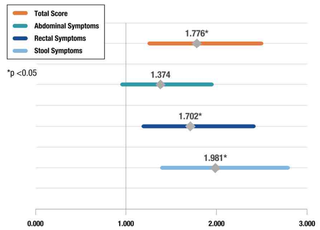


Figure 3c. The Likelihood of Achieving PAC-SYM (MCID ≥0.8 Reduction) Improvement at Wk 12: Naloxegol 12.5 mg vs. PBO Odds Ratio (95% CI)

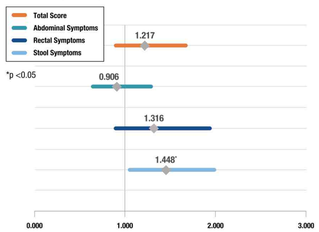
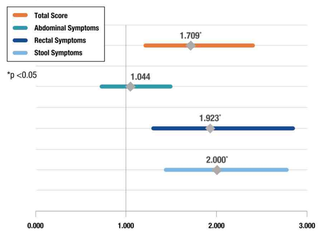


Figure 3d. The Likelihood of Achieving PAC-SYM (MCID ≥0.8 Reduction) Improvement at Wk 12: Naloxegol 25 mg vs. PBO Odds Ratio (95% CI)



SAFETY

- In the overall population, 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 clinically meaningful, constipation-related symptom improvement in patients with OIC. These improvements were dose-dependent, with significant gains demonstrated for naloxegol 25 mg at both MCID thresholds ≥0.5 and ≥0.8.**
- **In older (≥ 65 years) adults with OIC, naloxegol maintained clinically meaningful, constipation-related symptom improvement. This improvement was generally dose-dependent, with significant gains demonstrated for naloxegol at both MCIDs thresholds ≥0.5 and ≥0.8.**
- **Rectal and stool symptoms appear to drive the overall symptom improvement, consistent with the known effects of PAMORAs. Such symptom improvement may be an important clinical consideration in improving OIC management and patient satisfaction.**
- **Both naloxegol regimens were well-tolerated and demonstrated a favorable safety profile.**
- **These findings suggest naloxegol may enable clinicians to improve constipation related symptoms and quality of life in patients with OIC.**

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