Rapid Onset of Time to First Spontaneous Bowel Movement (SBM) and Predictable Efficacy of Naloxegol: Pooled Analysis of Two Global Randomized Controlled Trials

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BACKGROUND

- Opioid agonists can cause constipation by binding to opioid receptors located in the enteric nervous system,[1] leading to delay of gastric emptying, transit time of the small and large intestines, and increase in evacuation disorder, and a decrease in secretion of electrolytes and water into the intestinal lumen.[2]
- American Gastroenterological Association (AGA) reported opioid-induced constipation (OIC) affects 40-80% of patients taking chronic opioid therapy for pain.[3]
- Naloxegol (Movantik®), a peripherally acting mu-opioid receptor antagonist (PAMORA), which targets the GI tract to decrease the constipation effects of opioids, was shown to be effective in treating OIC in adult subjects with non-cancer related pain in two pivotal Phase 3 studies (KODIAC 4/5:NCT01309841/NCT01323790).[4]
- An international survey of 322 patients with OIC showed that the most bothersome gastrointestinal symptoms were constipation, straining, hard stools and incomplete evacuation.[5]

OBJECTIVE

- Given the clinical importance of rapid and predictable symptom response, this analysis aims to characterize the predictability of the onset of response (first post-dose SBM*) within 48 hours following the first dose of naloxegol (12.5 mg and 25 mg). Additionally, we evaluated the onset of first post-dose complete SBM (CSBM†) for both regimens.

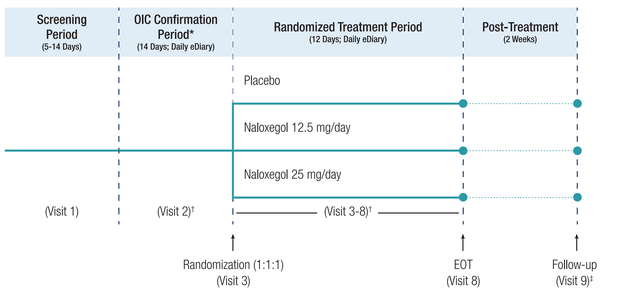
*SBM-defined as a BM without the use of rescue laxatives (bisacodyl or enema) in the previous 24 hours.
†CSBM-defined as Completeness of Evacuation, indicating a sense of complete evacuation accompanied by SBM.

METHODS

Study Design

The evaluation of naloxegol efficacy on OIC symptoms and safety was a pooled analysis of data from two identically designed Phase 3 studies with similar subject eligibility and enrollment criteria (Figure 1). Subjects who subsequently underwent randomization recorded their symptoms in electronic diaries (eDiaries) throughout the treatment period.

Figure 1. Study Design: KODIAC 4 and 5 Studies[6]



These studies were conducted in the US, Australia, and Europe from 3/14/11 to 8/16/12 (KODIAC-4) and 3/28/11 to 9/20/12 (KODIAC-5)[6]
Diagnosis of OIC and opioid dose stability confirmed by eDiary (provided at screening).
†Bisacodyl (10-15 mg: maximum of 3 doses/episode) and one-time use enema permitted as rescue.
‡Subjects could either complete the follow-up visit or enroll in a safety extension study.

METHODS (CONTINUED)

Patient-Reported Data Analysis

- Time to first post-dose SBM without the use of rescue laxatives within the previous 24-hrs for naloxegol vs. placebo was analyzed via the Cox proportional hazard model; treatment effect was analyzed via the hazard ratio (HR).
- The median time to first post-dose SBM was derived via the Kaplan-Meier method (KM).
- Onset of action was measured by the proportion of subjects with SBM from 4 hrs to 48 hrs of post-first dose, which reflects a clinically relevant timeframe. The same analytical procedures were conducted for the evaluation of CSBM.

BASELINE CHARACTERISTICS

- A total of 1337 subjects receiving naloxegol (12.5 mg, n=445; 25 mg, n=446) and placebo (n=446) were included in the Intent-to-Treat (ITT) analysis of KODIAC 4/5 trials (Table 1).
- Key demographics included mean age (52 years), ≥65 years of age (11%), female (62.4%), White (79%), and Black (18.6%). Back pain was the most common reason for pain (56.5%) followed by arthritis (9.8%). Subjects took their current opioid for an average of 3.6 years. The mean baseline opioid morphine equivalent daily dosage was 137.7 mg.
- Baseline OIC symptom burden was balanced across the naloxegol groups (12.5 mg and 25 mg) and placebo (Table 1)

Table 1. OIC Symptoms at Baseline* (KODIAC 4 and 5; ITT Population)

Mean (SD)*	KODIAC 4			KODIAC 5		
	Placebo (N=214)	12.5 mg (N=213)	25 mg (N=214)	Placebo (N=232)	12.5 mg (N=232)	25 mg (N=232)
SBMs/Wk	1.4 (0.89)	1.4 (0.85)	1.3 (1.11)	1.5 (0.95)	1.6 (1.05)	1.3 (0.85)
Days/Wk with ≥ 1 SBM	1.3 (0.85)	1.4 (0.81)	1.2 (0.94)	1.4 (0.89)	1.5 (0.86)	1.3 (0.84)
Straining†	3.3 (0.78)	3.1 (0.79)	3.2 (0.84)	3.3 (0.81)	3.1 (0.82)	3.2 (0.82)
Stool Consistency‡	2.8 (1.22)	2.9 (1.20)	2.9 (1.16)	3.0 (1.29)	3.0 (1.32)	3.0 (1.26)
%Days/Wk with ≥ 1 CSBM	6.0 (8.81)	6.5 (9.31)	5.4 (8.86)	6.0 (8.39)	7.0 (9.88)	5.4 (7.90)

*Values calculated during the OIC period. †Range of possible values are 1 = Not at all; 2 = A little bit; 3 = A moderate amount; 4 = A great deal; 5 = An extreme amount. ‡Range of possible values are 1 = Type 1 Separate hard lumps; 2 = Type 2 Sausage-shaped but lumpy; 3 = Type 3 Like a sausage but with cracks on its surface; 4 = Type 4 Like a sausage, smooth and soft; 5 = Type 5 soft blobs with clear-cut edges; 6= Type 6 Fluffy pieces with ragged edges; 7 = Type 7 Watery, no solid pieces.

RESULTS

Time to First Post-Dose SBM

- Time to 1st post-dose SBM was statistically significantly reduced by about twofold for the naloxegol groups (HR 1.58 for 12.5 mg ; HR 1.84 for 25 mg; both p<0.001) compared to placebo (ITT population). The KM curve showed clear separation of naloxegol treatments from placebo for 1st post-dose SBM.
- Median times to 1st post-dose SBM were shorter in the naloxegol groups (7.8 hrs [25 mg] and 19.9 hrs [12.5 mg]) compared to placebo (36.4 hrs) (Figure 2).
- Higher proportions of subjects achieved 1st post-dose SBM by ≤4 hr, ≤6 hr, ≤8 hr, ≤12 hr, ≤24 hr, and ≤48 hr after the initial dose for the naloxegol groups compared to placebo (Figure 3).

RESULTS (CONTINUED)

Figure 2. Median Time to First Post-Dose SBM: Pooled Data (KODIAC 4 and 5; ITT Population)

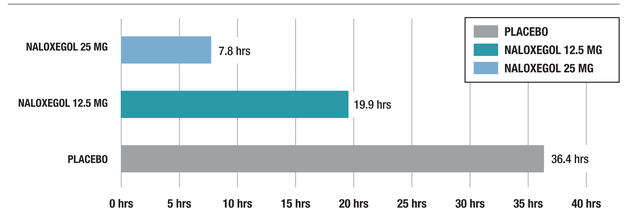
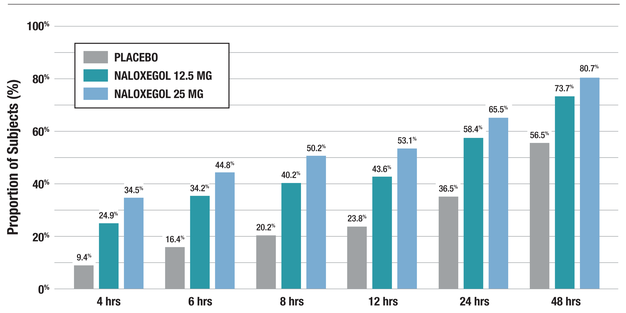


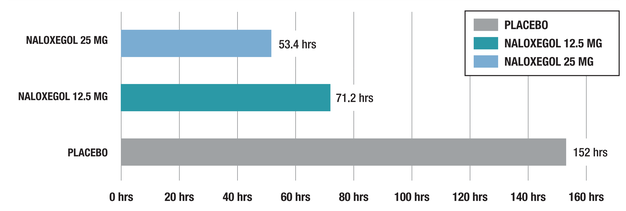
Figure 3. Proportion of Subjects Achieving First Post-Dose SBM: Pooled Data (4 hrs to 48 hrs) (KODIAC 4 and 5; ITT Population)



Time to First Post-Dose Complete SBM (CSBM)

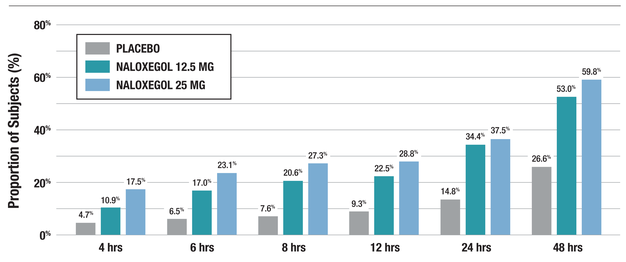
- The median time it took to 1st post-dose CSBM was 53% and 65% shorter relative to placebo for the 12.5 mg and 25 mg dose, respectively (HR 1.36 for 12.5 mg, HR 1.42 for 25 mg; both p<0.001). The KM curve showed clear separation of naloxegol treatments from placebo for 1st post-dose CSBM.
- Median times to 1st post-dose CSBM were 53.4 hrs (25 mg), 71.2 hrs (12.5 mg), and 152 hrs (placebo) (Figure 4).
- Higher proportion of subjects achieved 1st post-dose CSBM by ≤4 hr, ≤6 hr, ≤8 hr, ≤12 hr, ≤24 hr, and ≤48 hr for the naloxegol groups compared to placebo (Figure 5).

Figure 4. Median Time to First Post-Dose CSBM (hrs): Pooled Data (KODIAC 4 and 5; ITT Population)



RESULTS (CONTINUED)

Figure 5. Proportion of Subjects Achieving First Post-Dose CSBM: Pooled Data (4 hrs to 48 hrs) (KODIAC 4 and 5; ITT Population)



SAFETY

- The most commonly reported AEs with naloxegol (25 mg, 12.5 mg) and placebo were abdominal pain (21%, 12%, 7%, respectively), diarrhea (9%, 6%, 5%, respectively), and nausea (8%, 7%, 5%, respectively). Most AEs were mild to moderate in severity and occurred more commonly in the 25 mg group.[4]
- 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 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).

CONCLUSION

- This analysis of data from 2 large, methodologically rigorous randomized, controlled trials demonstrated that naloxegol (25 mg or 12.5 mg) was significantly more likely than placebo to provide:
  - Rapid onset of action for time to first SBM and first CSBM.
  - Higher proportions of subjects with an SBM and CSBM over the first 48 hours of treatment.
- Both naloxegol regimens were well-tolerated and demonstrated a favorable safety profile.
- This analysis showed that naloxegol provided clinically relevant early symptom relief and predictable efficacy in subjects with OIC, who experienced lack of bowel movements, and sense of incomplete evacuation.
- The rapid and predictable relief provided by naloxegol may be an important clinical consideration in improving patient experience and patient satisfaction in OIC management.

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Acknowledgments
Medical writing support was provided by Philip Yeung from Medical Affairs 360, LLC. (Carlsbad, CA, USA).