

Supplementary Materials

Supplemental Methods

Exclusion Criteria

Patients were excluded from study participation if they had a history of serious ventricular arrhythmia; family history of sudden cardiac death or long QT syndrome; recent history of myocardial infarction (MI) within 6 months prior to randomization; overt CV disease (eg, symptomatic heart failure); or prolonged repeat QTcF (>450 ms at screening, confirmed by repeat QTcF on electrocardiograms within a 5-minute period). Patients were not permitted to take opioid antagonists, mixed opioid agonist-antagonists, or strong cytochrome P450 3A4 inhibitors (eg, clarithromycin, itraconazole) or P-glycoprotein inhibitors (eg, cyclosporine).¹ The original protocol for these studies also included restrictions regarding medications that could potentially prolong the QT/QTc interval. These restrictions were removed after preliminary results from a thorough QT study were available (November 2011), which showed that naloxegol had no propensity to prolong the QT interval.

Timing of Vital Sign Assessments

In Studies A and B, vital signs (seated blood pressure [BP] and pulse) were evaluated at screening; at baseline prior to treatment; at 1 hour and 2 hours after the first dose of treatment; at Weeks 1, 2, 4, 8, and 12; and at follow-up. In Studies A and B, only the first postdose measurements of vital signs (1 hour after the first dose of treatment) were strictly specified in the protocol. Timing for subsequent vital sign measurements was

more variable relative to dosing. In Study C, baseline values were obtained from Study A, and vital sign assessments started at Week 12. In Study D, vital signs were evaluated at screening; at baseline prior to treatment; at Weeks 1 and 2; at Months 1, 3, 6, 9, and 12; and at follow-up.

Evaluation of Adverse CV Events

In each study, adverse events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) version 15.0. An independent CV adjudication committee (CVAC), blinded to treatment assignment, prospectively reviewed all deaths, serious adverse CV events, and CV events of special interest that were not characterized as serious by site investigators, including arrhythmias, syncope, and angina. All evaluated cardiovascular outcomes were prespecified by a Charter and included major adverse cardiovascular events (MACEs; defined as CV death, MI, and stroke), hospitalization for heart failure, unstable angina with or without coronary revascularization that required hospitalization, arrhythmias, and transient ischemic attack.

Supplemental Table 1. Included Studies

Study	ClinicalTrials.gov identifier	Study design	Treatment groups
A	NCT01309841	12-week, randomized, double-blind, parallel-group efficacy and safety study	<ul style="list-style-type: none">• Placebo• Naloxegol 12.5 mg• Naloxegol 25 mg
B	NCT01323790	12-week, randomized, double-blind, parallel-group efficacy and safety study	<ul style="list-style-type: none">• Placebo• Naloxegol 12.5 mg• Naloxegol 25 mg
C	NCT01395524	12-week, double-blind, extension study of Study A	<ul style="list-style-type: none">• Placebo• Naloxegol 12.5 mg• Naloxegol 25 mg
D	NCT01336205	52-week, randomized, open-label safety study	<ul style="list-style-type: none">• Usual care^a• Naloxegol 25 mg

^aUsual care was defined as a laxative treatment selected and prescribed by the investigator according to his/her usual clinical practice; no peripheral opioid antagonists or products containing naloxone were permitted as part of that treatment regimen.

Supplemental Table 2. Summary of Patients With Potentially Clinically Important ECG Abnormalities at 2 Hours After the First Dose of Study Drug

	Pooled placebo-controlled studies ^a			52-Week safety study	
	Placebo (n= 438)	Naloxegol 12.5 mg (n = 437)	Naloxegol 25 mg (n = 444)	Usual care (n = 232)	Naloxegol 25 mg (n = 478)
PR interval, msec					
≥210 and ↑ ≥15	8 (1.8)	9 (2.1)	7 (1.6)	4 (1.7)	7 (1.5)
≥240	4 (0.9)	6 (1.4)	4 (0.9)	3 (1.3)	4 (0.8)
QRS duration, msec					
≥120 and ↑ ≥15	0	0	2 (0.5)	0	0
≥140	7 (1.6)	7 (1.6)	11 (2.5)	1 (0.4)	6 (1.3)
QT interval, msec					
≥500	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.4)	0
QTcB interval, msec					
≥450 and ↑ ≥30	4 (0.9)	3 (0.7)	5 (1.1)	3 (1.3)	4 (0.8)

≥ 500	0	0	1 (0.2)	0	0
QTcF interval, msec					
≥ 450 to $\uparrow \geq 30$	0	2 (0.5)	2 (0.5)	1 (0.4)	2 (0.4)
Heart rate, bpm					
≤ 40	0	1 (0.2)	1 (0.2)	0	0
≥ 100 and $\uparrow \geq 20$	0	0	2 (0.5)	0	1 (0.2)
RR interval, msec					
≤ 600	7 (1.6)	5 (1.1)	10 (2.3)	3 (1.3)	7 (1.5)
$\geq 1,200$	14 (3.2)	17 (3.9)	14 (3.2)	10 (4.3)	8 (1.7)
ECG, electrocardiogram.					

Supplemental Table 3. Summary of Patients With Potentially Clinically Important ECG Abnormalities at Any Time During the Treatment Period

	Pooled placebo-controlled studies ^a			52-Week safety study	
	Placebo (n= 444)	Naloxegol 12.5 mg (n = 439)	Naloxegol 25 mg (n = 446)	Usual care (n = 234)	Naloxegol 25 mg (n = 479)
PR interval, msec					
≤110 to ↓ 15	2 (0.5)	2 (0.5)	1 (0.2)	0	0
≥210 and ↑ ≥15	13 (2.9)	14 (3.2)	10 (2.3)	11 (4.7)	20 (4.2)
≥240	6 (1.4)	6 (1.4)	7 (1.6)	4 (1.7)	5 (1.0)
QRS duration, msec					
≥120 and ↑ ≥15	0	3 (0.7)	2 (0.4)	2 (0.9)	2 (0.4)
≥140	7 (1.6)	11 (2.5)	12 (2.7)	1 (0.4)	7 (1.5)
QT interval, msec					
≥500	3 (0.7)	1 (0.2)	2 (0.4)	2 (0.9)	0
QTcB interval, msec					

≥ 450 and $\uparrow \geq 30$	22 (5.0)	20 (4.6)	21 (4.7)	15 (6.4)	41 (8.6)
≥ 500	2 (0.5)	3 (0.7)	2 (0.4)	2 (0.9)	0
QTcF interval, msec					
≥ 450 to $\uparrow \geq 30$	3 (0.7)	7 (1.6)	10 (2.2)	5 (2.1)	14 (2.9)
≥ 500	1 (0.2)	1 (0.2)	0	2 (0.9)	0
Heart rate, bpm					
≤ 50 and $\downarrow \geq 20$	2 (0.5)	0	2 (0.4)	2 (0.9)	1 (0.2)
≤ 40	2 (0.5)	1 (0.2)	1 (0.2)	2 (0.9)	0
≥ 100 and $\uparrow \geq 20$	10 (2.3)	8 (1.8)	7 (1.6)	4 (1.7)	21 (4.4)
≥ 120	1 (0.2)	3 (0.7)	1 (0.2)	1 (0.4)	2 (0.4)
RR interval, msec					
≤ 600	26 (5.9)	24 (5.5)	23 (5.2)	17 (7.3)	37 (7.7)
≥ 500	1 (0.2)	3 (0.7)	1 (0.2)	1 (0.4)	2 (0.4)
$\geq 1,200$	27 (6.1)	25 (5.7)	26 (5.8)	20 (8.5)	22 (4.6)
$\geq 1,500$	2 (0.5)	0	0	1 (0.4)	0

ECG, electrocardiogram.

References

1. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med.* 2014;370(25):2387-2396.