Evaluation of the Effect of Naloxegol on Cardiac Repolarization: A Randomized, Placebo- and Positive-Controlled Crossover Thorough QT/QTc Study in Healthy Volunteers

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ABSTRACT

Background: Opioid-induced constipation (OIC) is a common adverse effect associated with opioid use. Naloxegol is a PEGylated derivative of naloxone in clinical development as a once-daily oral treatment of OIC.

Objectives: A thorough QT/QTc study was conducted, according to International Conference on Harmonisation E14 guidelines, to characterize the effect of naloxegol on cardiac repolarization.

Methods: In this randomized, positive- and placebo-controlled crossover study, healthy men received a single dose of naloxegol 25 mg (therapeutic dose), naloxegol 150 mg (supratherapeutic dose), moxifloxacin 400 mg (positive control), or placebo in 1 of 4 sequences (Williams Latin square design). The washout time between treatment periods was at least 5 days. Digital 12-lead ECGs were recorded at baseline and at 10 time points over 24 hours after dosing in each treatment period. QT intervals were corrected for heart rate using the Fridericia formula (QTcF) and the Bazett formula (QTcB).

Results: A total of 52 subjects were enrolled (mean age, 28 years), and 45 received all 4 treatments. The placebo-corrected, baseline-adjusted, mean increases in QTcF with naloxegol 25 and 150 mg were both <5 msec at each time point, and all upper limits of the 2-sided 90% CI were <10 msec. Similar findings were observed using QTcB; the upper limits of the 2-sided 90% CI were <10 msec at all time points after dosing with naloxegol 25 or 150 mg. With moxifloxacin 400 mg, mean QTcF was increased by a maximum of 11.1 msec (90% CI, 9.3–12.9 msec), supporting assay sensitivity.

Conclusion: Naloxegol at 25 and 150 mg was not associated with QT/QTc interval prolongation in these healthy men, and at the proposed therapeutic dose of 25 mg/d, naloxegol is not expected to have a clinically relevant effect on cardiac repolarization in patients with OIC. ClinicalTrials.gov identifier: NCT01325415. (Clin Ther. 2013;35:1876–1883)

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Key words: cardiac repolarization, electrocardiography, naloxegol, opioid antagonist, opioid-induced constipation, peripheral μ-opioid receptor antagonist.

INTRODUCTION

Opioids are effective analgesics and are commonly used to treat moderate to severe pain.1,2 Opioid-induced constipation (OIC) is one of the most common and often debilitating adverse effects associated with opioid use.3 Depending on the population studied and the definitions used, OIC may occur in 15% to 81% of patients receiving opioids.4–8 Common treatments for OIC include laxatives and stool softeners; however, these are ineffective in many patients.3,9 Opioid antagonists possibly represent a more effective alternative to laxatives for the treatment of OIC.9 In particular, opioid antagonists that are restricted to the periphery should antagonize the actions of opioids in the gastrointestinal tract without affecting their analgesic effects or causing other central nervous system (CNS) opioid withdrawal effects. Naloxegol is a PEGylated derivative of naloxone that is in clinical development as a once-daily oral treatment for OIC.10 Naloxegol was designed to act as a peripheral opioid antagonist of μ-opioid receptors because the PEG moiety markedly reduces its capacity...
to cross the blood-brain barrier and enter the CNS. In a Phase 2 study, naloxegol was associated with a significantly increased frequency of spontaneous bowel movements in patients with OIC, without a reduction in opioid-mediated analgesia.

Many structurally diverse drugs have been shown to delay cardiac repolarization, demonstrated by a prolonged QT/QTc interval, which can lead to cardiac arrhythmias. This is particularly important in individuals receiving pain medication because some opioids (eg, methadone) can cause prolongation of the QT/QTc interval. The International Conference on Harmonisation (ICH) E14 guidelines recommend that all nonarrhythmic compounds undergo clinical evaluation and characterization of ventricular repolarization (QT/QTc) changes by means of a thorough QT/QTc study early in the course of their clinical development. The primary objective of this study was to evaluate the effects of 2 different single doses of naloxegol (25 and 150 mg, a therapeutic and a supratherapeutic dose, respectively) on the change in time-matched heart rate–corrected QT intervals according to the Fridericia method (QTcF) compared with placebo. Secondary objectives included evaluation of the effect of a single dose of moxifloxacin 400 mg (positive control) on time-matched and placebo-corrected changes in QTcF.

SUBJECTS AND METHODS
This study was designed and monitored in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice as defined by the ICH. An independent institutional review board (MidLands Independent Review Board, Overland Park, Kansas) approved the protocol before trial commencement, and all subjects gave written informed consent. The study was conducted at a single study center (Quintiles Phase I Unit, Overland Park, Kansas).

Inclusion and Exclusion Criteria
Study volunteers were healthy, nonsmoking men aged 18 to 50 years with a body mass index between 18 and 30 kg/m² and weight between 50 and 100 kg. Key exclusion criteria were an abnormal ECG; history of arrhythmia; QTcF >450 msec; abnormal vital signs; history or presence of cardiac, psychiatric, gastrointestinal, hepatic, or renal disease; excessive consumption of caffeine-containing products within 48 hours of each treatment period; history of or suspected drug or alcohol abuse; and use of any prescribed or over-the-counter medication within 2 weeks before the administration of the investigational drug.

Study Design
This randomized, 4-period, 4-treatment, single-dose crossover study consisted of 6 visits. During each 2-day treatment period, each volunteer received 1 of the 4 treatments in 1 of 4 treatment sequences, applying a Williams Latin square design in a double-blind fashion determined by a randomization schedule. The wash-out time between treatment periods was at least 5 days.

Subjects were screened within 30 days before randomization. Each subject received the following 4 treatments, administered in the order prescribed by the sequence to which the subject had been randomly assigned: naloxegol 25 mg, naloxegol 150 mg, open-label moxifloxacin 400 mg, and placebo. Subjects underwent a 10-hour fast before dosing, and no food intake was allowed until 4 hours after dosing.

Tolerability Assessment
Vital sign measurements, 12-lead safety ECGs printed on paper, physical examinations, and safety laboratory analyses involving routine hematology, serum chemistry, and urinalysis were obtained and reviewed by the investigator during the study and at a follow-up examination 7 to 10 days after the last treatment period. The subjects stayed at the phase 1 unit during all 4 dosing visits and were continuously monitored with ECG telemetry (real-time ECG display) from 30 minutes predose through 24 hours postdose. All adverse events (AEs) were evaluated by the investigator and characterized with respect to intensity, duration, relationship to study drug, and outcome.

Pharmacodynamic Measurements
Twelve-lead continuous digital ECG (dECG) recordings were obtained using a Schiller Cardiovit CS-200 recorder (Schiller AG, Baar, Switzerland). The analyses of all dECGs were performed at the AstraZeneca ECG Centre (AstraZeneca ECG Core Lab, Mölndal, Sweden) in a fully blinded mode (sequence, treatment, time, and subject identifier) using the EClYsis System (ECG Analysis, AstraZeneca proprietary tool,
Mölndal, Sweden), an automated reading method for dECG intervals allowing manual adjudication (ie, a semiautomatic analysis).15,16 Recordings were taken for 20 minutes at baseline and then for 5 minutes at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose using the same ECG machine at all time points in an individual subject, if possible. All dECG recordings were obtained after at least 10 minutes of rest in bed in the same supine body position at all time points and just before blood sample collections for pharmacokinetic (PK) assessments and blood pressure measurements.

The primary variable in this study was QTcF. The lead V2 was used as the primary lead, and lead V5 was used as the back-up lead for all time points when lead V2 was found to be unsuitable for analysis or evaluation. The QT interval was measured (in milliseconds) from the onset of the QRS complex to the end of the T wave. The end of the T wave was determined with the help of a tangent of the T-wave downslope crossing the isoelectrical line. With EClysis software, the tangent was derived between the 20% and 80% repolarization points of the T wave calculated from the top of the T wave to the isoelectrical line.16 The Fridericia correction method for heart rate is described subsequently. Other dECG-collected or -derived variables were heart rate (HR) in beats per minute; the RR interval, which is the time between corresponding points on 2 consecutive R waves in seconds; the PR interval, which is measured from the onset of the P wave to the onset of the QRS complex in milliseconds; the QRS duration, which is the interval measured from the onset of the QRS complex to the J point in milliseconds; and the QT interval corrected for heart rate using the Bazett formula (QTcB) in milliseconds. Ten-second dECGs were extracted every 30 seconds from the predefined 5- or 20-minute (baseline only) continuous recordings. The extracted data were averaged to arrive at a mean value for each time point. The QT interval was corrected for RR interval to obtain QTc variables. The general formula for QTc was QT/RRb, with QT intervals expressed in milliseconds and the RR interval in seconds. For QTcF, b = 1/3; for QTcB, b = 0.5.

Pharmacokinetic Measurements
Blood samples for PK analysis were collected within 30 minutes before investigational drug administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours following each treatment dose. AUC0–t, Cmax, Tmax were calculated for both naloxegol and moxifloxacin. Samples for determination of naloxegol and moxifloxacin concentrations in plasma were analyzed by Covance Laboratories (Indianapolis, Indiana) using HPLC-MS/MS.

Statistical Analysis
Assuming a 3-msec effect of naloxegol on QTcF, an 8-msec residual variability, and 20 postdose dECG assessments (10 time points × 2 treatments), 44 evaluable volunteers were needed to provide >90% power to conclude no effect on QTcF at or above the 10-msec threshold. The safety-analysis set consisted of all subjects who received at least 1 dose of naloxegol, moxifloxacin, or placebo and for whom any postdose data were available. The pharmacodynamic analysis set included all randomized subjects who received any study treatment and had any evaluable pharmacodynamic postdose data. The PK analysis set included all randomized subjects who received at least 1 dose of naloxegol or moxifloxacin and had at least 1 postdose PK measurement.

The analysis of change from baseline QTc was performed using a linear mixed-effects repeated measures model with treatment, period, and time as fixed categorical effects and baseline QTc as a continuous covariate; fixed-effect interactions for period and time and for treatment and time; volunteer within sequence was treated as a random effect, and the within-volunteer correlation was a first-order autoregression covariance structure.

For assessment of QTc prolongation, differences for naloxegol 25 and 150 mg versus placebo were statistically tested at each measurement time point, based on the mixed model using least squares (LS) mean differences and corresponding 2-sided 90% CI. A negative study requires all upper confidence limits to be <10 msec.

For assessment of assay sensitivity, differences between moxifloxacin versus placebo were statistically tested, averaging across the 1- to 4-hour range, based on the mixed model using LS mean differences and corresponding 2-sided 90% CI. Establishing assay sensitivity required that the lower limit of the CI be >5 msec.

RESULTS
A total of 52 male subjects were randomized, and 45 received all 4 treatments. Twenty-eight subjects (54%) were white; 22 (42%) were black; and 2 (4%) were
Native American or Native Alaskan. The age of the subjects ranged from 18 to 50 years (mean, 28 years; median, 25 years); body mass index ranged between 19 and 30 kg/m² (mean, 25 kg/m²; median, 24 kg/m²). Seven subjects withdrew from the study: 1 subject was removed for severe noncompliance with the protocol, 3 withdrew consent, and 3 were lost to follow-up.

**QTc Interval**

The placebo-corrected, baseline-adjusted mean QTcF for naloxegol 25 and 150 mg were both <10 msec (Figure 1). The maximum placebo-corrected, baseline-adjusted mean change in QTcF was 1.1 msec at 2 hours after dosing with naloxegol 25 mg and 3.1 msec with naloxegol 150 mg at both 1.5 and 2 hours after dosing (Table I). Similar findings were observed using QTcB; the upper limit of the 2-sided 90% CI was <10 msec at all assessed time points after dosing with naloxegol 25 or 150 mg.

With moxifloxacin 400 mg versus placebo, the largest placebo-corrected, baseline-adjusted mean change from baseline in QTcF was an increase of 11.1 msec (90% CI, 9.3–12.9 msec), which occurred at 3 and 4 hours after dosing (Figure 1, Table I).

Assay sensitivity was demonstrated by comparing moxifloxacin versus placebo QTcF averaged over the 1- to 4-hour range after dosing, using the mixed-effects repeated measures model. The lower limit of the 2-sided 90% CI for the difference (9.6 msec) of moxifloxacin versus placebo in ΔΔQTcF over the interval of 1 to 4 hours postdose was >5 msec, thereby establishing assay sensitivity.

### QTc Interval Increase From Baseline and Absolute QTc Interval Prolongation

Changes in QTcF from baseline to the observed maximum did not exceed 30 msec at any time point over the 24-hour period after dosing with naloxegol 25 or 150 mg or with placebo (Figure 2). One subject receiving moxifloxacin had a QTcF increase from baseline between 30 and 60 msec at 6 hours postdose. There were no subjects with absolute QTcF values >450 msec.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Naloxegol 25 mg (n = 51)</th>
<th>Naloxegol 150 mg (n = 49)</th>
<th>Moxifloxacin 400 mg (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTcF, msec</td>
<td>1.1</td>
<td>3.1</td>
<td>11.1</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.6 to 2.9</td>
<td>1.3 to 4.9</td>
<td>9.3 to 12.9</td>
</tr>
<tr>
<td>Time from administration to maximum absolute change from baseline in QTcF, h</td>
<td>2</td>
<td>1.5 and 2</td>
<td>3 and 4</td>
</tr>
</tbody>
</table>

QTcF = QT interval corrected using the Fridericia formula.

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**Table I. QTcF intervals with single-dose administration of naloxegol and moxifloxacin in healthy men. Values are maximum placebo-corrected, baseline-adjusted means.**
Changes in HR and RR, QT, PR, and QRS intervals were similar between naloxegol 25 and 150 mg and placebo. No clinically important changes in T-wave morphology were observed in this study.

**Pharmacokinetic Properties**

Naloxegol was rapidly absorbed following oral administration, with a median $T_{\text{max}}$ of 1 and 1.5 hours with the high and low doses, respectively (Table II). The geometric means of the dose-normalized PK parameters ($\text{AUC}_{0-\infty}$ and $C_{\text{max}}$) for naloxegol 25 and 150 mg were similar, suggesting dose proportionality over the dose range. The plasma concentrations and PK parameters of moxifloxacin were similar to values previously reported.\(^{17}\)

**Tolerability**

There were no deaths, serious AEs, or discontinuations of naloxegol due to AEs in the study. At least 1 AE was reported in 4 subjects (8%) with naloxegol 25 mg, in 9 subjects (18%) with naloxegol 150 mg, in 8 subjects (17%) with moxifloxacin 400 mg, and in 9 subjects (19%) with placebo. Most AEs were mild, not considered by the investigator as related to naloxegol, and resolved at study end. Naloxegol was not associated with clinically relevant changes in blood pressure, other vital signs, or laboratory values.

**DISCUSSION**

Excessive prolongation of cardiac repolarization indicated by QT interval lengthening/instability can lead to a life-threatening polymorphic ventricular tachycardia—torsades de pointes—which has a characteristic ECG pattern and can potentially cause sudden cardiac death.\(^{18}\) A number of structurally diverse noncardiac drugs can cause QT/QTc interval

### Table II. Pharmacokinetic parameters with single-dose administration of naloxegol and moxifloxacin in healthy men. Values are geometric means (%CV) unless otherwise noted.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Naloxegol 25 mg (n = 51)</th>
<th>Naloxegol 150 mg (n = 49)</th>
<th>Moxifloxacin 400 mg (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-\infty}$</td>
<td>156 (38.8)</td>
<td>921 (36.6)</td>
<td>19,800 (15.1)</td>
</tr>
<tr>
<td>$C_{\text{max}}$, ng/mL</td>
<td>6.25 (38.7)</td>
<td>6.14</td>
<td>—</td>
</tr>
<tr>
<td>$\text{C}_{\text{max}}$, ng/mL</td>
<td>37.7 (48.0)</td>
<td>291 (47.4)</td>
<td>1960 (27.3)</td>
</tr>
<tr>
<td>$T_{\text{max}}$, median (range), h</td>
<td>1.52 (0.52-4.03)</td>
<td>1.02 (0.52-4.02)</td>
<td>1.52 (0.52-6.03)</td>
</tr>
</tbody>
</table>
prolongation, and regulatory agencies recommend that all nonarrhythmic compounds undergo clinical evaluation for QT interval prolongation. The objective of this study was to assess the potential for naloxegol to provoke ventricular repolarization in human subjects at both therapeutic and supratherapeutic doses, and the results show that this is a negative thorough QT/QTc study based on the ICH E14 guidelines.

In the primary comparisons of QTcF for naloxegol versus placebo, all upper limits of the 90% CI for the difference in mean QTc interval between naloxegol 25 or 150 mg and placebo were <10 msec at all time points. Moreover, the baseline-adjusted, placebo-corrected mean changes in QTcF for both naloxegol doses were <5 msec at all time points.

Assay sensitivity was established with the positive control, moxifloxacin. The PK results of this study demonstrated that adequate exposure was achieved for the therapeutic and supratherapeutic doses of naloxegol and for moxifloxacin in these healthy subjects. The PK data together with the assay sensitivity results allowed for the valid assessment of QT effects of naloxegol.

No tolerability concerns for naloxegol were identified in this study up to a supratherapeutic dose of 150 mg. The proportions of subjects who experienced an AE were similar across treatment groups, and most AEs were judged to be unrelated to treatment. Moreover, there were no discontinuations from the study due to AEs. Thus, naloxegol appeared to be generally well tolerated.

Opioids are effective and commonly used in the treatment of severe pain. However, their use is often limited by adverse effects that can sometimes lead patients to reduce or abandon opioid therapy. OIC is a common adverse effect during long-term opioid use, and OIC significantly affects patients’ quality of life and daily activities to the extent that some patients would rather endure the pain than the constipation that accompanies opioid use. Treatments for OIC include laxatives and stool softeners; however, these are ineffective in many patients and do not affect the underlying cause of OIC—activation of opioid receptors in the gastrointestinal tract that decrease gastric motility, intestinal propulsion, and intestinal secretion. Opioid antagonists represent a possible alternative to laxatives for the treatment of OIC. However, opioid antagonists that penetrate the CNS may generate central effects, leading to inadequate pain control. Opioid antagonists that are restricted to the periphery should antagonize the activity of opioids in the gastrointestinal tract without affecting their analgesic effects. Naloxegol is a PEGylated derivative of naloxone in clinical development as a once-daily oral treatment for OIC. Naloxegol was designed to act as a peripheral opioid antagonist of μ-opioid receptors because the PEG moiety markedly reduces its capacity to cross the blood-brain barrier and enter the CNS. In a Phase 2 study, naloxegol restored gastrointestinal function by increasing the frequency of spontaneous bowel movements in patients with OIC, without reversing or reducing opioid-mediated analgesia.

Individuals receiving opioid therapy for pain management are predominantly white, married women aged >40 years with numerous comorbidities, including depression and other mental health disorders. Concomitant drug use in these individuals is high and may include antidepressants, hypnotics, sedatives, antiemetics, and other psychoactive drugs. Because some members of these drug classes (eg, tricyclic antidepressants) as well as methadone (commonly used as pain medication in the United States but infrequently in Europe) are known to prolong the QT interval, it is important that naloxegol, a drug in development for the proposed indication of OIC, had no effect on QT interval prolongation.

CONCLUSION
Naloxegol at doses up to 150 mg was not associated with QT/QTc interval prolongation in these healthy male subjects. Placebo-corrected, baseline-adjusted mean QTcF values for naloxegol were <5 msec at all time points, and there were no absolute QTc interval increases >30 msec with naloxegol. Based on these data, naloxegol at the proposed therapeutic dose of 25 mg/d does not have a clinically relevant effect on cardiac repolarization in patients with OIC.

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CONFLICTS OF INTEREST
AstraZeneca LP, the manufacturer of naloxegol, sponsored this study. The authors—Christer Gottfridsson, Glenn Carlson, Jaakko Lappalainen, and Mark Sostek—are employees of the study sponsor, AstraZeneca LP, and have a stockholder interest. The authors of this manuscript as well as other employees of the study sponsor and of Quintiles Inc., the contract research organization involved in this study, were involved in the study design and/or the collection, analysis, or interpretation of the data. The decision to submit the manuscript for publication was made by the authors. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

REFERENCES


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