ORIGINAL ARTICLE

Population Exposure-Response Modeling Supported Selection of Naloxegol Doses in Phase III Studies in Patients With Opioid-Induced Constipation

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Naloxegol is approved for the treatment of opioid-induced constipation (OIC) in adults with chronic noncancer pain. Population exposure-response models were developed using data from a phase II study comprising 185 adults with OIC. The weekly probability of response defined as having $\geq$3/week spontaneous bowel movements (SBMs) and $\geq$1 SBM/week increase over baseline was characterized by a longitudinal mixed-effects logistic regression dose-response model, and the probability of time to discontinuation was modeled with a Weibull distribution function. The predicted probability of SBM in a given week increased with increasing naloxegol dose. The model predicted that 12.5, 25, and 37.5 mg doses would produce median response rates of 40%, 50%, and 60%, and dropout rates of 13.3%, 16.7%, and 23.3%, respectively. The large overlap of predicted difference of the response rate between placebo and the 25 or 37.5 mg doses suggested little utility of using a 37.5 mg dose in phase III studies.

Study Highlights

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WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Naloxegol is a peripherally acting μ-opioid receptor antagonist for the treatment of OIC. Both 25 and 50 mg of naloxegol was statistically significant over placebo in a phase II study, but adverse events with increased frequency and severity were observed in the 50 mg dose cohort.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study supported the highest dose to be tested in phase III studies during the phase III study planning stage.

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WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ Based on the simulated trials, the distribution of mean difference from placebo significantly overlaps between the 25 mg and 37.5 mg dosing groups, suggesting that there would be little utility to using both the 25 mg and 37.5 mg dose levels in a single study.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
☑ This model prospectively defined dosing regimens for naloxegol, which was demonstrated to be effective in the later conducted phase III studies.

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Opioid-induced constipation (OIC) is a common side effect associated with opioid treatment. The estimated prevalence of OIC ranges between 15% and 90% in patients receiving opioids for noncancer pain,[1] most of whom regard OIC as the most bothersome side effect with at least a moderate negative impact on quality of life.[2] Naloxegol (previously known as NKTR-118) is a polyethylene glycol derivative of naloxone that has been approved in the United States as an oral, once-daily treatment for OIC in adults with chronic noncancer pain.[3] In the European Union, naloxegol is approved for the treatment of OIC in adults who have had an inadequate response to laxatives.[4] Because naloxegol has limited ability to cross the blood-brain barrier, central analgesic properties of opioid agonists are maintained.[5]

The pharmacokinetic (PK) profile of naloxegol has been studied in healthy subjects as well as patients with OIC.[6,7] Its PK is approximately dose proportional from 5–1,000 mg in healthy subjects and from 5–50 mg in patients.[6,7] The PKs of naloxegol is also time independent following multiple dosing when characterized at doses up to 250 mg.[8]

Naloxegol is rapidly absorbed following oral administration to patients and healthy volunteers, exhibiting peak plasma concentrations in <2 hours.[6,7] Following once-daily administration, steady state is achieved within 2–3 days with minimal accumulation.[8] The primary route of naloxegol elimination is via hepatic metabolism, with renal excretion playing a minor role.[9] Naloxegol is a substrate for cytochrome P450 (CYP)3A enzymes as well as the P-glycoprotein (P-gp) efflux transporter. Naloxegol has no significant inhibitory or induction effect on the activity of major CYP3A enzymes. Naloxegol is also not an inhibitor of P-gp, breast cancer resistance protein, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion-transporting peptide (OATP)1B1 and OATP1B3.[10]

Randomized, double-blind, placebo-controlled phase II (Study 07-IN-NX003)[5] and phase III studies (K4 and K5)[11] have demonstrated the efficacy of naloxegol in patients with OIC for noncancer pain. Patients used an eDiary to record all spontaneous bowel movements (SBMs), defined as bowel movements that occurred in the previous 24 hours

without the use of rescue laxatives. In the phase II study, multiple naloxegol doses (5 mg, 25 mg, and 50 mg) were tested against placebo in patients with OIC. The naloxegol 25 mg and 50 mg daily doses for 4 weeks were significantly more effective than placebo in increasing the number of SBMs per week over baseline, whereas 5 mg had no significant effect.[5] However, the incidence of treatment-emergent adverse events was higher in patients who received 50 mg naloxegol (85.7%) compared with those who received placebo (56.8%).[5] Two identical, multicenter, double-blind, phase III studies (K4 and K5) randomized >1,350 patients to naloxegol 12.5 or 25 mg/day or placebo.[11] Response rates were significantly higher in patients with 25 mg of naloxegol than those with placebo in both studies and were also higher in the group treated with 12.5 mg of naloxegol in one study.[11]

During the design of the phase III trials, the US Food and Drug Administration recommended that the primary efficacy endpoint for the pivotal phase III efficacy studies should be the response rate and not the increase in SBMs from baseline, as evaluated in the phase II study. The primary endpoint in the pivotal studies based on response rate was to be multifactorial, ensuring patients had to demonstrate a clinically relevant improvement in SBM frequency, which was durable and maintained across the 12-week treatment period. To be considered as a responder, patients had to have ≥3 SBMs per week with at least 1 SBM/week increase over baseline for at least 9 of the 12 treatment weeks and for 3 of the last 4 treatment weeks. The phase II data were re-analyzed using response as an efficacy endpoint, in which response was defined as having at least 3 SBMs/week and at least 1 SBM/week increase over baseline for at least 3 of the first 4 weeks of treatment. This paper presents application of modeling and simulation during naloxegol development to (1) develop a population exposure-response model to quantify changes in response rate and dropout rate upon dosing with naloxegol, and (2) predict response rate and dropout rate in patients taking 12.5 mg/day, 25 mg/day, and 37.5 mg/day of naloxegol that can be used to support dose selection in the phase III studies.

METHODS
Subjects and study design
The clinical results of the phase II study (Study 07-IN-NX003) were reported previously.[5] Briefly, this was a double-blind, randomized, placebo-controlled, multiple-dose, and dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with OIC. Patients with confirmed OIC entered a 1-week, single-blind, placebo run-in period, followed by 4 weeks of randomized double-blind treatment with naloxegol or placebo. Randomization was stratified based on the total daily opioid dose at baseline. The doses of naloxegol were originally scheduled to be 5 mg, 25 mg, 50 mg, and 100 mg once daily with about 54 patients randomized in a 1:1 ratio of active: placebo within each cohort. However, upon review of safety data from the 50 mg cohort, a decision was made not to continue with the fourth dose cohort at 100 mg. Eventually 208 patients were randomized and 207 patients were

evaluated in 3 cohorts. The studies were approved by local ethics committees and were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

The primary efficacy endpoint was a change in SBMs per week from baseline to the end of week 1 of the double-blind treatment period. An SBM was defined as a bowel movement that occurred without the use of a rescue laxative within the previous 24 hours. Baseline SBMs per week were determined during the 2-week run-in period. Model development was based on the modified intention-to-treat population, defined as patients who were randomized and received at least one dose of double-blind study treatment, had a baseline value, and evaluable data at week 1 of the double-blind study period. A patient was defined as a responder if he had ≥3 SBMs per week and ≥1 SBM change from baseline for at least 3 of 4 weeks. Response rate was then calculated as the number of responders in a particular treatment group divided by the number of modified intention-to-treat patients in that group. Dropouts were considered nonresponders.

Model development
A longitudinal mixed-effects logistic regression model was developed using the phase II study data to characterize the relationship between naloxegol dose and the weekly probability of response. Achieving response in any week was defined as both ≥3 SBM and ≥1 SBM change from baseline in that week. The logit of the probability of response P was given by the equation:

$$log\left(\frac{P}{1-P}\right) = E_0 + \alpha \times Dose + \eta$$

where E_0 is the logit of the baseline probability of response without drug (on placebo), α is the odds ratio of response per mg of naloxegol dose, $Dose$ is the daily dose of naloxegol in mg, and η is an individual random effect. All available values of response at weekly visits in each individual were included in estimation of model parameters.

In addition, a model for the time to study discontinuation (dropout) was developed. We used the Weibull distribution to model the probability density of time to discontinuation parameterized in terms of the median time to discontinuation $\tilde{t}$:

$$p(t) = ln2 \times \gamma \times \frac{1}{\tilde{t}} \times \left(\frac{t}{\tilde{t}}\right)^{\gamma-1} \times e^{-ln2 \times \left(\frac{t}{\tilde{t}}\right)^{\gamma}}$$

where γ is the shape parameter of the Weibull distribution. The median time to discontinuation was modeled as a linear function of naloxegol daily dose:

$$\tilde{t} = B + \beta \times Dose$$

where B is the median time to discontinuation on placebo (days) and β is a coefficient relating dose to median discontinuation time. Parameters of the two models were estimated jointly by calculating likelihood of data using probability of response P and probability of time to

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Table 1 Observed number and proportion of responders in each cohort of the phase II study

	First cohort		Second cohort		Third cohort	
	Placebo	5 mg	Placebo	25 mg	Placebo	50 mg
No. of patients	31	31	27	29	37	30
No. of responders[a]	10	12	5	20	6	20
% of responders	32	39	19	69	16	67
No. of completed weeks 1–4	26	27	27	28	31	21

[a]Responders: $\geq$3 spontaneous bowel movements (SBM) per week with at least 1 SBM/week increase over baseline for at least 3 of the 4 treatment weeks.

discointinuation *p(t)*. First, the baseline components of the models were estimated using placebo data to ensure the baseline models were adequate. Then, both baseline and drug-related components of models were estimated on all data. The two models were used together to predict response rate in a simulation of a phase III study. The modeling used the following assumptions: (1) dropouts occured at random on placebo and (2) the hazard of drop-out from the study increased with the dose monotonically.

Parameters of the model were estimated using the Laplace estimation method in NONMEM version 7.2 (ICON Development Solutions, Hanover, MD). Model development was guided by successful convergence and calculation of SEs, reductions in objective function values for hierarchical models, and overall goodness-of-fit. In addition, the stability of the models was evaluated throughout model develop-ment. All database processing was completed using SAS software version 8.2 (SAS Institute, Cary, NC; 2002). S-Plus version 8.2 (MathSoft, Seattle, WA) and R version 3.1.1 (www.r-project.org) software packages were used for preprocessing or postprocessing of NONMEM estimation and simulation results and for simulation purposes.

Model evaluation
The predictive performance of the final model of probability of response was evaluated with a visual predictive check (VPC).[12] Simulation of 1,000 new datasets replicating the design and dose regimen was carried out using the final model with the estimated fixed-effects and random-effects model parameters. The 95% prediction intervals were cal-culated and compared for observed and simulated data.

The models were also simulated to predict the proportion of responders (response rate) to compare with the observed proportions in the phase II study. Simulations were con-ducted using the final model with the estimated fixed-effects and random-effects model parameters, as well as parameter uncertainty. A total of 500 datasets with the same number of subjects and doses as in the phase II study were simulated using the estimated between-subject variability. Responder status was calculated from simulated weekly response and dropout values using the same definition as in the phase II study. Dropouts were considered nonresponders. Simula-tions were summarized by the median proportion of respond-ers and the 90% prediction interval over simulated datasets.

Model simulation
Simulations were conducted to predict the percentage of responders (response rate) in a future phase III study at dif-ferent dose levels with consideration of dropout. Probability of response and probability of dropout were simulated using

the models with estimated parameter values over weekly visits for 4 weeks. The response rate was then calculated by excluding simulated subjects predicted to drop out from the study and counting the number of remaining subjects with response for at least 3 of 4 weeks. A total of 500 trials of 4-weeks duration with 200 subjects per dose group were simulated using estimated between-subject variability. Each trial was simulated using an independent draw from the asymptotic multivariate normal distribution of estimated parameter values. Simulated doses were 0, 12.5, 25, and 37.5 mg. The distributions of mean difference of the propor-tion of responders between each naloxegol dose group from placebo were summarized.

RESULTS

A total of 185 patients with OIC from the placebo-controlled phase II study were included in this exposure-response analysis. These patients had a mean age of 49.7 years and the majority (62.2%) were women. The 86.5% of this popula-tion were white patients, followed by black patients (11.4%). Body weight ranged from 50.2–182.1 kg in this patient popu-lation. The median change from baseline in SBMs per week across the 4-week double-blind treatment period was statisti-cally significant for both 25 mg and 50 mg of naloxegol com-pared to placebo, but was not statistically significant for the 5 mg dose of naloxegol.[5] The percentages of responders over the total duration of treatment in each treatment group are summarized in **Table 1**. The number of patients started and completed in each cohort are also listed. The patients in the 50 mg treatment group had the highest dropout rate of 30% within 4 weeks.

Linear models of the relationship between naloxegol dose and probability of response and median time to dropout described the data well. Parameters were estimated with adequate precision (**Table 2**). Probability of response on pla-cebo in any given week is estimated to be 0.38. The odds ratio of response is predicted to be about 1.8 for every 10 mg increase of naloxegol dose. The median time to dropout on placebo is 110 days and it decreases on average by 12 days for every 10 mg increase of naloxegol dose.

A VPC was used to evaluate the predictive ability of the final model. The VPC plots showed the predicted median proportion of responders at each week to be consistent with the observed geometric mean proportion of responders for all doses in the study and throughout the duration of treatment (**Figure 1**). The observed proportions of respond-ers were generally contained within the 95% prediction interval. Based on the VPC results, the response model

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Table 2 Final model parameter estimates

Parameter	Description (unit)	Estimate	%RSE
E_0	Baseline logit of response (nondimensional)	−0.51	34
α	Odds ratio of response per mg of drug dose (1/mg)	0.061	15
B	Median time to discontinuation on placebo (days)	110	28
β	Coefficient relating dose to median discontinuation time	−1.2	57
γ	Shape factor of the Weibull distribution (nondimensional)	1.4	12
ϖ^2_{E0}	Interindividual variance of E_0	2.6	24

developed for naloxegol was considered adequate for further simulation.

The effect of different doses of naloxegol on the percentage of responders was illustrated by simulations using the final model with consideration of the dropouts. The predicted response rate increased with naloxegol dose. The model predicted that 12.5, 25, and 37.5 mg doses would produce median response rates of 40%, 50%, and 60%, and dropout rates of 13.3%, 16.7%, and 23.3%, respectively (**Figure 2 and Table 3**). The higher predicted than observed response rate at 25 mg is explained by the fact that the the predicted dropout rate of 17% is based on modeling all data, whereas the dropout rate of 3% in the 25 mg cohort of the phase II study seemed to be uncharacteristically low. A higher dropout rate would drive the response rate down because dropouts were considered nonresponders in the study and the simulation.

Based on the simulated naloxegol dose response, the distribution of the mean difference of the proportions of responders from placebo overlaps significantly between the 25 mg and 37.5 mg dosing groups (**Figure 3**), suggesting that there would be little utility to using both 25 mg and 37.5 mg dose levels in a single study. The mean proportion of responders over simulated trials was 25% for 25 mg naloxegol and 34% for 37.5 mg. There were 86% of trials with the response rate difference of 15% between naloxegol and placebo on 25 mg, whereas there were 97% of trials with this difference on 37.5 mg.

DISCUSSION

Modeling and simulation has been extensively applied in the clinical development of naloxegol to support dose selection, development decisions, as well as the regulatory submission and labeling. Exposure-response analysis of the phase III data demonstrated that the 12.5 mg dose could provide a clinical benefit over placebo with comparable
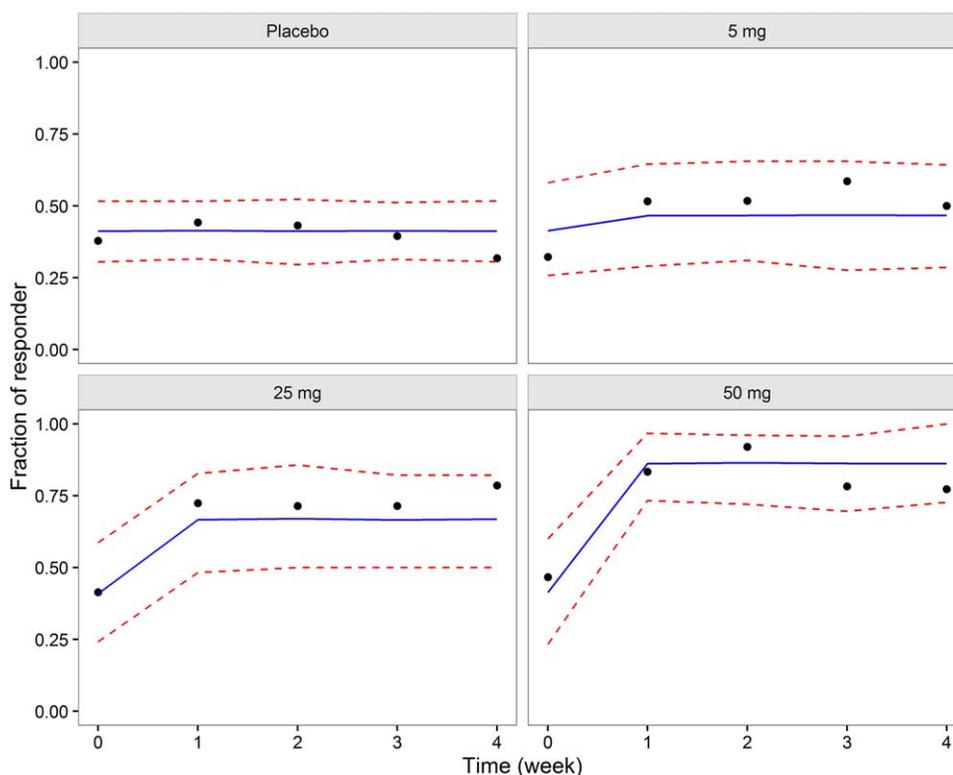
Figure 1 Visual predictive check plots of final spontaneous bowel movement response model grouped by daily naloxegol dose. Each panel shows simulations for naloxegol dose 0, 5, 25, and 50 mg. Blue line: predicted median; red dashed line: 95% prediction interval; black dots: observed proportion of subjects with response in the phase II study.

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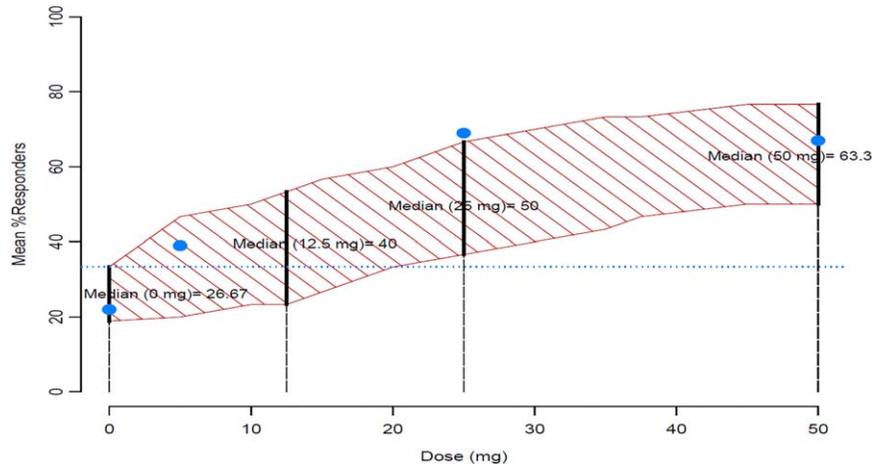
Figure 2 Predicted response rate with 90% predictive interval based on simulation of 1,000 trials compared to the response rate observed in the phase II study. The blue dots were observed values in the phase II study for placebo, 5 mg, 25 mg, and 50 mg, respectively. The vertical black line and median values were model-simulated values and 95% prediction interval for placebo, 12.5 mg, 25 mg, and 50 mg doses.

efficacy to the 25 mg dose.[13] In combination with clinical drug-drug interaction results, the physiologically based pharmacokinetic models reasonably predicted naloxegol exposure when coadministered with CYP3A and/or P-gp modulators and provided comprehensive dosage recommendations for naloxegol.[14] The current analysis demonstrated another modeling and simulation application of naloxegol to define/select appropriate doses for critical phase III studies, which resulted in a positive outcome.

Model simulations supported observations in the phase II study that the increased dose of naloxegol leads to an increased response rate for every week during the study of 4 weeks (**Figure 1**). It was also demonstrated that naloxegol achieved the efficacy as measured by the SBM response at week 1 and efficacy stayed in the similar range over the 4-week treatment period for both the 25 mg and 50 mg dose groups. The 5 mg dose group did not result in a larger response than the placebo (**Figure 1**). In addition, the higher dose of naloxegol was associated with a higher rate of dropout compared with the lower doses. The observed response rate in the 25 mg dose cohort (69%) was quite high and similar to that observed in the 50 mg dose cohort, however, the final model predicted the response rate in the 25 mg dose cohort was about 50%.

In the 25 mg dose group, the actual dropout rate was very low (3.4%; **Table 3**) relative to the other groups resulting in a high observed response rate. The model predicted that the dropout rate for the 25 mg dose group to be 16.7% resulting in the lower predicted response rate. This prediction was based on the dropout model that integrated information from all cohorts and is likely to be more predictive.

The high dropout rate (~30%) in the 50 mg dosing group in the phase II study suggested that 50 mg was not appropriate to be tested in the phase III studies. Whether a dose between 25 mg and 50 mg should be tested was a question during the design of a phase III study. The model predicted that 25 and 37.5 mg doses would produce median response rates of 50.0% and 60.0%, respectively. But considering large overlap in the prediction range (**Figure 3**), the differences of response rates between placebo and naloxegol-treated subjects were not significantly different among these dose groups. Considering the 37.5 mg dosing group would have higher dose related dropouts, the 25 mg dose was recommended as the highest dose to be tested in phase III studies.

The modeling and simulation were performed prior to conducting two phase III studies, and predictions were further confirmed with clinical observations in these two

Table 3 Model predicted response and dropout rate at different doses of naloxegol

	Model predicted % response rate median (5th–95th)	Observed % response rate	Model predicted % dropout rate median (5th–95th)	Observed % dropout rate
Placebo	26.7 (18.9–33.4)	22[a]	11.1 (6.7–16.7)	11.6
12.5 mg	40.0 (23.3–53.3)	NA	13.3 (3.3–23.3)	NA
25 mg	50.0 (36.7–66.7)	69	16.7 (6.7–30.0)	3.4
30 mg	56.7 (40.0–70.0)	NA	20 (10.0–33.3)	NA
37.5 mg	60.0 (46.7–73.3)	NA	23.3 (13.3–36.7)	NA
50 mg	63.3 (50.0–76.7)	67	33.3 (20.0–46.7)	30

NA, not applicable.
[a]Average from three cohorts.

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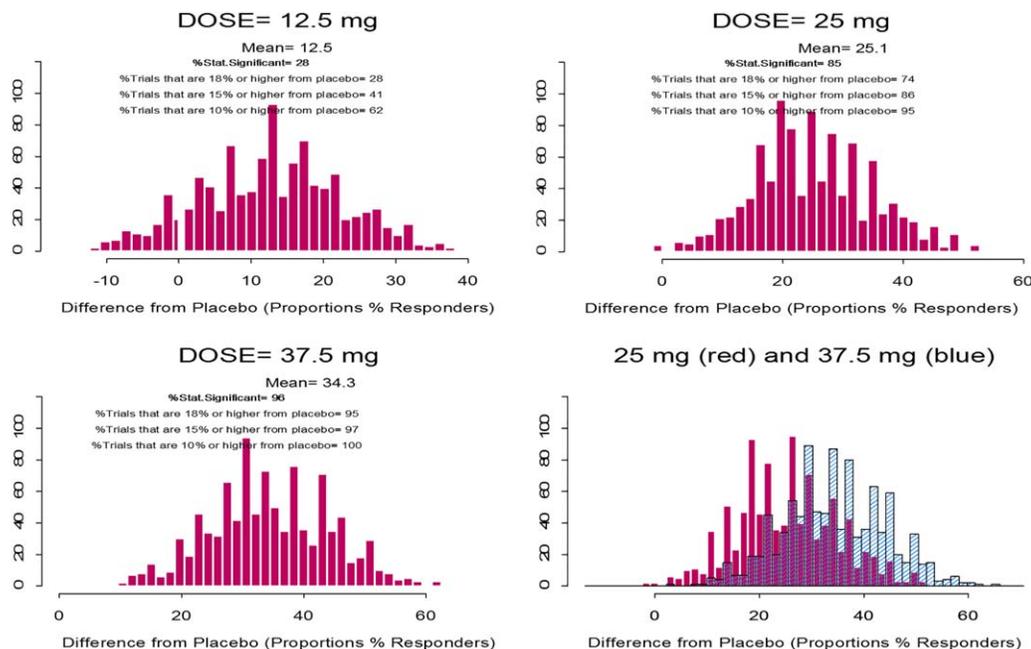
Figure 3 Simulated distribution of mean difference of the proportion of responders from placebo across simulated trials.

phase III studies. Because most of protocol-defined study/treatment discontinuation occurred in the first 3 weeks due to adverse events, it was assumed that the hazard will remain constant after the first 4 weeks. This assumption allowed us to translate our inference into the phase III study design (i.e., the responder rates at 4 weeks would be predictive of the responder rates at 12 weeks). Thus, dose selections were based on dose response analysis of a 4-week endpoint, which was assumed to be correlated with a 12-week endpoint. In the simulation of dose response based on the phase II data, accounting for dropout, the difference of response rates between 12.5 mg (40%) and 25 mg naloxegol (50%) was about 10% (**Table 3**). In the phase III studies, the difference of response rates between the 12.5 and 25 mg groups was similarly small, 3% and 5%, respectively.[11] The observed response rates in the phase III studies at 12.5 and 25 mg were lower but in a similar range as those predicted by the model (35% and 41% in the studies vs. 40% in model simulation for 12.5 mg and 44% and 40% vs. 50% for 25 mg). This is expected because the response rates from the phase III studies were obtained over a longer duration (12 weeks vs. 4 weeks in the simulation) and, hence, would have higher dropout rates because droupouts were considered as nonresponders, as well as because the criteria for the definition of a responder were more stringent than those used in this simulation. Responders in the phase III studies were defined as ≥3 SBMs per week with at least 1 SBM/week increase over baseline for at least 9 of the 12 treatment weeks and for 3 of the last 4 treatment weeks compared to ≥3 SBMs per week with at least 1 SBM/week increase over baseline for 3 of the 4 treatment weeks in the model simulation.

In conclusion, a naloxegol response and dropout model was developed and confirmed to be predictive of the redefined response rates observed in the phase II trial. The model was used to recommend the highest dose used in the phase III studies. The model predictions of the difference in response rates between 12.5 mg and 25 mg of naloxegol were consistent with the results of phase III studies and supported the approval of both naloxegol doses in the United States and in the European Union.

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