Research Article

Population Analyses of Efficacy and Safety of ABT-594 in Subjects with Diabetic Peripheral Neuropathic Pain

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Received 5 October 2011; accepted 31 January 2012; published online 11 February 2012

Abstract. ABT-594, a neuronal nicotinic acetylcholine receptor ligand, is 30- to 100-fold more potent than morphine in animal models of nociceptive and neuropathic pain. Efficacy and safety of ABT-594 in subjects with painful diabetic polyneuropathy was evaluated in a phase 2 study. The objective of this work was to use a nonlinear mixed effects model-based approach for characterizing the relationship between dose and response (efficacy and safety) of ABT-594. Subjects ($N=266$) were randomized into four groups in a double-blind, placebo-controlled, 7-week study to receive twice daily regimens of placebo or 150, 225, and 300 μg of ABT-594. The primary efficacy variable, pain score (11-point Likert scale), was assessed on five occasions. The probability of change from baseline pain score of ≥ 1 , ≥ 2 , and ≥ 3 was modeled using cumulative logistic regression with dose and days of treatment as explanatory variables. The incidence of five most frequently occurring adverse events (AEs) was modeled using linear logistic regression. ABT-594 ED_{50} values (improvement in 50% of subjects) for improvement in pain scores of ≥ 1 , ≥ 2 , and ≥ 3 were 50, 215, and 340 μg , respectively, for the average number of days (33) on treatment. The rank order of ED_{50} values for AEs was nausea, vomiting, dizziness, headache, and abnormal dreams; nicotine users were less sensitive to AEs. Population pharmacodynamic models developed to characterize the improvement in pain score and incidence of adverse events indicate an approximately twofold separation between the ED_{50} values for efficacy and AEs.

KEY WORDS: dose–response; logistic regression; modeling; neuropathic pain; population analyses.

INTRODUCTION

Pain is one of the most common symptoms of disease and the most frequent complaint with which patients present to physicians. Neuropathic pain is a frequent sequela of diabetes, cancer, acquired immunodeficiency syndrome (AIDS), and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome (1). Chronic neuropathic pain, including diabetic neuropathic pain, is often undertreated and is considered to be one of the most common causes of suffering and disability in the industrialized world (2).

Worldwide, diabetic neuropathic pain is present in approximately 20% of patients with more than a 10-year history of diabetes (3). Historically, the most effective treatments have been anticonvulsants (*e.g.*, gabapentin) and antidepressants (*e.g.*, tricyclic antidepressants), often being prescribed off-label. Many of these therapies have a delayed onset of analgesia and require dose titration. The recent introduction of duloxetine (4) following approval of pregabalin (5) has expanded the treatment options for

diabetic neuropathic pain. Even with these new approvals, current treatment options provide effective pain relief (greater than 50% reduction in pain) to less than 50% of patients and have many undesirable side effects (6,7). In addition, opioids are also used to treat neuropathic pain but the long-term benefits of opioids in this pain state have not been well characterized. As a result, the development of novel therapeutics for the treatment of neuropathic pain is highly desirable to achieve an improved balance of efficacy and safety for those patients most in need.

ABT-594 [(*R*)-5-(2-azetidylmethoxy)-2-chloropyridine] is a nonopioid, non-NSAID analgesic. It is a neuronal nicotinic acetylcholine receptor (nAChR) ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception (8). ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway (8). It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states (8).

In a phase 1 study in healthy volunteers, ABT-594 was generally well tolerated at fixed doses up to 300 μg twice daily (BID) for 14 days. Adverse events, which were significantly different than placebo, for subjects receiving 300 μg BID for 14 days included: dizziness, nausea, vomiting, asthenia, and diarrhea (all of which were considered to be mild in the

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opinion of the investigator). In another study in healthy volunteers that included titrated doses up through 450 μg BID for 5 days, results suggested that a short period of dose escalation at the initiation of therapy improved tolerability. In all phase 1 studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3 to 4 days of repeated dosing (the period in which most adverse events occur). Data from phase 1 and 2 studies suggested that ABT-594 was generally well tolerated at doses higher than previously studied in phase 2 trials (higher than 75 μg BID). In addition, data from previous phase 2 trials suggest that, because a trend toward analgesic efficacy was seen at 75 μg BID, a study of higher doses may demonstrate greater analgesic efficacy.

The efficacy and safety of ABT-594 in subjects with painful distal symmetric diabetic polyneuropathy was evaluated in a randomized, double-blind, placebo-controlled, parallel group, multicenter 7-week phase 2 dose-ranging study (9). The objective of this work was to use a nonlinear mixed effects model-based approach for characterizing the relationship between dose and response (efficacy and safety) of ABT-594 in subjects with diabetic peripheral neuropathic pain.

METHODS

Study Subjects

Male and female subjects (age 18 or older) who had painful diabetic polyneuropathy were screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. For eligibility into the study, subjects had a diagnosis of diabetes mellitus (type I or II) with distal symmetric diabetic polyneuropathy and have good control (in the opinion of the investigator) of the subject's serum glucose for at least the last 3 months prior to the screening visit; subjects had distally and symmetrically decreased or lost vibratory, pin, and/or light touch sensation on neurological exam, and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy; subjects had distal symmetric diabetic polyneuropathy symptoms (including pain) which were stable for at least the last 3 months prior to the screening visit (defined by the opinion of the investigator). Additionally, subjects had an average of ≥ 4 points on the diary-based 11-point Likert pain rating scale during the baseline pain assessment phase (days -7 to -1) and ≥ 4 points on the site-based 11-point Likert pain rating scale at the baseline visit (day 1). Subjects were excluded from the study if they had a positive test result for drugs of abuse or viral hepatitis or known history of a positive test result for HIV; recent (< 5 years) history of drug or alcohol abuse or dependence; an acute or chronic renal or hepatic disorder; psychiatric disease or disorder or any uncontrolled medical illness; an active malignancy or a history of malignancy; taken an investigational drug within 1 month prior to administration of study treatment or was scheduled to receive an investigational drug other than ABT-594 during the course of this study; diastolic blood pressure greater than 95 mmHg and/or a systolic blood pressure greater than

170 mmHg (sitting) at the screening visit; orthostatic hypotension (defined as a decrease in systolic blood pressure of at least 20 or 10 mmHg in diastolic blood pressure from supine to standing sustained after 1 min of standing) at the screening visit; or a history of syncope or presyncopal symptoms, clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, and clinically significant electrocardiographic abnormalities. Additionally, subjects were ineligible for the study if they had a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease, or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject could not differentiate from the neuropathy pain. Those subjects who took tricyclics, serotonin-specific reuptake inhibitors, antiepileptic drugs, or other analgesics for the treatment of their pain discontinued these drugs at least 7 days prior to initiation of the study.

The study was conducted at 29 clinical sites, and the corresponding institutional review boards approved the study protocol. Before the performance of any screening and study-specific procedures, applicable informed consent was obtained from each subject.

Study Design

This was a phase 2 dose-ranging, double-blind, placebo-controlled, parallel group, multicenter 7-week study in subjects with painful distal symmetric diabetic polyneuropathy. The study was divided into five phases: screening phase (days -22 to -8), baseline pain assessment phase (days -7 to -1), primer phase (days 1 to 7), treatment phase (days 8 to 49), and posttreatment phase (days 50 to 59). Day 1 was the first day of study drug administration. Subjects ($N=266$) were approximately equally randomized into four groups to receive twice daily (BID) regimens of placebo or 150, 225 and 300 μg of ABT-594 for 49 days. During the primer phase (days 1 to 7), subjects received a fixed dose escalation of study drug. Subjects were initiated at 75 μg BID, and the dose increased every 2 days in 75- μg BID increments until the subject took their assigned treatment dose (150, 225, or 300 μg BID), which was the treatment phase (days 8 to 49).

Subjects rated their pain intensity by completing the pain rating scale in their diaries. The 11-point Likert pain rating scale is one of the most widely used quantitative measure of pain intensity to assess treatment efficacy in clinical trials for analgesics in general, and for neuropathic pain trials in particular (10-13). There are 11 numbers (0-10), each of which represents a different severity of pain: 0=no pain and 10=worst pain possible. The 11-point Likert pain rating scale was used in this study to assess the severity of pain that a subject experienced over the 24-h period preceding the assessment. These assessments were completed daily at approximately the same time each morning: at approximately 11:00 a.m. during the baseline pain assessment phase and at approximately 3 h after the morning dose of study drug during the primer and treatment phases. The primary efficacy variable was the change in the average diary-based pain score from baseline (average of 7 days before randomization) at each treatment visit (average of last 7 days on study drug) on study days 14, 21, 35, and 49; subjects were allowed a window

of ± 3 days for each treatment visit. In addition, at each treatment visit, the site-based pain rating scale, neuropathic pain scale, the subject and clinician global impression of change (study day 49 only), and SF36 Health Status Survey (study day 49 only) were assessed. All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the subject, were reported.

Population Pharmacodynamic Analyses—Efficacy

The primary efficacy variable, the observed pain score (observed cases) on the 11-point Likert scale at each visit (average of diary-based pain score for last 7 days on study drug) was modeled. The change from baseline (Y) in the 11-point Likert scale pain score was used to model analgesic efficacy. The population analyses were performed using NONMEM Version VI (14).

The probability of change from baseline (Y) pain score (improvement, m) of ≥ 1 , ≥ 2 , and ≥ 3 was modeled with dose and days of treatment as explanatory variables using cumulative logits in NONMEM (15,16). The set of probabilities were fit with ordinal multinomial model for each degree of improvement in pain score.

The model for the probability of $Y \geq m$ is given by:

$$g\{P(Y \geq m)\} = f_p + f_d + \eta_Y \quad (1)$$

where f_p is the function describing the placebo effect, f_d is the function describing the drug effect, η_Y represents the random individual effect, which has a mean of zero and variance of Ω , and $g\{x\}$ denotes the logit transformation of a probability of improvement in pain score.

The placebo effect, f_p was modeled as:

$$f_p(m) = \sum_{k=1}^m \beta_k \quad (2)$$

where β_k represents the parameters of the placebo model.

The basic cumulative logit model (Eq. 2), where a set of baseline probabilities (15) quantify the degree of reduction in pain intensity at each observation (*i.e.*, study visit) was found to adequately capture the time course of placebo response. Therefore, a structural model to capture any additional time dependency of the placebo response (16) was not necessary.

The relationship between dose and drug effect (f_d) was initially explored using simple $E_{\max}$ and sigmoidal $E_{\max}$ models within the logistic regression framework. However, these models failed to adequately characterize the data, probably due to overparameterization. Subsequently, drug effect (f_d) was characterized using a linear model within the logistic regression framework:

$$f_d(\text{dose}, \text{day}) = \alpha_1 \cdot \text{DOSE} + \alpha_2 \cdot \text{DAY} + \alpha_3 \cdot \text{DOSE} \cdot \text{DAY} \quad (3)$$

where α_k represents the parameters of the drug effect model.

The effect of nicotine use, sex, and age on the reduction in pain score from baseline was explored within the logistic regression framework. In a stepwise manner, each covariate was allowed to increase or decrease the probability of $Y \geq m$ in Eq. 1.

The Laplacian approximation method was used to estimate the probabilities of $Y \geq m$ (Eq. 1). The traditional model building procedure of stepwise forward selection ($P < 0.05$) followed by backward elimination ($P < 0.005$) of explanatory variables (dose, day, dose-by-day interaction and covariates) was employed. Difference in NONMEM minimum value of objective function (MVOF) was used for testing (chi-square approximation) the significance of each effect by dropping them, one at a time, from the above model during backward elimination.

Once the final model was identified, a nonparametric bootstrap analysis was performed to quantitate central values and 95% confidence intervals for parameter estimates. In order to estimate confidence intervals of the model parameters, 500 bootstrap replicates were constructed by randomly sampling (with replacement) N subjects from the original dataset, where N is the number of subjects in the original dataset. Model parameters were estimated with each of the bootstrap replicates, and the resulting values were used to derive medians and confidence intervals. Bootstrap statistics were based only on successfully converged replicates. The medians and 95% confidence intervals for bootstrap model parameters were derived as the 50th percentile and the range from the 2.5th to the 97.5th percentiles of the results from individual replicates. Model parameters based on the original dataset were compared against the bootstrap results in order to ensure that they correspond to a robust global minimum in the likelihood profile.

The ED_{50} values, *i.e.*, ABT-594 dose at which 50% of subjects see an improvement in pain relief of ≥ 1 , ≥ 2 , and ≥ 3 , for any number of days on treatment was calculated as:

$$ED_{50} = - \left\{ \frac{\alpha_2 \cdot \text{DAY} + f_p}{\alpha_1 + \alpha_3 \cdot \text{DAY}} \right\} \quad (4)$$

when $P(Y \geq m) = 0.5$ and $g\{P(Y \geq m)\} = 0$.

Population Pharmacodynamic Analyses—Safety

The incidence of five most frequently occurring adverse events, *viz.* nausea, vomiting, headache, dizziness, and abnormal dreams, were modeled using linear logistic regression. The relationship between the occurrence of adverse events and ABT-594 dose, day (*i.e.*, time), age, sex, and nicotine use status was modeled using repeated measures logistic regression analyses. The generalized estimating equations method was used for estimating the parameters of the logistic regression model with the SAS procedure GENMOD. A compound symmetry structure for the working correlation matrix to account for the dependence among observations within a subject was assumed.

The model is represented as:

$$\text{logit}(\pi) = \log\left(\frac{\pi}{1-\pi}\right) = \alpha + \beta_1 \cdot \text{DOSE} + \beta_2 \cdot \text{DAY} + \beta_3 \cdot \text{AGE} + \beta_4 \cdot \text{SEX} + \beta_5 \cdot \text{NICOTINE} + \beta_6 \cdot \text{DOSE} \cdot \text{DAY} \quad (5)$$

where π is the probability of having an adverse event.

ED₅₀ (when $\pi=0.5$ and $\text{logit}(\pi)=0$) for average number of days on treatment and average age for each sex and nicotine use combination may be calculated as:

$$ED_{50} = \frac{-(\alpha + \beta_2 \cdot \overline{\text{DAY}} + \beta_3 \cdot \overline{\text{AGE}} + \beta_4 \cdot \text{SEX} + \beta_5 \cdot \text{NICOTINE})}{(\beta_1 + \beta_6 \cdot \overline{\text{DAY}})} \quad (6)$$

RESULTS

Adult subjects who had painful diabetic polyneuropathy ($N=266$, 145 males and 121 females) were enrolled in the study with 138 subjects (81 males and 57 females) completing the study (Table I). The mean (standard deviation) baseline pain scores of subjects were 6.5 (1.43), 6.6 (1.69), 6.7 (1.51), and 6.7 (1.74) in the placebo ($n=65$), 150 ($n=65$), 225 ($n=69$), and 300 ($n=67$) microgram BID dose groups, respectively. A total of 663 ABT-594 change from baseline pain scores from 222 subjects were used for nonlinear mixed effects analyses.

The reduction in pain score from baseline and dropout for the various dose groups are captured in Fig. 1. This figure shows the number of observations (subjects) available at each visit and the distribution of reduction in pain scores (compared to baseline pain score) among the observations. For the purpose of this figure, decrease in pain intensity score (m) on the Likert scale from baseline measurement of $m \leq 0$, $0 < m < 1$, $1 \leq m < 2$, $2 \leq m < 3$, and $m \geq 3$, represents “none,” “a little,” “medium,” “a lot,” and “complete” pain relief, respectively. This figure also reveals the rate of dropouts from the study with time and dose, and that a higher fraction of the subjects had relief from pain as the dose of ABT-594 increased. The high dropout rates observed in this study were dose-dependent and primarily due to the five most common adverse events, *i.e.*, nausea, vomiting, headache, dizziness, and abnormal dreams.

The ABT-594 had a statistically significant ($P < 0.001$) dose- and time-dependent effect on reduction in pain scores. Additionally, a statistically significant ($P < 0.001$) interaction between dose and time effect was detected indicating that reduction in pain scores with time were not parallel across the three tested doses. The removal of effect of dose (DOSE),

time (DAY), dose-by-time interaction (DOSE $\times$ DAY) from the final model (Eq. 1) resulted in increase in MVOF of 15 to 72 points ($P < 0.001$). Exploration of the effects of nicotine use, sex, and age on the reduction in pain score from baseline did not reveal any statistically significant effects. Results of the final efficacy model parameters are summarized in Table II.

The three-dimensional representation of the model-predicted relationship between ABT-594 dose and days of treatment and probability of various levels of pain relief are presented in Fig. 2. Figure 2 illustrates the increase in pain relief with increase in both dose and duration of treatment. In general, the relationship with dose was steeper than the relationship with duration of treatment. Figure 2 also shows the model fit to the data. The efficacy model adequately captured the increase in placebo and drug effect with time and dose for majority of the data. However, in a subset of subjects receiving 300 μg ABT-594 and achieving high drug response (≥ 2 -point change from baseline pain score), the efficacy model underpredicted drug effect initially (< 30 days), and slightly overpredicted at later times (> 30 days). This was likely due to higher dropout and limited data as only 11 and 8 of 67 subjects enrolled in this dose group achieved ≥ 2 - and ≥ 3 -point improvement, respectively.

The robustness of the final model was evaluated using nonparametric bootstrap. Out of the 500 bootstrap data sets, the final model successfully converged for 494 data sets. The model-predicted ED₅₀ values (*i.e.*, improvement in 50% of subjects receiving ABT-594) for improvement in pain scores of ≥ 1 , ≥ 2 , and ≥ 3 were 50, 215, and 340 μg , respectively, for the average number of days on treatment (33 days in this study).

Adverse events were the primary reason for discontinuation in all ABT-594 regimens. The discontinuation rates were 22%, 38%, 57%, and 75% for placebo, 150, 225 and 300 μg BID dose groups (9). The occurrence of five most common adverse events, *i.e.*, nausea, vomiting, headache, dizziness, and abnormal dreams, was modeled. The observed rates (number of events/[days of treatment $\times$ number of subjects]) of these five adverse events were: nausea (12%; 1,083/8,724), vomiting (2%; 151/8,715), headache (4%; 312/8,713), dizziness (6%; 565/8,734), and abnormal dreams (8%; 658/8,758).

Table I. Subject Demographics

	BID treatment groups ($N=266$)			
	Placebo ($N=65$)	150 mg ABT-594 ($N=65$)	225 mg ABT-594 ($N=69$)	300 mg ABT-594 ($N=67$)
Age (years)	60.2 $\pm$ 11.4	60.8 $\pm$ 10.8	61.8 $\pm$ 11.8	64.7 $\pm$ 11.1
Weight (lbs.)	205 $\pm$ 36.4	200 $\pm$ 40.0	199 $\pm$ 34.6	203 $\pm$ 34.9
Sex				
Female	27 (42%)	31 (48%)	33 (48%)	30 (45%)
Male	38 (58%)	34 (52%)	36 (52%)	37 (55%)
Nicotine usage ^a				
Former user	29 (45%)	24 (37%)	18 (26%)	25 (37%)
Nonuser	32 (49%)	31 (48%)	40 (58%)	38 (57%)
Current user	4 (6%)	10 (15%)	11 (16%)	4 (6%)

Age and weight are presented as mean $\pm$ SD. Sex and nicotine usage are presented as N (in percent).

^a Former users and current users were combined for efficacy and adverse events analyses

Fig. 1. Reduction in pain score from baseline and dropout over time and across dose levels. The decrease from baseline in pain intensity score (m) on the Likert scale of $m \leq 0$, $0 < m < 1$, $1 \leq m < 2$, $2 \leq m < 3$, and $m \geq 3$, represents “none,” “a little,” “medium,” “a lot,” and “complete” pain relief, respectively

The estimated ED_{50} values for adverse events are summarized in Table III. The average number of days on drug and average age were used for computation of ED_{50} values. The average number of days on drug was 34.3 and 36.8 for female nicotine nonusers and users, and 30.6 and 30.2 for male nicotine nonusers and users, respectively. The average age was 64.3 and 56.1 for female nicotine nonusers and users, and 60.6 and 57.3 for male nicotine nonusers and users, respectively.

Analyses of adverse events indicate that, as expected, the incidence rates significantly increase with dose (P value < 0.0391) for nausea and vomiting. The time effect (DAY) was statistically significant for nausea and vomiting (P value < 0.0484)—the slopes were negative. The effect for dose-by-day interaction was not significant for nausea and vomiting, however, the effect

for dose-by-day interaction was significant for abnormal dreams, dizziness, and headache.

Nicotine use status was a significant covariate for all five adverse events of nausea, vomiting, abnormal dreams, dizziness, and headache. Sex was also a significant covariate for all adverse events modeled, except for nausea. Age was a significant covariate for all adverse events modeled, except for headache.

DISCUSSION

A mixed effects model-based approach was used to characterize the relationship between dose and response

Table II. Pharmacodynamic Parameter Estimates for Reduction in Pain Score

Parameter	Estimate (95% confidence interval) ^a
Baseline model parameters	
θ_1	-1.31 (-2.61 to -0.267)
θ_2	-2.45 (-3.00 to -2.02)
θ_3	-1.78 (-2.25 to -1.37)
β_1	-1.31
β_2	-3.76
β_3	-5.54
Drug model parameters	
α_1	5.24×10^{-3} (5.00×10^{-5} – 1.14×10^{-2})
α_2	1.79×10^{-2} (2.00×10^{-4} – 4.86×10^{-2})
α_3	2.83×10^{-4} (1.09×10^{-4} – 4.47×10^{-4})
ω^2	10.9 (7.34–16.2)

Model parameters of Eqs. 1, 2, and 3. $\beta_1 = \theta_1$; $\beta_2 = \theta_1 + \theta_2$; $\beta_3 = \theta_1 + \theta_2 + \theta_3$; β_k represents the parameters of the placebo model. α_1 , α_2 , and α_3 represent the slopes of the DOSE, DAY, and DOSE×DAY effects, respectively. ω^2 =intersubject variance

^a Approximate 95% confidence interval from bootstrap analyses

(efficacy and safety) of ABT-594 in subjects with diabetic peripheral neuropathic pain. The dose–response model for efficacy predicted greater than 200 μg of ABT-594 would be required to achieve ≥ 2 -point improvement in pain score from baseline in approximately 50% of the subjects. The dose–response model for adverse events indicate doses greater than 400 μg would result in significant fractions (40–50%) of subjects experiencing nausea, vomiting, dizziness, and headache.

Significant dose-dependent improvement in pain score and adverse events were observed in the study (Fig. 1). During efficacy model building, both higher dose and longer duration of treatment were found to significantly increase pain relief, even after accounting for the time course of placebo response. Deletion of the dose, day, or dose-by-day interaction effects from the model resulted in significant increases of the MVOF, confirming that ABT-594 provides significant dose and duration of treatment (time) dependent relief from pain ($P < 0.001$). Therefore, the final model included dose, day, and dose-by-day interaction effects (Table II).

The effect for dose-by-day interaction was significant indicating nonparallel dose–response curves across treatment days as illustrated in the three-dimensional dose–response surface in Fig. 2. At the 200- μg BID ABT-594, the dose–response model predicted 44% and 12% of the subjects could achieve ≥ 2 and ≥ 3 points improvement in pain score from baseline, compared with 4% and 0.7%, receiving placebo, respectively (the average number of days of treatment was 33 in this study). It should be recognized that Fig. 2 illustrates the “true” dose–response surface and not clinical outcome or a clinically meaningful dose. A clinically relevant dose will depend on adverse events, dropout rates, titration schemes, and tolerability development in addition to efficacy. The dose–response (efficacy and adverse events) models presented in this paper, coupled with dropout models can be used to explore, through clinical trial simulations that incorporate the multidimensional dependencies of clinical outcome, clinically relevant doses and novel titration schemes that optimize efficacy while reducing the incidence of adverse events (17).

Fig. 2. Model-predicted probabilities of reduction in pain score at various ABT-594 doses and number of days of treatment. The vertical axis describes the probability (i.e., percentage of subjects) with a defined decrease from baseline in pain intensity score (m) on the Likert scale. The symbols represent the observed mean decrease from baseline in pain intensity score at various ABT-594 doses and treatment visit days, and the three-dimensional mesh surface represent the model prediction

Table III. Estimated ED₅₀ Values

Adverse events	Estimated ED ₅₀ (μg)			
	Female		Male	
	Nicotine user	Nicotine nonuser	Nicotine user	Nicotine nonuser
Abnormal dreams	962	955	869	943
Dizziness	579	408	590	418
Headache	660	688	534	552
Nausea	529	444	423	333
Vomiting	480	398	504	410

The high rate of dose-dependent adverse events resulted in significant dose-dependent dropout from the study (Fig. 1). The rank order of ED₅₀ values, on average, for the five adverse events modeled was nausea, vomiting, dizziness, headache, and abnormal dreams. The effect for dose-by-day interaction was significant for abnormal dreams, dizziness, and headache, indicating nonparallel dose-response curves across treatment days. The day effect had statistically significant negative slopes for nausea and vomiting indicating development of tolerance, *i.e.*, the incidence of nausea and vomiting decreases with time, consistent with clinical observations of development of mild tolerance to nausea and emesis with continued dosing.

In general nicotine use status, sex, and age were significant determinants of the probability of an adverse event. The ED₅₀ values for females compared to males were lower for vomiting but higher for nausea. As nicotine shows high affinity to the $\alpha_2\beta_4$ subtype in the brain, it was warranted to evaluate the clinical profile of ABT-594 in nicotine and nonnicotine users. In general, nicotine nonusers had lower ED₅₀ values, suggesting they were more sensitive to adverse events than nicotine users, which is not surprising given the known tolerance to side effects of nicotine use.

Clinical evidence of pain reduction in a controlled clinical trial is evaluated based on (1) benefit to the individual patient with respect to reduction in pain from baseline pain level observed at study start, and (2) treatment benefit with respect to mean difference in pain score between drug and placebo regimens at final visit, as well as responder rates. Minimal ("slightly better") to meaningful ("much better") clinically important reduction in pain for an individual patient receiving pain treatment is typically associated with a one- to two-point reduction (on a 0–10 rating scale) from baseline pain score, where one-point (or about 15% from baseline) reduction is considered minimally clinically important difference and two-point (or about 30% from baseline) is considered meaningful improvement (11,12). However, a 2-point mean difference in pain reduction between analgesic and placebo is not necessary to demonstrate treatment benefit of a new analgesic—even a 1-point mean improvement over placebo in the 11-point Likert scale can be considered to be a clinically meaningful effect of a drug (11,12). These values are also consistent with a meta-analysis model-based mean placebo response of approximately 1.6 points (on the 11-point Likert Scale) over 12 weeks and an additional approximately 1-point mean pain relief from drug over placebo (13). Furthermore, to evaluate differences between groups (*e.g.*, analgesic vs. placebo), often responder rates are compared (18,19). Therefore, ABT-594 doses greater than 200 μg (ED₅₀ for ≥ 2 -point improvement from baseline was 215 μg) would be expected to provide clinically meaningful pain relief. At doses of 200 μg or greater, ABT-594 would be expected to provide efficacy that is comparable to currently approved treatments (pregabalin and duloxetine) for neuropathic pain (13).

Nausea, vomiting, and dizziness observed in ABT-594 treatment groups are commonly observed with currently used analgesics including dizziness and somnolence with gabapentin and pregabalin, nausea, somnolence and dizziness with duloxetine, nausea with selective serotonin–norepinephrine reuptake inhibitors, somnolence with tricyclic antidepressants,

and nausea, vomiting, somnolence, and dizziness with opioids (4,5,9,13). ABT-594 did not show side effects associated with opioid treatment such as constipation, sedation, pruritus, somnolence, and respiratory depression (9,13). The incidence rate of side effects observed with the ABT-594 regimens with a fixed short dose titration used in this study are high; doses greater than 400 μg (ED₅₀ values for nausea, vomiting, dizziness, and headache ranged from 400 to 600 μg , Table III) are expected to result in significant adverse events without a longer and possibly flexible titration regimen. Doses for many commonly used analgesics, particularly in neuropathic pain (4,5), are titrated to manage side effects. Since tolerability to adverse events has been observed in this study and other studies (unpublished data), a therapeutic window could be defined for ABT-594 based on a suitable titration scheme—similar to other drugs (pregabalin and duloxetine) approved for neuropathic pain associated with diabetic peripheral neuropathy (4,5).

CONCLUSION

Population pharmacodynamic models were developed to characterize the improvement in pain score and incidence of adverse events as a function of dose and time. An approximately twofold separation was observed between the ED₅₀ values for efficacy and adverse events. The dose-response (efficacy and adverse events) models presented in this paper, coupled with dropout models can be used to explore, through clinical trial simulations that incorporate the multidimensional dependencies of clinical outcome, clinically relevant doses and novel titration schemes that optimize efficacy while reducing the incidence of adverse events.

ACKNOWLEDGMENTS

The funding for this study was provided by Abbott, Abbott Park, IL. Dr. Dutta and Dr. Awni are stockholders and employees of Abbott. Dr. Hosmane is a consultant for Abbott.

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