Model Based Insights to Lamotrigine for Pain Associated with Diabetic Peripheral Neuropathy

Jeffrey Wald1, Jagdev Sidhu2, David Blum3, and Marianne Silver1
GlaxoSmithKline, 1Research Triangle Park, North Carolina, USA and 2Harlow, UK

ABSTRACT

Summary: LAMOTRIGINE was studied for pain associated with diabetic peripheral neuropathy in replicate, randomized, double-blind, placebo-controlled, multicenter studies. Population PK/PD modeling was used to elucidate the exposure (post hoc estimates of lamotrigine steady-state AUC) versus effect (response on an 11-point ordered categorical scale) as a function of time and baseline pain scores.

Methods: Each study included a 2-4 week screening phase, a 1-week baseline phase, a 7-week dose-escalation phase, and a 19-week treatment period. A total of 720 subjects were enrolled in the 2 studies at doses of 0, 200, 300, and 400 mg/day (given BID). A longitudinal PK/PD model for ordinal response data was fit to individual patient diary pain data using NONMEM. The model accounted for the temporal profile of PBO response, individualized exposure to drug, and baseline pain status.

Results: The primary outcome, pain intensity change from baseline to week 19, was achieved for only the 400mg/day dose in one of the two studies. Moreover, the dose-response relationship was not rank ordered in comparison to efficacy for 1 of the 2 trials. The PK/PD model was successful in characterizing the major features of trial results. Moreover, the model successfully accounted for the time profile and distribution of PBO responses. Lamotrigine steady-state AUC and baseline were both strongly significant predictors of effect. The model was used to explore the relationship between change from baseline (pain intensity score) and systemic lamotrigine exposure (AUC) and predict outcomes versus time across the quintiles of LTG exposure (FIGURE 1).

Each subject rated his/her pain intensity during the past 24 hours using an 11-point numerical rating scale with 0 as “no pain” and 10 as “worst pain possible”. A maximum of 5 blood samples was collected from each subject for the measurement of LTG serum concentrations over the duration of the study. Patients reported the time of dosing prior to PK sampling times. A total of 444 (62%) subjects completed the 2 studies. A higher percentage of subjects in the LTG 400mg treatment group withdrew compared with the other treatment groups. The most common reason for premature discontinuation was AE (16%). A greater percentage of subjects in the LTG 400mg group (22%) prematurely discontinued due to an AE compared with the placebo group (11%).

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Introduction

Lamotrigine (LTG), originally developed and licensed as an antiepileptic, has been found to have analgesic properties. The mechanism of action of LTG for pain relief has been shown to be related to the modulation of voltage-gated sodium channels in the sensory neurons. LTG has been shown to have a high degree of affinity for the sodium channel and to block the influx of sodium ions into these channels, thereby reducing the propagation of pain signals in the peripheral nervous system. This action results in a decrease in the perception of pain.

The effect of LTG on pain intensity was assessed using the Numerical Rating Scale (NRS), which is a 11-point scale ranging from 0 (no pain) to 10 (worst pain). The primary outcome measure was the change in pain intensity from baseline to week 19. The secondary outcomes included the proportion of patients who achieved a 30% reduction in pain intensity and the proportion of patients who were pain-free (NRS = 0) at week 19.

Methods

This was a randomized, double-blind, placebo-controlled, multicenter study conducted in the USA. Eligible subjects with pain from diabetic neuropathy were randomized to receive either placebo or one of three doses of LTG (200, 300, or 400 mg/day). Each study included a 2-week screening phase, a 1-week baseline phase, a 7-week dose-escalation phase, and a 19-week treatment period. The dose-escalation phase featured a staggered start so that patients not participating in an extension study. The titration phase was designed to achieve the target dose by the end of the titration period, and placebo effect. Backwards elimination of model terms indicated strong justification for inclusion in the model. The model was used to explore the relationship between change from baseline pain intensity score and systemic LTG exposure and predict outcomes versus time across the quintiles of LTG exposure (FIGURE 1).

Discussion

The model demonstrated that increasing systemic lamotrigine exposure (AUC) confers an increasing probability of pain score reduction. AUC and baseline pain score significantly improve the characterization of PDN patient response. The dose arms with the highest reduction.

Simulations of Week 19 responses without titration failures and with model predicted values for patients that withdrew from the trial predicted larger efficacy responses than seen in the present trials.

References: