A two-part mixed-effects model for semi-continuous data to describe the effect of transdermal rotigotine on restless legs symptoms in adults

Objectives

To quantify the dose-exposure-response relationship of rotigotine in adult patients suffering from restless legs syndrome (RLS) and to assess the expected efficacy response to daily administration of rotigotine transdermal patches at different dose levels via simulations.

Methods

DATA

Pharmacokinetic (PK) and efficacy data from 3 large placebo-controlled clinical trials in adult RLS patients were used. Rotigotine dose was up-titrated during the first 2 to 4 weeks until the target maintenance dose was reached. Patients continued treatment on the maintenance dose level for 6 months in the two phase 3 studies, and for 1 month in the phase 2 dose-ranging study. At the end of the study the dose was reduced in a step-wise fashion during the taper period. PK samples were taken from about 20% of the patients in the phase 3 studies and from all patients in SP792.

The dataset used for modeling included all patients receiving placebo and all patients receiving active treatment that had at least one valid PK measurement (N=709). Data from the remaining patients (n=582) were retained for external validation of the model.

PK MODEL

A simple PK model was developed to describe the average concentration at steady state (Cav,ss). Given the transdermal application of rotigotine the fluctuation of plasma concentrations within a dosing interval was low, such that the measured trough levels are a reasonable representation of average concentrations.

PKPD MODEL

A two-part mixed-effects model for semi-continuous data [1] was employed, linking predicted Cav,ss to International Restless Legs Syndrome Rating Scale (RLS) score. The RLS has been used in clinical trials with dopamine agonists (e.g. cabergoline, pergolide, ropinirole, and pramipexole) and represents an increasingly accepted international standard for the clinical assessment of RLS severity [2]. RLS scores were transformed to the logit-scale to avoid predictions outside of the range of the scale (0 [no symptoms] – 40 [most severe]).

IRLS scores >0 were treated as continuous data with sub-models for the placebo effect (Plmax) and the drug effect. A lower baseline IRLS score was estimated for patients in SP792 (24.1) compared to the patients from the two other studies (29.5). The effect developed over time with a half-life to reach the maximum of 2.8 days. For the drug effect an EC50 of 0.218 ng/mL was estimated, corresponding to a dose of about 1.5 mg/24h in a typical patient.

The visual predictive check on the validation dataset (i.e. data not used for modeling) demonstrated close correspondence between observed and simulated RLS scores (Figure 4).

Clinical trial simulations were conducted to illustrate the dose-response curve and to derive the probability for a change of IRLS score over placebo > 3 as a function of dose after 6 months of treatment. Like in the original studies, missing observations due to dropout were imputed applying the ‘Last observation carried forward’ method.

Conclusions

- A clear exposure-response relationship between rotigotine Cav,ss and the accepted standard measure of restless legs syndrome severity (IRLS score) could be established.
- The two-part mixed-effect model previously described by Olsen et al.[1] was successfully implemented in NONMEM and proved useful in modeling data with observations at the boundary of the measurement scale.
- The concentration-IRLS model provides a framework to simulate the expected response to rotigotine administration in other populations in order to aid in designing future clinical studies.

References


The work was sponsored by UCB Pharma.

24th Annual Meeting of the Population Approach Group in Europe | Hersonissos, Greece June 2 – 5, 2015