ALTASCIENCES

CASE STUDY

Evaluating the Abuse Potential of Mirogabalin

STUDY OVERVIEW

The current standard in the management of neuropathic pain (as per the International Association for the Study of Pain) includes a range of pharmacological interventions, including selective ligands for the α2δ subunit of voltage-gated calcium channels, such as gabapentin and pregabalin. While both these compounds are effective, they have been shown to exhibit the potential for abuse and misuse, especially in individuals with a history of opioid or benzodiazepine use. In addition, they have been associated with a high incidence of adverse events (AEs), particularly dizziness and somnolence.

Mirogabalin is a novel α2δ ligand that has been shown to have effective analgesic properties. This is based on a recently completed Phase II proof-of-concept study in patients with diabetic peripheral neuropathic pain. Our clinical site in Kansas (Vince and Associates) was selected to work with Daiichi Sankyo in evaluating mirogabalin as a well-tolerated α2δ ligand with low abuse potential.

STUDY DETAILS

- Study Design: Randomized, placebo and active-controlled crossover study involving recreational polydrug users who had a history of CNS depressant use.

STUDY PURPOSE

To evaluate the abuse potential of mirogabalin versus a) placebo and diazepam, and b) placebo and pregabalin, in recreational drug users.

METHODS

The human abuse potential study was designed as two independent studies. Each study was divided into two parts: a qualification phase intended to enrich the study population with subjects that could provide accurate subjective assessments (reducing the number of false positives and negatives), and an assessment phase where mirogabalin was formally evaluated against the corresponding positive and negative controls.

Mirogabalin/Diazepam

The study comparing mirogabalin to diazepam was a randomized, placebo and active-controlled crossover study involving recreational polydrug users with a history of CNS depressant use. Subjects fulfilling the inclusion/exclusion criteria entered a qualification phase where they were assessed for their ability to discriminate 20 mg of diazepam from a matching placebo in a crossover design. A validated electronic visual analog scale (VAS) was used to measure Drug Liking and determine eligibility to enter the assessment phase.

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The assessment phase was designed as a 5-way crossover study in which subjects were randomized to either a 15 or 45 mg dose of mirogabalin, a 15 or 30 mg dose of diazepam, or matching placebo tablets, in each treatment period. Subjective VAS ratings on the likeability and general effects of the treatment were recorded at specific times in each period. Safety monitoring and pharmacokinetics were also assessed. To ensure subject compliance and safety, all participants were confined in the clinic for the duration of the assessment phase (approximately 30 days). Of the 38 subjects who entered the assessment phase, 32 completed the study.

Mirogabalin/Pregaballin

In evaluating the abuse potential of mirogabalin against pregabalin, a single ascending dose study in 24 subjects was first conducted to evaluate three doses of mirogabalin. The data from this study was used to select the doses for the abuse potential study, which had a similar design to the diazepam study. Subjects that were successfully able to discriminate between 300 mg of pregabalin and the matching placebo during the qualification phase were entered into the assessment phase of the study, which was conducted as a 6-way crossover design. In each period, subjects were randomized to a 15, 60, or 105 mg dose of mirogabalin, a 200 or 450 mg dose of pregabalin, or matching placebo tablets. Subjective VAS ratings on the likeability, similarity, and general effects of the treatment were recorded at specific times in each treatment period. As in the diazepam study, safety monitoring, pharmacokinetic sampling, and a long confinement period were incorporated into the study design. Of the 56 subjects who entered the assessment phase, 44 received all 6 treatments, and 41 completed the study.

RESULTS

In both studies, the planned therapeutic dose of mirogabalin (15 mg) did not have maximal Drug Liking scores different from the placebo. These scores were also found to be significantly less than therapeutic doses of diazepam and pregabalin. At supratherapeutic doses of 45 mg, the maximal effects of mirogabalin on Drug Liking, Positive Effects High, and Good Drug Effects were not significantly different from the placebo and markedly less than either dose of diazepam. In comparison to 200 mg pregabalin, doses of greater than 4 times the therapeutic dose of mirogabalin were required to achieve a similar level of abuse potential. The overall incidence of AEs of 15 or 45 mg of mirogabalin was comparable to, or lower than, placebo in both studies. The incidence of AEs of mirogabalin was comparable to 200 mg of pregabalin, only at supratherapeutic doses.

Overall, these studies showed that a therapeutic dose of mirogabalin is a safe and well-tolerated α2δ ligand with low potential for abuse in recreational polydrug users.

ABOUT ALTASCIENCES

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