Background

• Lacosamide immediate release (IR), Vimpat®, is approved for the treatment of partial onset seizures.
• Drooling limit adverse events associated with lacosamide IR include central nervous system (CNS) effects such as headache and dizziness.

• Lacosamide IR has a rapid rate of rise in plasma concentration (t<sub>max</sub> < 1 h), and we hypothesized that reducing the initial rate of rise in plasma concentration may reduce CNS adverse events.

Objective

The objective of these studies was to correlate the rate of rise is lacosamide plasma concentrations with CNS side effects, measured as an impairment of motor coordination in rodents using the rotarod.

Methods

Mouse Pharmacokinetics (PK) and Rotarod Pharmacology Studies

The PK profile and the effects on rotarod performance of lacosamide was determined following a single oral dose at 55 mg/kg. Male Sprague Dawley rats (Charles River, Germany) underwent iPRECIO pump implantation surgery 1-2 days later. Following a 3-day recovery period, all rats that met the rotarod training criterion (at least 120 s in 2 consecutive trials) were assigned to the rotarod study. Each group (N=8-10/group) such that the mean time on the accelerated rotarod was similar between groups within a study. Dose levels were chosen to produce plasma and brain concentrations that were comparable to those reached in previous Adamas PK studies. The dose of lacosamide for IR in rats (7 mg/kg) was selected to produce plasma and brain levels at t<sub>max</sub> that are similar to those observed in previous Adamas PK studies for 10, 30, 60 or 90 mg/kg lacosamide. Accelerating rotarod testing was conducted 5, 15, 30 and 60 min post-dose. Data is presented as Mean ± SEM. Plots of lacosamide concentrations for 10, 30, 60 or 90 mg/kg were linear or quadratic. The slow ER-like profile resulted in a 6.4 fold increase in dose and 8.1 fold increase in exposure without significant CNS impairment.

• Delivery of lacosamide by implanted iPRECIO pump and IP bolus injection was conducted. A stepped infusion protocol with six different infusion rates (0.1, 0.5, 1.0, 1.5, 2.0 and 2.5 µL/h) and infusions of 18 h were simulated to produce plasma and brain concentrations that were comparable to those reached in previous Adamas PK studies. In rats, the 18 h infusion (ER Profile) and single IP bolus dose of lacosamide (IR Profile) produced similar terminal blood levels and C<sub>max</sub> in IP and IR animals.

• The single IP bolus dose produced a significant deficit in rotarod performance (55.0 ± 22.5% decrease from baseline in the treated group compared to a 3.5 ± 6.9% increase from baseline in vehicle animals).

• Slow rise infusions of lacosamide to a similar C<sub>max</sub> did not produce any deficit in rotarod performance.

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Conclusion

Our initial studies in the mouse indicated a clear dose-dependent impairment of rotarod performance in a plasma range relevant to those reported to produce clinical adverse effects with Lacosamide IR. In rats, the 18 h infusion (ER Profile) and single IP bolus dose of lacosamide (IR Profile) produced similar terminal blood levels and C<sub>max</sub> in IP and IR animals.

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