Pharmacokinetic Evaluations of ADS-4101 (Lacosamide) Modified Release Capsules versus Lacosamide IR in Two Phase 1 Studies up to 600 mg

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Background

Lacosamide immediate release (IR), WMAP®, is approved for the treatment of partial onset seizures. Base-line-lowering adverse events associated with lacosamide IR include nausea and dizziness, which may be related to the rapid rise in plasma concentrations (WMAP® Package Insert).

AD5-4101 (lacosamide IR) modified-release (MR) formulation was designed to reduce the rate of first-pass metabolism and delay the absorption of lacosamide IR to provide high and sustained plasma concentrations during the day when the burden of seizures is highest.

Objective

The objective of the Phase 1 study (Study 1) was to evaluate the pharmacokinetic and safety profile of four ADS-4101 MR formulations for further development.

The objective of the Phase 2 study (Study 2) was to evaluate the steady state pharmacokinetic (PK) profiles of lacosamide IR in healthy volunteers comparing the PK profile, safety, and tolerability of ADS-4101 (lacosamide IR) modified-release formulations to lacosamide IR.

Study Design and Methods

Study 1

- This was a randomized, open-label, single-dose PK study in 24 healthy volunteers comparing four PK profiles, safety, and tolerability of four ADS-4101 (lacosamide IR) modified-release formulations to lacosamide IR.
- A single 400 mg dose (2 x 200 mg) was administered for each of the four formulations.
- This study was divided into 2 separate cross-over (A/B) groups, where each group had 36 subjects.
- Group 1 received Formulations 1, 2, and 3, and group 2 received Formulations 1, 4, and B (Figure 3).

Study 2

- This was an open-label, single-center, 3-treatment, and 3-period (run-in period) crossover study in 24 healthy volunteers comparing the PK profile, safety, and tolerability of ADS-4101 (lacosamide IR) modified-release formulation to lacosamide IR.
- At 600 mg/day, ADS-4101 provided plasma concentrations that were equivalent or higher than the Cmax of 400 mg/day lacosamide IR at each time point throughout the 24-hour dosing interval.

Patient Demographics / Disposition

Table 1. Demographic and Baseline Characteristics (Safety Population)

Patient Safety

- Adverse events were reported for a greater proportion of subjects administered lacosamide IR (88.9%) than any of the ADS-4101 MR formulations (55.6%).
- Following administration of ADS-4101, the most frequently reported AEs were oral hypoesthesia (11 subjects [45.8%] and dizziness [9.6%]).
- The incidence of oral hypoesthesia and dizziness was greatly reduced in the ADS-4101 IR formulation (10%).
- For each ADS-4101 MR formulation, no AE was reported for more than two subjects.
- ADS-4101 formulation 3 was chosen for further evaluation in a multiple-dose phase 1 study (Study 2) due to the longer l1/2 and lower Cmax...

Conclusions

- ADS-4101 600 mg achieved higher lacosamide plasma concentration at each time point throughout the 24-hour dosing interval and comparable tolerability relative to the approved maximum dose (300 mg) of lacosamide IR tablets, in healthy volunteers.
- ADS-4101 was safe and well tolerated across all three doses.

When dosed once-daily at bedtime, ADS-4101 provides high lacosamide plasma concentrations in the morning when patients wake up and throughout the day.

These results support the clinical development of ADS-4101 up to 600 mg/day for partial onset seizures.

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