ALTASCIENCES

CASE STUDY

Achieving a 505(b)(2) Regulatory Approval: Multiple NDA-enabling Studies

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STUDY OVERVIEW

A sponsor approached Altasciences to take on multiple NDA-enabling studies that were part of a 505(b)(2) regulatory filing with the FDA. Their drug is active within the CNS and had a modification to the formulation compared to the current approved product. In the span of two years, Altasciences conducted a driving simulator study, a bioavailability study, and a multiple ascending dose (MAD) study of the new formulation. By successfully conducting those protocols, Altasciences was able to provide the sponsor with key components of their NDA dossier.

STUDY DETAILS

- **Indication:** A number of neurological disorders
- **Population Type:** Healthy Normal Participants

	BIOAVAILABILITY STUDY	MAD STUDY	DRIVING STUDY
# of Volunteers	24	24	72
Time to recruit panel	4 weeks	4 weeks	4 weeks
Study Design	Laboratory-blinded, Randomized, Balanced, Single-Dose, 3-Treatment, 3-Period, 6-Sequence, Crossover	Open-label, Multiple-Dose, 1-Period	Randomized, Double Blind 3-Period Crossover
Key Inclusion Criteria	Appropriate contraception methods used by both male/female subjects	• Appropriate contraception methods used by both male/female subjects • Ability to comply with study requirements (in clinic 14 days)	• Possess a valid driver's licence • Driven 10,000 miles (16000 km) in the last 3 years • Sufficient score on simulator sickness questionnaire
Key Exclusion Criteria	No known drug hypersensitivity	No known drug hypersensitivity	History of difficulty falling asleep
Services Provided	Clinic, DM, Biostats, MW	Clinic, DM, Biostats, MW	Clinic

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STUDY PURPOSE

The sponsor was developing a product that isolated the active enantiomer and made an extended release formulation. These modifications were significant enough to warrant additional clinical studies to help provide a robust dossier for the FDA to review.

Altasciences provided support in three key studies:

1. A bioavailability study comparing two lots of extended-release investigational products manufactured via different processes
2. A study to assess the safety, tolerability, and pharmacokinetics of multiple ascending doses of the investigational product from the bioavailability study.
3. A driving simulator study to assess a patient's ability to drive or operate heavy machinery both after an acute dose or at steady state

Altasciences' core expertise includes more than just straightforward bioavailability and bioequivalence studies – we also conduct specialty studies that are becoming increasingly critical to successful completion of a submission for regulatory approval.

Altasciences worked with the sponsor to help design and conduct a driving study that would generate data for a fulsome assessment on the impact of the drug's sedating effects, and potentially help justify a modification of the label compared to the RLD.

METHODS

Bioavailability

For the relative bioavailability study, male and female subjects underwent a screening period up to 28 days prior to conduct of the study to ensure that 24 subjects were enrolled. For all three treatment periods, subjects reported to the clinic on the evening prior to dose administration and fasted overnight for at least 10 hours. Subjects were randomized to either Treatment A, Treatment B, or Treatment C on the morning of the first treatment period. Study drug was administered after pre-dose clinical assessments and a blood sample (0 hour) had been taken. The subjects remained at clinic for 36 hours after dosing, during which time blood samples were collected at 14 intervals. There was a 7-day washout between each treatment period.

Multiple Ascending Dose

Finally, in the multiple ascending dose study, subjects entered the clinic on the evening prior to the first dose and received multiple-dose oral administration of the investigational product, starting on Day 1. Similar to the BA study, subjects were admitted to the clinic on the evening prior and fasted for at least 10 hours prior to the first drug administration. Subjects also had pre-dose clinical assessments and a 0 hour blood draw. Subjects received the initial dose of drug on Day 1. On Day 4, dose was increased by 20 mg and on Day 7 by another 20 mg. Dosing was conducted using AM/PM dosing exactly 12 hours apart. Pharmacokinetic assessments were conducted throughout the study, both during AM and PM dosing. Subjects remained sequestered at the study site for the duration of the clinical study (through Day 13). The total duration of this study, excluding screening, was expected to be at least 14 days.

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Driving Simulation

The driving study was a randomized, multiple-dose, double-blind, placebo-controlled, Latin-square design with 3-period (full) crossover study, with subjects randomized to treatment sequences (one treatment group per period for three periods). Subjects completed all three treatment periods within the treatment group they were randomized to.

During each treatment period, subjects were dosed with active treatment (two dose levels), or matching placebo BID and diphenhydramine or placebo every morning (QAM) for 15 days. Study drug (morning dose) was administered by site staff on Days 1, 6, 11, 15, 21, 26, 31, 35, 41, 46, 51 and 55. Subjects self-administered the drug at home on all other study days.

Cognitive testing and driving simulation were conducted approximately 2.5 hours and 3 hours post dosing, respectively. Subjects then continued their assigned study dosing at home, with titration of study drug at 5-day intervals. Subjects returned to the CRU for morning dosing on titration days. Prior to the Day 15 dose for each treatment period, subjects returned to the clinic and remained overnight. They were dosed the following morning and underwent cognitive and driving simulation testing approximately 2.5 and 3 hours post morning dose.

The study conducted cognitive testing via CogScreen Symbol Digit Coding and driving performance via the CRCDS-Mini Sim.

RESULTS

In the driving study, sensitive, objective measures of sedation, including driving performance, alertness, and attention, demonstrated that performance following the initial starting dose of study drug was non-sedating. Steady-state treatment with study drug at two-fold the starting dose had a potentially mild sedating effect, which was less severe than that caused by a common over-the-counter antihistamine (i.e., diphenhydramine HCl 50 mg).

For the bioavailability study, the rate and extent of absorption was equivalent between the reference product and the extended release manufactured with the alternate manufacturing process.

In the MAD study, systemic exposure of the investigational compound increased proportionally when the dose was doubled. Steady-state disposition was attained within one to two days after initiating twice-daily administration. The study drug was fairly well tolerated at all doses. Increased treatment emergent adverse events (TEAE) were noted at the doubled dose; however, they were consistent with the known safety profile.

A Single-Center, Double-Blind, Placebo-Controlled, Randomized, Adaptive, First-in-Human Study to Assess Safety, Tolerability, Pharmacokinetics, and Food Effect of Single and Multiple Ascending Doses of a Novel Small Molecule Administered Orally in Healthy Male and Female Subjects

CONCLUSION / WHAT SETS US APART

All three studies met their primary endpoints and were successfully conducted. Important to note is that the studies generated the data the sponsor required, and recruitment and data delivery timelines were met, allowing the sponsor to achieve their submission deadline. In conducting these three different types of studies, Altasciences' team members worked closely with the sponsor to develop the protocols, schedule and recruit each study with the appropriate subjects, and conduct the studies as outlined to provide data to address key areas of the sponsor's 505(b)(2) submission: a driving study to assess drug impairment for the product monograph, a bioavailability study compare two lots of the new formulation, and that dose escalation evaluations of this new extended release formulation of the drug were safe and well-tolerated. Since the drug is one that will likely be titrated by physicians in the patient population, having this data provides regulatory reviewers with another key piece of information to make a sound benefit-risk decision. Altasciences can design, conduct, analyze and report on all the clinical pharmacology studies required for an NDA and this example shows how we can provide support across numerous studies types all while delivering superior levels of quality.

References

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf

Acknowledgements

CRCDS-MiniSim and CogScreen are registered trademarks of Cognitive Research Corporation

ABOUT ALTASCIENCES

Altasciences is a forward-thinking, mid-size contract research organization offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.