ALTASCIENCES

CASE STUDY

Drug-Drug Interaction Studies

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STUDY OVERVIEW

A sponsor developing a novel treatment for cardiovascular disease approached Altasciences to conduct its first two drug-drug interaction studies, assessing the effect their drug would have on the pharmacokinetics and pharmacodynamics of the commonly prescribed treatments, clopidogrel (antiplatelet) and warfarin (anticoagulant). While their drug likely would not affect the metabolism of each of the aforementioned treatments, based on its own metabolic profile, these studies were conducted to address a potential concern for excessive bleeding. This is a wonderful example of Altasciences' expertise extending beyond a simple drug-drug interaction study. Altasciences helped design, recruit, and conduct these studies to assess not only the pharmacokinetic impact of co-administration, but the impact on the antiplatelet/anticoagulant properties of the drugs noted above, mindful of the population required for such a trial, as well as the timing of assessments needed to sufficiently observe changes in the pharmacodynamics of the co-administered products.

STUDY DETAILS

- **Drug Development Phase:** Phase 1
- **Class of Drug:** antisense oligonucleotide
- **Indication:** Cardiovascular Disease (CVD)
- **Population Type:** healthy normal volunteers (both studies)
- **# of Volunteers:** 18 subjects / study
- **Time to recruit panel:** 14 days
- **Study Design:** open-label, single-sequence, two-treatment, two-period design (both studies)
- **Key Inclusion Criteria:** Males and females, non-smokers, ages 18-60, BMI 18.5-30 (inclusive), appropriate contraception use
- **Key Exclusion Criteria:** History of bleeding disorders, active pathological bleeding, sensitivity to the investigational products, positive drug screen, prior exposure to an investigational product in last 4 weeks
- **Services Provided:** Full Service

STUDY PURPOSE

The primary objective of both drug-drug interaction studies was to evaluate the effect of 2 doses of the sponsor's investigational product on the PK of multiple oral doses of clopidogrel and warfarin in healthy adult subjects. The studies also looked at the safety and tolerability of the investigational product when co-administered with multiple oral doses of clopidogrel and warfarin, as well as evaluating the effect on the PD (antiplatelet activity).

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METHODS

While the overall objectives and the inclusion/exclusion criteria of both studies were the same, the methodology for each trial was different. This was due to the differences in the activity and half-life of both drugs, which required slightly different washout periods and dosing schedules.

DOSING SCHEDULE FOR THE CLOPIDOGREL INTERACTION STUDY:

DAY (PERIOD)	Study Drug Administered
Days 1-7 (Period 1)	A single 75 mg oral dose of clopidogrel administered alone once daily
Washout Period (Days 8-18)	
Day 19 (Period 2)	A single 75 mg oral dose of clopidogrel and a single 40 mg subcutaneous injection of investigational product administered concomitantly
Days 20-24 (Period 2)	A single 75 mg oral dose of clopidogrel administered alone once daily
Day 25 (Period 2)	A single 75 mg oral dose of clopidogrel and a single 40 mg subcutaneous injection of investigational product administered concomitantly

DOSING SCHEDULE FOR THE WARFARIN INTERACTION STUDY:

DAY (PERIOD)	Study Drug Administered
Day 1 (Period 1)	A single 25 mg oral dose of warfarin administered alone
Washout Period (Days 2-7)	
Day 8 (Period 2)	A single 40 mg subcutaneous injection of investigational product administered alone
Washout Period (Days 9-14)	
Day 15 (Period 2)	A single 25 mg oral dose of warfarin and a single 40 mg subcutaneous injection of investigational product administered concomitantly

Subjects involved in the clopidogrel interaction study were confined to the clinic for 9 nights for each period for a total of 18 overnights. In the warfarin interaction study, subjects were confined to the clinic in Period 1 for 3 nights, then 3 additional nights at the end of Period 1 and the start of Period 2. Subjects were then housed 7 additional nights when dosed in Period 2, for a total of 13 overnights.

Pharmacokinetic blood samples were taken 13 times during both Period 1 and Period 2 for the clopodigrel study pre-dose through Hour 48 (2 days post dose). The warfarin interaction study collected pharmacokinetic blood samples through hour 144 (6 days post-dose) during both periods: 17 samples to assess warfarin-alone pharmacokinetics in Period 1; 13 samples to assess investigational product pharmacokinetics during the first part of Period 2; another 17 samples to assess levels of both drugs during co-administration.

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In the clopidogrel interaction study, pharmacodynamic blood draws were conducted a total of 7 times, 2 times during individual administration of each product, and 5 times during co-administration. PD evaluation was done by analyzing ADP-induced platelet function. In the warfarin interaction study, 12 blood draws were taken to assess platelet function by means of hematology lab parameters focused on platelet activity: activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ration (INR) which is derived from the PT value. In addition, safety labs and adverse events were collected and evaluated throughout the course of subject participation.

RESULTS

Both studies were conducted in a single subject panel – thus allowing for quick completion of the clinic portion of the trial.

Following multiple doses of investigational product, no clinically significant effects were observed on the pharmacokinetic and pharmacodynamic effects of clopidogrel.

The warfarin study showed that co-administration with the investigational product did not affect the peak concentration or extent of exposure of either product. Also, the maximum observed effect and the area under the effect-time curve for the pharmacodynamics lab parameters were not significantly affected by dosing both products together.

Both studies had no deaths, serious adverse events, and no clinically significant vital signs, ECG parameters of physical examinations.

CONCLUSION/WHAT SETS US APART

Altasciences was challenged with trying to conduct two studies with a new molecular entity in combination with another drug that had the potential to cause a serious effect on subjects. While it may have been easier or less costly to simply replicate the studies, or perhaps combine them together, the project team worked with the client to design two different studies, with different timepoints of measurements, which had the same objectives. In doing so, the efficiencies of working with the same team across both projects were utilized, and both studies were treated with the utmost care, from study design, recruitment, clinic conduct, data management, all the way through biostatistical analysis, and report writing. Our success is predicated on leveraging our scientific experience in drug-drug interaction studies, executing clinical trials, and developing close partnerships with our clients to understand their goals and work to achieve them in the best way possible.

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.

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