RARE DISEASE PRECLINICAL CHALLENGE. COMPLEX DOSING PROTOCOL SOLUTION.

A DART Case Study

Amicus Therapeutics, based in Cranbury, NJ (USA), focuses on finding treatments for a range of devastating rare and orphan diseases. Its lead biologics program is ATB200/AT2221, a uniquely engineered Pompe disease enzyme replacement therapy that will be administered in combination with a pharmacological chaperone and tested in multiple human genetic diseases.

Their dialogue with Covance began at the 2017 Society of Toxicology conference, and resulted in a large series of DART studies being awarded to Covance at its Greenfield, IN, facility. Early in the engagement, Covance's most experienced US-based DART team member provided consultation on study design to make it more consistent with FDA guidelines and expectations. The original proposed dosing interval may not have been tight enough to provide a robust assessment of developmental toxicity.

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> **~ Richie Khanna, PhD**
> *Director, In Vivo Pharmacology*
> *Amicus Therapeutics*

Given the limited window of organogenesis (the period of highest sensitivity when organs are forming), and the short half-life of the investigational drug, the possibility existed that this embryo-fetal study would miss key exposure periods of organogenesis.

The subsequent recommendation of every other day dosing made the study considerably more challenging to execute, but also more likely to be viewed favorably by regulators. This senior level expertise made Amicus more comfortable with the revised design path.

These studies involved highly complicated dosing protocols, including two oral administrations (antihistamine and a chaperone), followed by an infusion of the investigational drug. The three doses needed to be administered at precise (and narrow) time intervals. According to the DART Study Director, "We had to become an orchestra to get everything dosed properly."

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In addition to the resource-intensive dosing, the project became further complicated by dosing changes, reprogramming the protocol and changing labels. Client expectations were high, and the Covance-Greenfield team rose to the challenge.

As the program progressed to difference species, a series of in-person meetings helped build understanding and trust. The dose range finding studies started smoothly, and Covance's level of scientist involvement and technical expertise kept this extremely complex study on track.

For a small company with a limited number of pipeline assets, Amicus's interest and scrutiny of this project were high. Richie Khanna, PhD, was one of Amicus's first employees, and currently she is Director, In Vivo Pharmacology and the principal investigator for the investigational drug's bioananalysis: "These studies are so very important – everything is dependent on toxicology."

"I never had any doubts in Covance's capabilities," Khanna notes. "They were on top of everything transparent, accommodating, very responsive. It was exactly how I envisioned things should be with a partner." After some initial bumps, "We developed a mutual trust and confidence that has continued throughout the engagement."

Since kickoff, more than 60 Covance staff members have touched this study. Amicus has since awarded four new juvenile DART studies to Covance, continuing its quest to find a cure for Pompe Disease and other human genetic diseases.