ALTASCIENCES

CASE STUDY

GLP-1 RA: Overcoming Known Pharmacological Effects

STUDY OVERVIEW

Altasciences was contracted to conduct an IND-enabling study in dogs involving once-daily oral tablet administration of a GLP-1 receptor agonist. These molecules are known to decrease gastric emptying and increase satiety. In addition, they inhibit the release of glucagon from pancreatic alpha cells which results in decreased sugar liberation and production in the liver. With decreased gastric emptying and increased satiety, a common pharmacological effect observed when conducting these studies is a decrease in food consumption and body weight loss. This presents a challenge since we are evaluating the test article for potential toxicological effects, but the test article is designed to produce decreased food consumption and body weight loss. These points need to be considered to maintain the health of the animals and complete the 28-day study supporting the IND.

STUDY DETAILS

- **Drug Development Phase:** IND-enabling
- **Class of Drug:** Small molecule
- **Indication:** Weight loss / type 2 diabetes (T2D)
- **Animal Model:** Dog
- **# of Animals:** 21 per sex
- **Dose Route:** Oral administration
- **Dose Regimen:** Once daily for 28 days

STUDY DESIGN

The preclinical study included the following data:

- Clinical observations
- Body condition scores
- Food consumption
- Body weights
- Ophthalmology
- Electrocardiography
- Neurological assessments
- Toxicokinetics
- Clinical pathology
- Anatomic pathology

STUDY PURPOSE

To evaluate systemic toxicity and toxicokinetic characteristics of a GLP-1 RA test article and potential reversibility of any findings.

METHODS

Dogs were dosed once daily for 28 days via tablets with a water flush to ensure administration. Standard toxicological observations and measurements were performed over the course of the study, including detailed clinical observations, body weights, food consumption, ophthalmic examinations, electrocardiograms, clinical pathology, and anatomic pathology.

Animals were euthanized on Day 29. Complete necropsies were conducted, and standard organ weights recorded. A full set of tissues were collected from all animals, processed to slide, stained with hematoxylin and eosin (H&E), and evaluated by Altasciences' board-certified veterinary pathologist.

Group	Test Material	Dose Level (mg/animal)	Dose Concentration (mg/tablet)	Dose Amount (tablet/animal)	Terminal		Recovery	
					M	F	M	F
1	Placebo Tablet 1	0	0	1	3	3	2	2
2	Placebo Tablet 2	0	0	1	3	3	2	2
3	TA Tablet 1	10	10	1	3	3	0	0
4	TA Tablet 2	30	30	1	3	3	0	0
5	TA Tablet 3	100	100	1	3	3	2	2

RESULTS

During an acclimation period (at least two weeks prior to the start of dosing) and throughout the course of the study, the dogs were provided a certified canine dry diet that contained a higher composition of fat/protein. In addition, the animals were provided daily canned and wet food. This non-standard diet was used to begin the dosing phase with animals at a higher starting body weight in anticipation of the expected weight loss.

The combination of a non-standard daily food offering (dry and wet food high in fat/protein) increased the starting weight of the dogs, which combated the weight loss due to decreased food consumption, the expected pharmacological effect of the drug. These results allowed the animals to complete the full 28 days of dosing, and the potential systemic toxic effects and toxicokinetic characteristics of the test article were evaluated without the need for a dose holiday.

The dogs' food consumption and body weight decreased over the course of the study in a dose-dependent manner with overall body weight loss at 4%, 10%, and 14% when compared to control dogs.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company 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, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.