TERN-501, a potent and selective agonist of thyroid hormone receptor beta, strongly reduces histological features and biomarkers of non-alcoholic steatohepatitis associated pathology in rodent models

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INTRODUCTION
Liver inflammation and damage resulting from hepatic fat accumulation are key drivers in the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH). Selective agonism of thyroid hormone receptor beta (THR-beta) in the liver has been shown to markedly reduce liver fat, hepatic inflammation, and damage, raising the prospect of an efficacious NASH treatment in the future.¹

AIM
The aim of the study was to investigate the potency and selectivity of TERN-501 in a biochemical assay and to assess the translation into efficacy and safety in rodent models capable of measuring THR-beta agonism.

METHODS
The potential of TERN-501 to become a therapeutic agent for the treatment of NASH was established in multiple pre-clinical settings:

- The ability of TERN-501 to selectively agonize THR-beta was assessed biochemically using THR-beta or THR-alpha / RXR heterodimeric assays.²
- Male ICR rats (4 individuals per dosing group) were fed a cholesterol-enriched, otherwise normal, diet (1.5% cholesterol & 0.5% cholic acid) for 14 days. Compound(s) were administered via the intraperitoneal route (IP). Blood was collected at t = 0 (pre-treatment) and t = 24 hrs. Serum levels of cholesterol and triglycerides (TG) were determined for these two time points. Additionally, t = 6 hours plasma samples were prepared and analyzed to confirm test article exposure.
- Male C57BL/6J mice (8 individuals per dosing group) were fed a cholesterol-enriched, otherwise normal, diet (1.5% cholesterol & 0.5% cholic acid) for 14 days. Compound(s) were administered via the intraperitoneal route (IP). Blood was collected at t = 0 (pre-treatment) and t = 24 hrs. Serum levels of cholesterol and triglycerides (TG) were determined for these two time points. Additionally, t = 6 hours plasma samples were prepared and analyzed to confirm test article exposure.

TERT-501 Highly Effective in Rat Hypercholesterolemic Model³

Liver Histology: TERN-501 Effects on Liver Steatosis and Fibrosis in Mouse NASH Model

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RESULTS

- TERN-501 Biochemical Potency and Selectivity
- TERN-501 Mouse PK

Liver inflammation and damage resulting from hepatic fat accumulation are key drivers in the progression of non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH). Selective agonism of thyroid hormone receptor beta (THR-beta) in the liver has been shown to markedly reduce liver fat, hepatic inflammation, and damage, raising the prospect of an efficacious NASH treatment in the future.¹

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REFERENCES

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