INTRODUCTION

THR-β Agonism for Treatment of NASH

• Thyroid hormone receptor-beta (THR-β) is the major form of THR expressed in the liver and plays a key role in energy balance and metabolism of fatty acids and lipids, whereas THR-α predominates in the heart and muscle/skeletal system and is responsible for most cardiovascular and musculoskeletal effects of thyroid hormone stimulation.

• THR-β agonism is a promising mechanism for the treatment of nonalcoholic steatohepatitis (NASH) because of its potential to reduce hepatic steatosis and improve metabolic function and dyslipidemia in NASH patients.

• Serum binding globulin (SHBG) is a protein produced in the liver following activation of THR in hepatocytes and is a marker of THR α-target engagement.

TERN-501 Background

• TERN-501 is a potent and selective THR-β agonist with enhanced liver distribution in development for the treatment of NASH.

• TERN-501 lowered cholesterol in hypercholesterolemic rats and significantly reduced liver steatosis, inflammation, and fibrosis in a diet-induced mouse model of NASH at exposures of approximately 3,330 ng/hr.

• Key attributes of TERN-501:
  - Highly selective for THR-β to minimize effects of THR-α agonism
  - Designed to minimize potential drug-drug interactions
  - Low pharmacokinetic variability to avoid the need for individual patient dose adjustments and/or therapeutic drug monitoring
  - Slow clearance to support a low, once-daily oral dose, making it amenable to coadministration with other NASH treatments

• Here we present results from TERN501-1003, a Phase 1 first-in-human (FIH) study in healthy subjects receiving single oral doses of TERN-501.

OBJECTIVES

Primary Objective:

• Assess the overall safety and tolerability of single ascending doses of TERN-501 in healthy subjects

Secondary Objectives:

• Evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TERN-501 in healthy subjects following single ascending doses of TERN-501

METHODS

Single Ascending Dose (SAD)

Healthy male and non pregnant, non lactating female subjects were eligible to participate.

• 18-65 years of age (inclusive)

• Fasted LDL cholesterol ≥ 30 mg/dL

Safety was assessed throughout the study.

• Safety monitoring included total liver tumor in human study designs, with additional assessments performed post dosing.

• Adverse events (AE) were assessed using the standard Medical Dictionary for Adverse Events (MedDRA), and laboratory evaluations were performed:
  -_initially before dosing
  -after dosing

• Three dose levels were determined using weight-based median lethal dose (LD50) for 14-day rat studies.

CONCLUSIONS

1. Single ascending doses of TERN-501 up to 60 mg were overall safe and well tolerated in healthy volunteers

2. Single doses of TERN-501 exhibited dose-proportional plasma exposures with low variability

3. TERN-501 half-life was >13 hours at all single dose levels, supportive of once-daily dosing

4. Renal excretion of unchanged TERN-501 was minimal, indicating renal elimination is a minor pathway

5. Significant increases in SHBG were observed following a single dose of 2 mg TERN-501, with dose-dependent increases through 30 mg TERN-501 at Day 4

6. Significant decreases in LDL-c, total cholesterol, and Apo B were observed Day 2 following single dose administration of TERN-501 in one or more dose groups with dose-dependent reductions on Day 4

7. No significant increases in triglyceride levels were observed after a single dose of TERN-501

8. Changes in SHBG and Apo B were exposure-dependent

REFERENCES


3. Acknowledgments: The study was sponsored by Terns Pharmaceuticals. Key contributors were D. Barry Crittenden, MD, and D. Barry Crittenden, MD. We thank all the study volunteers for their time and efforts, and we would like to thank the study sites for their invaluable contributions.

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DISCLOSURES

The authors report no conflicts of interest.

ACKNOWLEDGEMENTS

We thank all the study volunteers for their time and efforts, and we would like to thank the study sites for their invaluable contributions.

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