THYROID HORMONE BETA RECEPTOR AGONIST TERN-501 DEMONSTRATES DOSE- AND EXPOSURE-DEPENDENT INCREASES IN SEX HORMONE BINDING GLOBULIN WITH ASSOCIATED DECREASES IN Atherogenic LIPIDS IN HEALTHY SUBJECTS

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KEY TAKEHOME MESSAGE

TERN-501 demonstrated positive change in sex hormone binding globulin (SHBG) with dose- and exposure-dependent effects on SHBG with decreases in LDL-c, total cholesterol, and triglycerides. Data support TERN-501 for evaluation in the Phase 2 dose-ranging DUET study in patients with premenopausal NAHS.

INTRODUCTION

• THR-beta is the major form of thyroid hormone receptor (THR) expressed in liver
• THR-beta agonism reduces LDL-c, Apo B, and TG
• SHBG is a key marker of hepatic THR-beta target engagement
• In NASH patients receiving a THR-beta agonist, high SHBG response (> 75% increase from baseline) has been associated with hepatic steatosis regression and liver histological improvement

TERN-501 is a novel, metabolically stable, highly selective THR-beta agonist

In a first-in-human study, TERN-501 was well tolerated, and a dose-dependent significant SHBG increases as well as atherogenic lipid decreases

Here we describe the PK/PD and PD/PD relationships observed with 14-day TERN-501 administration in the first-in-human study

OBJECTIVES

• To evaluate the relationship between TERN-501 pharmacokinetics and pharmacodynamic response

• To evaluate the relationship between SHBG response and changes in other pharmacodynamic markers of TERN-501

METHODS

• PK parameters estimated by noncompartmental analysis (WinNonlin)

• PK/PD analyses performed in GraphPad Prism using linear and nonlinear regression

• SHBG responder was defined as > 25% increase in SHBG from baseline

REFERENCES


CONCLUSIONS

• SHBG increases were strongly correlated to TERN-501 dose and plasma exposures, with overlap in both exposure and SHBG response in subjects receiving 6 mg and 10 mg TERN-501, indicating little potential for further increase in response with TERN-501 doses >6 mg.

• High SHBG response (>75% increase from baseline) was dose-dependent, with the greatest number of responders in the 10 mg TERN-501 group and in 5 of the 6 subjects (83%) in the 6 mg group after a short treatment duration (Day 15)

• No subject in the placebo or 1 mg TERN-501 groups achieved a high SHBG response by end of treatment (Day 15)

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