Design and Rationale for a Real World Observational Cohort of Patients with Nonalcoholic Fatty Liver Disease: The TARGET-NASH Study

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INTRODUCTION

- Nonalcoholic fatty liver disease (NAFLD) is highly prevalent in both children and adults
- NAFLD can lead to cirrhosis, hepatocellular carcinoma and death from liver disease
- NAFLD is also associated with increased risk of type II diabetes and cardiovascular events
- Current treatment, limited to weight loss and exercise, are difficult for patients to achieve and sustain.
- Thus, pharmacologic therapies are greatly needed, and many are in various stages of development
- To date, clinical trials have relied on surrogate markers (primarily liver histology) to show benefit due to the prolonged natural course of NAFLD
- Large, observational cohorts are needed to better understand the spectrum of NAFLD by obtaining real-world data that avoids ascertainment bias from studies in tertiary care centers alone and allows for further validation of histology and noninvasive biomarkers

AIMS

TARGET-NASH is a long-term, observational study of pediatric and adult patients with NAFLD designed to address questions that go beyond those explored in registration trials. The aims of TARGET-NASH are:

- To establish an understanding of the current natural history of NASH at community and academic medical centers
- To evaluate diagnostic modalities and treatment regimens for NAFLD currently being used in usual clinical practice
- To provide post-marketing data on clinical effectiveness and safety once pharmacologic agents for the treatment of NAFLD are available
- To collect and maintain a bio-specimen repository linked to carefully collected clinical data for translational studies and biomarker validation

METHODS

- Research plan is developed by the Steering Committee, which is comprised of academic thought leaders, regulatory agencies, patient advocates and pharma partners
- Academic and community sites representing gastroenterology, hepatology, endocrinology and primary care are included
- Multilevel data monitoring is performed to ensure completeness / accuracy
  - TARGET databases are 21 CFR Part 11 compliant, meet CDISC standards and incorporate WHODRUG and MEdDRA coding
- Patients are consented for submission of medical records, biospecimens and patient reported outcomes surveys (PROs)
- Biospecimens are collected annually
- Patient comorbidities, concomitant medications, interventions for NAFLD and disease progression are assessed
- Adverse outcomes, including cardiovascular and neoplastic complications and those related to medications are recorded

DISEASE CLASSIFICATION

For this study, NAFLD is defined as the full spectrum of nonalcoholic liver disease, from simple steatosis to steatosis with inflammation without evidence of other causes for secondary hepatic fat accumulation (such as heavy alcohol consumption). Its subdivisions are:

	Clinical Diagnosis	Pathological Diagnosis
NAFL	Evidence of steatosis on imaging	Steatosis confirmed by biopsy
NASH	Meets clinical diagnosis with 1 and 2 and one or more of 3 1. Evidence of steatosis on biopsy or imaging 2. Elevated alanine aminotransferase levels (ALT) of >19 U/L for women, >30 U/L for men 3. One or more: • Obesity (body mass index [BMI] ≥30.0) or; • Type 2 diabetes or; • Dyslipidemia or; • Metabolic syndrome (at least 3 of 5): ➢ Hypertension: systolic of ≥ 130 mmHg or diastolic ≥ 85 mmHg or on treatment for hypertension ➢ Hyperglycemia: fasting glucose of ≥ 100 mg/dL ➢ Abdominal obesity: waist circumference of ≥ 40 inches for men and ≥ 35 inches for women ➢ Triglyceride level of ≥ 150 mg/dL ➢ HDL cholesterol of ≤ 40 mg/dL for men and ≤ 50 mg/dL for women	Steato-hepatitis confirmed by biopsy

RESULTS

As of 23MAY2017:

- 35 sites in the United States
- **1,441 enrolled patients**
- Data and bio-specimens are being collected
- Interim analysis is being initiated using data from the first 1,000 enrolled patients

CONCLUSIONS

- TARGET-NASH is a large, diverse, real-world cohort of patients with NAFLD who represent the full spectrum of the disease
- Patients are being studied without ascertainment bias at both academic and community practices
- Longitudinal collection of patient level data and disease outcomes will be leveraged to develop and validate non-invasive biomarkers for the diagnosis and progression of NAFLD and to identify clinically meaningful endpoints for treatment trials of NASH

Green: actively enrolling sites
Yellow: sites in start-up

DISCLOSURES

TARGET-NASH is a study sponsored by TARGET PharmaSolutions (TPS). TPS is a real-world clinical data company based in Chapel Hill, NC. Dr. Vos has research funding or is an advisor to Allergan, Boehringer-Ingelheim, Immuron, Intercept, Resonance Health, Shire and TPS. Dr. Barritt participates in clinical trials sponsored by Intercept, Genfit, Conatus, NuSirt and BMS and serves as consultant to TPS. Dr. Gitlin receives research grants and serves as consultant to Abbvie, BMS, CymaBay, Genfit, Gilead, Intercept, Merck, Novartis, Nusirt and TPS. Dr. Klein is a consultant for Johnson & Johnson, Merck and TPS and a shareholder of Aspire Bariatrics. Dr. Lok receives research grants from BMS and Gilead for HBV/HCV studies and serves as a consultant to TPS for this NASH study. Dr. Loomba receives funding from Gilead, Merck, Intercept, NuSirt, Genfit, Promedior, Kinemed, Adheron, Tobira, Immuron, Galmed, Intercept, Arisaph, Shire, BMS, Galectin, Immuron, NGM, Siemens, Eli Lilly, GE, Octeta and Daiichi-Sankyo Inc., serves on advisory committees for Gilead, Galmed, Intercept, Nimbus, Gemphire, Arrowhead Research, Tobira, NGM, Conatus and Octeta, is consultant for Gilead, Novo Nordisk, Pfizer, BMS, Fibrogen, NGM, Alnylam, DeuteRx, Zafgen, RuiYi, Shire, Receptos, Enanta, Celgene, Boehringer Ingleheim, Eli Lilly, Ionis, Viking, Metacrine, Madrigal, CohBar, Scholar Rock, Bird Rock Bio, Intercept, GNI, GRI, Glympse Bio, Conatus, Janssen Inc. and TPS and is co-founder of Liponexus Inc; he also has disclosures with the National Institutes of Health, National Science Foundation and American Gastroenterology Association. Laura Malahias is an employee of TPS. Dr. Weiss has no conflicts of interest. Dr. Cusi receives research grants or has research agreements with Janssen, Lilly, Novartis, Novo Nordisk, Nordic, Octeta and Zydus; he also serves as a consultant to Amgen, Deuterex, Lilly, Novo Nordisk, Zydus and TPS. Dr. Neuschwander-Tetri is a consultant or advisor for Nimbus Therapeutics, Bristol Myers Squibb, Boehringer-Ingelheim, Janssen, Conatus, Enanta, Novartis, Galmed, Zafgen, Receptos, Pfizer, Allergan, MedImmune/AstraZeneca, ConSynance, Tobira, Karos, Afimmune NuSirt and TPS. Dr. Sanyal is the President of Sanyal Biotechnology, has stock options in Genfit, Akarna, Exhalenz, Tiziana, Durect and Indalo, receives royalties from Elsevier and UptoDate, provided consultation on advisory boards or independently for Intercept, Tobira, Gilead, Galectin, Merck, Bristol Myers, Nordic Bioscience, Novo Nordisk, Nitto Denko, Immuron, Octeta, Fractyl and Syntlogic without remuneration and consultation for Hemoshear, Novartis, Pfizer, Lilly, Astra Zeneca, Salix, Allergan, Amarin, Ardelyx, Yuhan, SunDise, Durect and TPS with remuneration. The authors would like to thank all the investigators, participants and research staff associated with TARGET-NASH. ClinicalTrials.gov Identifier: NCT02815891