Tolimidone

A novel clinical stage drug candidate for treatment of Nonalcoholic Steatohepatitis (NASH)

Melior Pharmaceuticals is pioneering work in the area of lyn kinase activation. Tolimidone is the most advance lyn kinase activator from Melior's pipeline, currently in development for Type 2 Diabetes Mellitus (T2DM) and nonalcoholic steatohepatitis (NASH).

Compelling profile in NASH

Results from a comprehensive pre-clinical model of NASH demonstrate:

- Improvement in NAS score
- Reduction in steatosis
- Decrease in liver weight
- Reduction in adiposity

Existing clinical efficacy and safety data in Type 2 Diabetes

- Successful completion of Phase 2a study in T2DM
- Results from Phase 2b study in T2DM available by Q1 2019
- Large safety database, with over 300 clinical exposures to date and over 700 total clinical exposures expected by Q1 2019

Potential to leverage diabetes data to accelerate NASH clinical development, enabling initiation of Phase 3 NASH registration studies within 24-36 months.

Overview

Melior Pharmaceuticals Inc. is developing tolimidone, a therapeutic candidate for nonalcoholic steatohepatitis (NASH), a disease of hepatic fat accumulation, projected to become the leading cause of liver transplantation by 2020. There are currently no approved therapies for the disease. The market opportunity for future NASH therapeutics is projected to reach $30 B.

Lyn kinase is an enzyme that modulates insulin sensitivity and dyslipidemia, while also promoting liver regeneration. Tolimidone is a potent and specific first-in-class activator of lyn kinase.

It serves as a dual non-PPAR insulin sensitizer and lipid regulator that has demonstrated improvement in multiple components of NASH pre-clinical models, including, reduction in adiposity, decrease in liver weight and reduction in insulin resistance.

Melior plans to initiate a Phase 2b proof of efficacy study in NASH subjects in early 2019.

Background

Tolimidone has already demonstrated clinical efficacy, safety and tolerability in a 130-patient Phase 2a Type 2 Diabetes study.

Melior is now developing tolimidone in NASH, given an increased understanding of the role of lyn kinase activation in hepatic disease.

Melior has generated positive preclinical data from a comprehensive NASH model showing:[Note 1]

- Improvement in NAS score
- Reduction in steatosis
- Decrease in liver weight
- Reduction in adiposity

Additional data from independent investigators demonstrate:

- Modulation of lipid pathways to reduce fat accumulation in the liver [Note 1]
- Improved cell survival and hepatocellular regeneration.[3, Note 2]

Tolimidone will have achieved over 700 clinical patient exposures by Q1 2019, following completion of the Ph 2b Type 2 Diabetes dose ranging study.

Partnering Thesis

Melior is seeking investors to support accelerated clinical development of Tolimidone in NASH. The current plan is to initiate a Phase 2b NASH study in 1H 2019. A successful Phase 2b study will advance tolimidone to US registration studies within 24-36 months, positioning tolimidone as one of the latest stage NASH candidates in clinical development.

Team and Track Record

Melior Pharmaceuticals is a mid-staged biopharmaceutical company developing a pipeline of de-risked, molecules in therapeutic areas of significant unmet need. Our management team has had a track record of success identifying de-risked drug targets that have potential for accelerated clinical development in therapeutic areas with significant unmet needs. [Note 3]

Contacts

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References

1. Saporito MS, Ochman AR, Lipinski CA, Handler JA, Reaume AG. (2012) MLR-1023 is a potent and selective allosteric activator of Lyn kinase in vitro that improves glucose tolerance in vivo. J Pharmacol Exp Ther. 342(1):15-22.

2. Ochman AR, Lipinski CA, Handler JA, Reaume AG, Saporito MS. (2012) The Lyn kinase activator MLR-1023 is a novel insulin receptor potentiator that elicits a rapid-onset and durable improvement in glucose homeostasis in animal models of type 2 diabetes. J Pharmacol Exp Ther. 342(1):23-32.

3. Gringeri E, Carraro A, Tibaldi E, D'Amico FE, Mancon M, Toninello A, Pagano MA, Vio C, Cillo U, Brunati AM. (2009) Lyn-mediated mitochondrial tyrosine phosphorylation is required to preserve mitochondrial integrity in early liver regeneration. Biochem J. 23;425(2):401-12.

Note 1

In addition to Melior's direct evidence of reduction of hepatic triglycerides and improved NAS score in an animal model of NASH (Figures 1, 2, 3), Melior's academic collaborators have generated extensive information demonstrating induction of lypolysis pathways and cell survival benfits with treatment of tolimidone

Figure 1

Liver Histology in Mouse Model of NASH

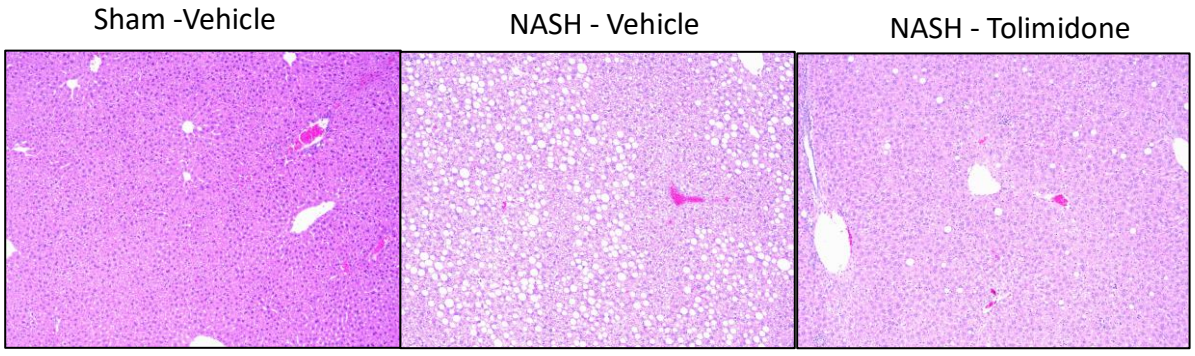


Figure 2

Quantitation of Liver Histology in Mouse Model of NASH with NAFLD Activity Score (NAS)

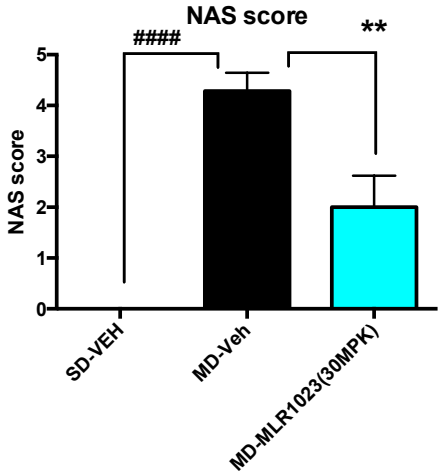
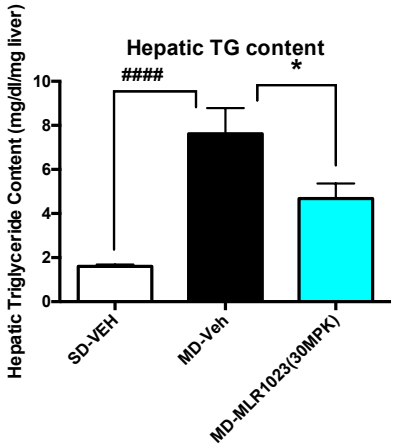


Figure 3

Quantitation of Hepatic Triglycerides in Mouse Model of NASH



Note 2

In addition to the studies by Gringeri et al (3) showing the importance of lyn kinase for hepatocellular regeneration Melior's collaborators have generated extensive information showing the importance of lyn kinase and the activity of tolimidone on promoting cell survival (confidential information).

Note 3

Management Team

Andrew Reaume, PhD, President & CEO

Dr. Reaume founded Melior Discovery Inc fourteen years ago and built it into a robust self-sustaining drug discovery organization. He subsequently spun off two sister companies with proprietary clinical stage candidates (Melior Pharmaceuticals I, Inc., Melior Pharmaceuticals II, LLC). As he has grown, first Melior Discovery, and then launched and grown the Melior Pharmaceutical companies he has been responsible for raising over $15 MM of investment capital and completed over $40MM in partnering deals including research partnerships with global pharmaceutical companies. He was responsible for spearheading and continues to oversee a complex global development partnership with an Asian pharmaceutical partner. Dr. Reaume's previous experience includes leadership roles in drug discovery and business analytics at Pfizer and Cephalon with more than twenty-five years of experience in the pharmaceutical industry.

M**ahen Gundecha, BSc, MBA, Chief Business Officer**

Mahen Gundecha is a seasoned health sciences leader with extensive business development, alliance management, new product commercialization and franchise P&L leadership experience across a range of companies, including Juno Therapeutics (Celgene), Novartis Group, Novo Nordisk, Endo Pharmaceuticals and GSK. Mahen has had hands on experience building business development strategies in multiple therapeutic areas and has executed foundational deals. Mahen's most recent experience has involved managing complex global oncology and gene editing partnerships, spanning R&D, manufacturing and commercialization. Mahen brings a broad base of therapeutic experience to Melior, including Neurosciences, Endocrinology, Hematology, Oncology, Rare Diseases, Cell Therapeutics and Gene Editing. Mahen will be leading investment and business development activities at Melior.

Ramana Kuchibhatla, PhD, Head of Clinical Development & Biostatistics

Over the span of his career, Dr. Kuchibhatla has built deep experience in Clinical Development, Biostatistics and Data Management within large and small pharmaceutical companies. He has led filing of multiple INDs and sNDAs, including Zyban® and Lamictal® and has helped to bring several NCEs into clinical development. He was closely involved in several successful in-licensing and out-licensing deals. He is leading development of accelerated clinical development and registration strategies to shorten time to pivotal data read outs. Dr. Kuchibhatla's previous experience includes leadership roles at GSK, Targacept and QED Pharma.

Vivian Cong, PhD, Head of Cardiovascular and Metabolic Disease

Dr. Cong has 12 years of research experience in metabolic diseases including diabetes, obesity, fatty liver disease and NASH. She was a pioneer in the field of NASH having established one of the first comprehensive and predictive animal models to assess development of fatty liver disease and NASH and has authored or co-authored over 20 peer-reviewed articles in metabolic diseases and NASH. She has also had extensive experience in metabolic alterations in neurodegenerative diseases including Alzheimer's disease and Parkinson's disease. Dr. Cong conducted her postdoctoral training at the Hospital for Sick Children in Canada and was a research fellow at the US National Institute on Aging where she worked closely with Dr. Josephine Egan, the investigator responsible for first describing the GLP-1 receptor as a promising therapeutic target.