MN-001 (tipelukast), a novel, orally bioavailable drug, reduces fibrosis and inflammation and down-regulates TIMP-1, collagen Type 1 and LOXL2 mRNA overexpression in an advanced NASH (non-alcoholic steatohepatitis) model

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BACKGROUND

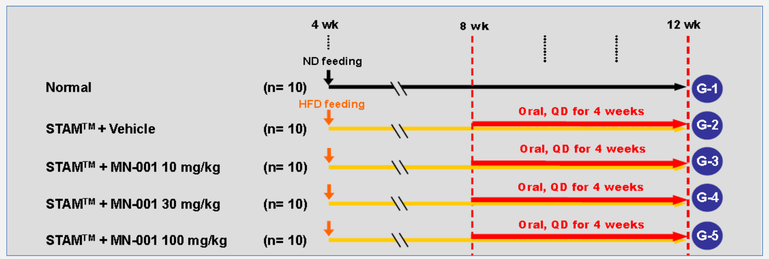
- MN-001 (tipelukast) is a novel, orally bioavailable small molecule compound with anti-inflammatory and anti-fibrotic activity in preclinical models.
- Known MOAs are inhibition of phosphodiesterases (PDE) 3 and 4, 5-lipoxygenase (5-LO) and leukotriene (LT), phospholipase C(PLC).
- In NASH mouse model study, MN-001 significantly down-regulated MCP-1, CCR2, collagen Type 1 and TIMP-1 mRNA expression.
- Developed for other indications, MN-001 has been exposed to more than 600 subjects with a good safety profile.

OBJECTIVES

- To build upon the previous NASH study findings, we evaluated MN-001's effects and further mechanism in advanced STAM™ mouse NASH-HCC model

MATERIALS & METHODS

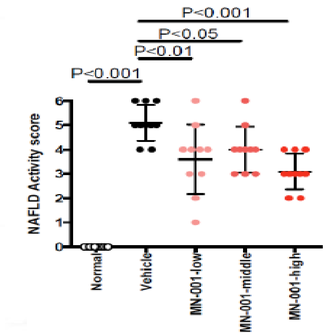
- NASH was induced in mice by a single SQ 200 µg streptozotocin (STZ) 2 days post-birth and high fat diet (HFD, 57kcal% fat, cat#:HFD32) after 4 wk of age (STELIC Institute & Co., Tokyo, JP).
- NASH mice were treated daily with either vehicle or 10, 30, or 100 mg/kg MN-001 (tipelukast) QD at 8 wk of age for 4 wk.

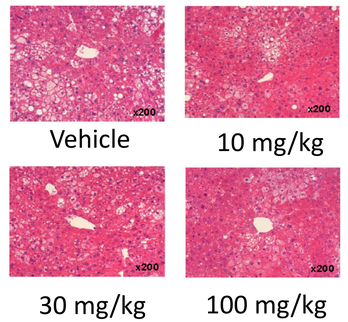


- Weight, survival, clinical signs, behavior of mice monitored daily
- Histology evaluation
  - HE staining (NAFLD activity score = NAS)
  - Sirius-red staining (% fibrosis area)
  - α-SMA immunostaining (% of αSMA-positive area)
- Gene expression : TIMP-1, LOXL2
- Statistical analysis included Bonferroni Multiple Comparison Test, P values < 0.05 considered statistically significant

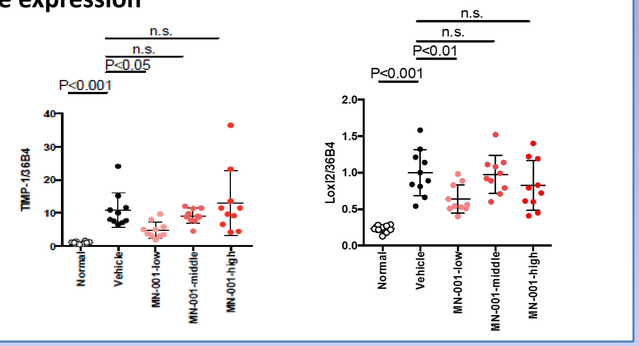
4. RESULTS

MN-001 significantly reduced NAFLD activity score (NAS) compared to vehicle

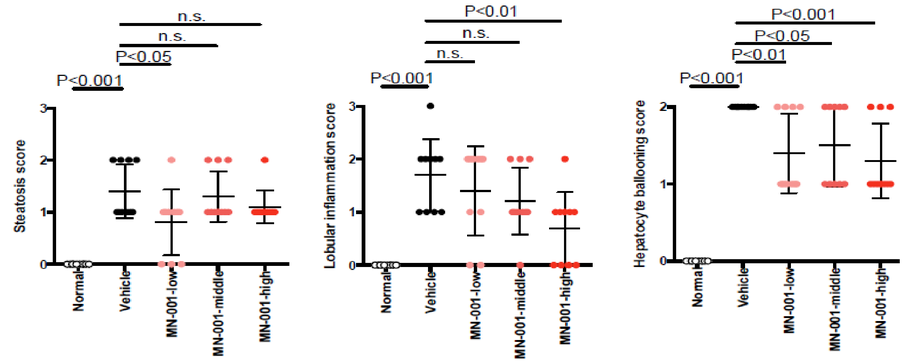




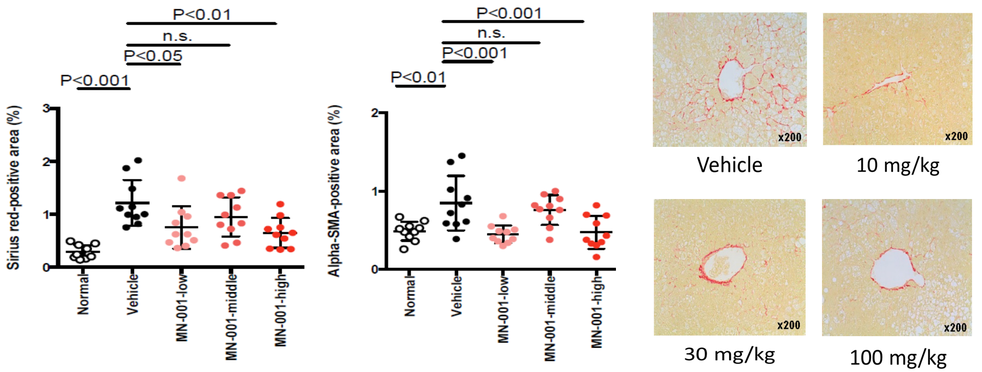
MN-001 significantly down-regulated TIMP-1 and LOXL2 gene expression



MN-001 significantly reduced NAS in all components of NAS (steatosis, lobular inflammation, and hepatocyte ballooning)



MN-001 significantly reduced % area of fibrosis and α-SMA positive area



CONCLUSIONS

- Three different dose of MN-001 were evaluated in advanced STAM™ mouse NASH-HCC model
- The advanced STAM™ mouse NASH-HCC model developed apparent histological findings of NASH with fibrosis
- MN-001 had no effect on body weight or general condition of the mice compared to vehicle
- All doses of MN-001 significantly reduced NAS, attributed to significant reductions in steatosis, lobular inflammation and hepatocyte ballooning scores.
- Reduction of NAS was more significant than observed in the previous NASH mouse model study
- MN-001 significantly reduced % area of fibrosis and αSMA-positive staining area
- In addition to down-regulation of MCP-1, CCR2, TIMP-1 and Collagen Type 1, MN-001 also significantly down-regulated mRNA expression of LOXL2
- A Phase 2 trial to evaluate the safety and efficacy of MN-001 in NASH patients is planned

DISCLOSURES

Dr. Kazuko Matsuda and Dr. Yuichi Iwaki are employed by Medicinova, Inc.