DUR-928, an endogenous regulatory molecule, exhibits anti-inflammatory and antifibrotic activity in a mouse model of NASH

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INTRODUCTION

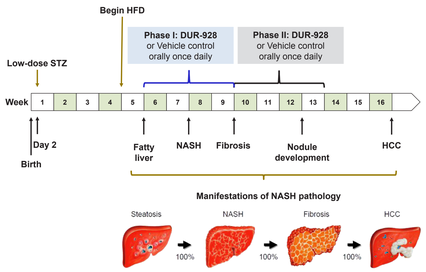
Non-alcoholic steatohepatitis (NASH) is marked by the presence of fatty liver, inflammation and fibrosis

DUR-928 is an endogenous regulatory molecule that has been previously shown to reduce hepatic lipid accumulation and inflammation in various animal models of non-alcoholic fatty liver disease (NAFLD)

OBJECTIVE

The aim of this study was to investigate the efficacy of DUR-928 to ameliorate the progression of NASH and liver fibrosis in the STAM™ mouse model

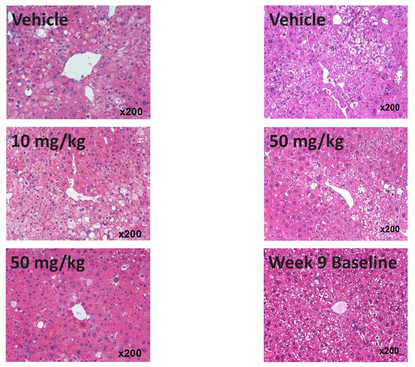
MATERIALS & METHODS



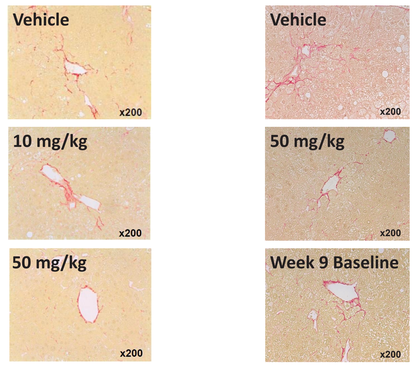
- **STAM™ mouse model of NASH[1]**
  - NASH was induced by a single subcutaneous injection of 200 ug streptozotocin solution 2 days after birth in male C57BL/6J mice, followed by high fat diet (57 kcal % fat) feeding at 4 weeks of age until end of the study
- **Dosing regimen and schedule**
  - **Phase I**: Weeks 5–9, daily oral doses of 10 or 50 mg/kg DUR-928 or Vehicle (n=8-9/treatment group)
  - **Phase II**: Weeks 9–13, daily oral doses of 50 mg/kg DUR-928 or Vehicle (n=6-8/treatment group)
  - Studies were terminated upon completion of dosing
  - Baseline measurements were collected from untreated STAM™ mice at Week 9
- **Phenotypic analysis**
  - Hematoxylin & eosin (H&E) staining on liver sections and histopathological analysis by a certified veterinary pathologist were performed to generate NAFLD activity scores (NAS)
  - Percent (%) liver fibrosis as measured by presence of Sirius Red staining and digital quantification
  - Hepatic gene expression analyses by real-time reverse transcription quantitative polyermase chain reaction and normalized to Vehicle
  - Statistical analysis: One-way ANOVA with Dunnett's Multiple Comparison

RESULTS

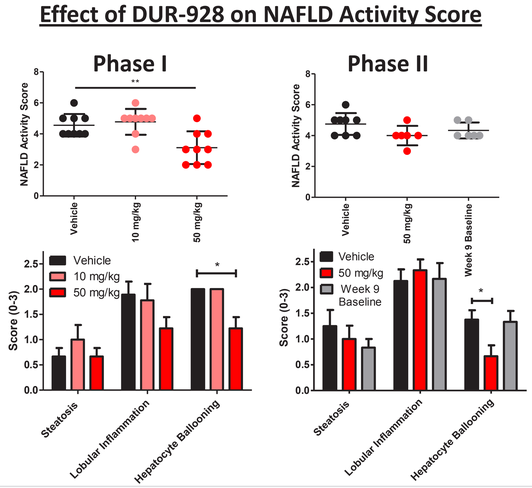
H&E Staining



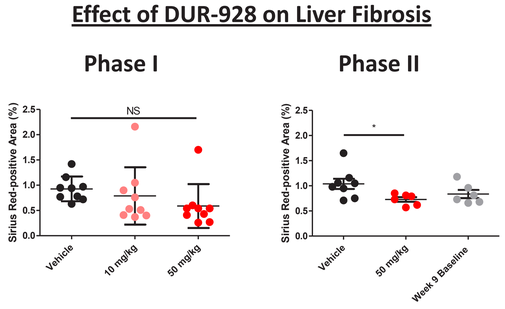
Sirius Red Staining for Collagen (fibrosis)



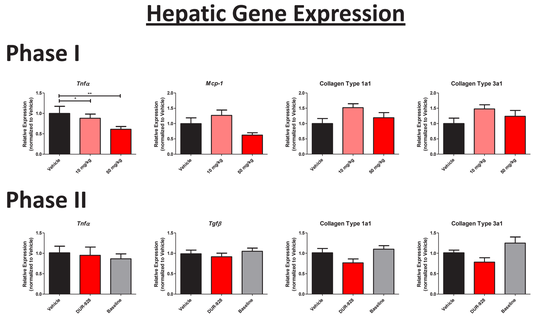
Effect of DUR-928 on NAFLD Activity Score



Effect of DUR-928 on Liver Fibrosis



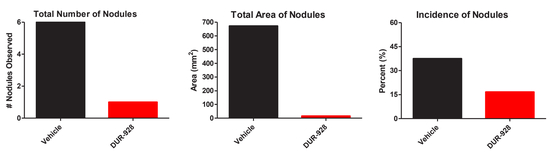
Hepatic Gene Expression

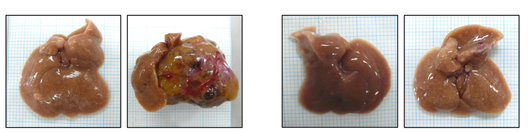


*p<0.05, **p<0.01

Hepatic Nodule Formation

By Week 12, nodule formation starts to occur in STAM™ mice. Four weeks of 50 mg/kg DUR-928 treatment that was concluded at the end of Week 13 (Phase II) was associated with reduced size and incidence of nodules





SUMMARY & CONCLUSIONS

Phase I – Weeks 5-9

- Four weeks of daily oral DUR-928 treatment during the early stages of NAFLD/NASH exhibited dose-dependent effects:
  - Significant decrease in NAS
  - Trend of decrease of liver fibrosis was observed
  - Significant reduced hepatic expression of *Tnfα* and trend of decrease of *Mcp-1*

Phase II – Weeks 9-13

- Four weeks of daily oral DUR-928 treatment when liver fibrosis was established resulted in:
  - Significant decrease in liver fibrosis
  - Significant decrease in hepatocyte ballooning
  - Trend of reduced hepatic expression of fibrotic genes, Collagen 1a1 and 3a1
- Hepatic nodule formation, which progresses to hepatocellular carcinoma in this model, was also reduced in total number, size and incidence in DUR-928-treated mice

Conclusions

DUR-928 has the capability to improve liver morphology by its anti-inflammatory and antifibrotic activity in STAM™ mice. These data support the clinical development of DUR-928 for the treatment of NASH and other inflammatory or fibrotic liver diseases

ACKNOWLEDGEMENTS

- The STAM™ mouse model used in this study was developed and characterized by SMC Laboratories (Tokyo, Japan)
- We acknowledge Drs. Hongwei Wu, Andy Miksztal and Neil Verity for their scientific contributions to this study

REFERENCE

1. Fujii M, Shibazaki Y, Wakamatsu K, Honda Y, Kawauchi Y, et al. (2013) A murine model for non-alcoholic steatohepatitis showing evidence of association between diabetes and hepatocellular carcinoma. Med Mol Morphol 46: 141–152

DISCLOSURES

- Mee J. Kim and WeiQi Lin are employees of DURECT Corporation and may hold company stock/options
- This presentation includes discussion of an investigational drug not approved for use in humans

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