Integrated transcriptomics of Rencofilstat treatment in a Phase 2a NASH trial confirms anti-fibrotic effect of pan-cyclophilin inhibition and identifies Rencofilstat-specific biomarkers.

P. Mayo1, S. Harrison2, T. Hobbs1, D. Ure1, D. Trepanier1, E. Foster1, C. Zhao1, R. Foster1
1 Hepion Pharmaceuticals Inc - 2 Summit Clinical Research.

INTRODUCTION

The progression of liver fibrosis in Non-Alcoholic Steatohepatitis (NASH) has been directly linked to increased mortality and morbidity. To date, numerous drug candidates have failed to show a significant benefit in fibrotic endpoints for NASH subjects enrolled in clinical trials. Rencofilstat (RCF), a non-immunosuppressive pan-cyclophilin inhibitor has demonstrated pleiotropic effects well-suited for the treatment of NASH and fibrosis.

AIM

To use transcriptomics to elucidate the effects of RCF in patients with biomarker identified F2/F3 NASH subjects.

- Identify Gene – Clinical Trait Modules
- Identify Key Driver Genes in each Module
- Evaluate if RCF antifibrotic effect is linked to collagen synthesis and catabolism
- Develop a biomarker panel for RCF responsiveness

METHOD

- RNA sequencing data was obtained from a 28-day Phase 2a trial of RCF in F2/F3 NASH subjects (NCT04480710).
- Complete data was obtained from N=31 subjects on 75 mg or 225 mg RCF active treatment.
- RNA was stabilized and isolated from whole blood on Day 1 and Day 28.
- RNA sequencing transcripts were evaluated using edgeR with quantification in Salmon v1.4.0.
- Differential expression analysis (DEA) was performed using edgeR in R v4.1.1.
- Co-expression networks were constructed using weighted gene correlation network analysis (WGCNA).
- DEA was combined with WGCNA to enhance the discriminating ability of highly related genes as potential biomarkers.
- Weighted Key driver analysis (wkDA) was performed on trait modules using Mergeomics with network plotting and community detection in Cytoscape 3.9.1.
- Functional enrichment was performed using cosine similarity implemented via GeneWalk.

RESULTS

CONCLUSIONS

- The ALT module demonstrated great heterogeneity in function including anti-inflammatory and anti-viral properties in addition to collagen regulation consistent with cyclophilin pharmacology.
- The C6M module had great heterogeneity in scope with only three key driver genes identified modulated by RCF treatment.
- The ProC3 module demonstrated the greatest specificity involving regulation of collagen synthesis.
- ProC3 Key Driver network directly interacts with cyclophilins.
- Treatment of these NASH subjects with RCF modulates a large collagen regulatory network including synthesis and catabolism.
- Key driver genes and their regulatory networks can be utilized as biomarkers for RCF pharmacodynamics.
- Gene networks identified in this study support further development in the treatment of NASH and hepatocellular carcinoma.

REFERENCES


CONTACT INFORMATION

P. Mayo, PhD, (E) Clinical Pharmacology & Analytics, Hepion Pharmaceuticals Inc - pmayo@hepionpharma.com