

Stable Gut Microbiome Composition and Diversity with NGM282 (Aldafermin) Therapy in Patients with Non-alcoholic Steatohepatitis

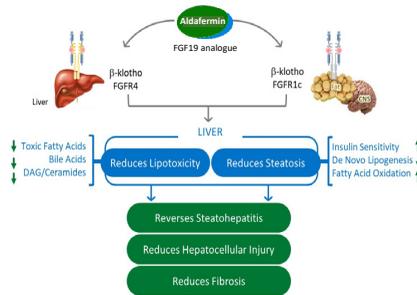


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INTRODUCTION

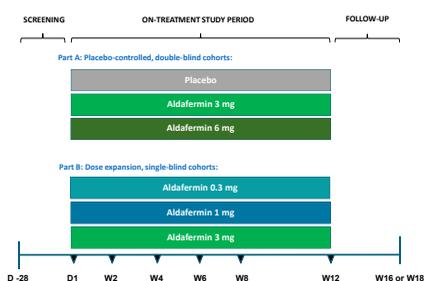
- The composition of the human gut microbiota is linked to health and disease¹, and knowledge of the impact of therapeutics on the microbiota is essential to decipher their biological roles and to gain new mechanistic insights
- NGM282 (aldafermin), a non-tumorigenic FGF19 analogue, significantly inhibited bile acid synthesis, reduced steatosis, hepatic inflammation and fibrosis in patients with nonalcoholic steatohepatitis (NASH)^{2,6}
- Here we report the effect of aldafermin on the gut microbiota in a pooled phase 2 studies of double-blind, placebo-controlled cohorts⁴ and single-blind, dose expansion cohorts⁵⁻⁶ in patients with NASH

Pharmacologic Activity of Aldafermin in NASH



METHODS

- 144 NASH subjects, with NAS ≥ 4 (at least 1 point in each component), stage 1-3 fibrosis and absolute liver fat content by MRI-PDFF $\geq 8\%$, received aldafermin 0.3mg, 1mg, 3mg, 6mg or placebo daily for 12 weeks (W12), and had both baseline (BL) and W12 stool samples collected^{4,6}
- Samples were extracted and sequenced using the 16Sv4 region at Diversigen (Houston, TX)
- We compared pre- and post-treatment in alpha diversity, beta diversity and taxonomy
- A principal coordinate analysis was used to show differences between groups
- P values were calculated using Kruskal-Wallis or Mann Whitney tests with Benjamini-Hochberg false discovery rate correction
- A general linear model (GLM) was used to incorporate additional covariates

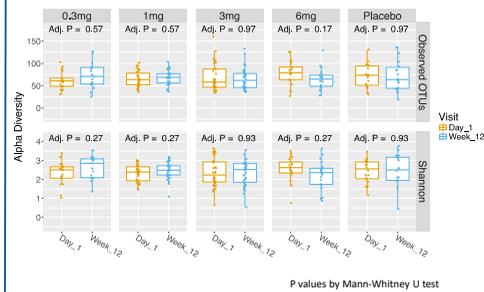


RESULTS

Alpha Diversity

- 85% of reads produced were mapped to the SILVA database
- Microbial richness and evenness were measured by alpha diversity
- There were no differences seen among the different treatment groups at both time points in both observed operational taxonomic units (OTUs) and the Shannon Diversity Index
- There were no differences in alpha diversity for each treatment group at baseline or Week 12

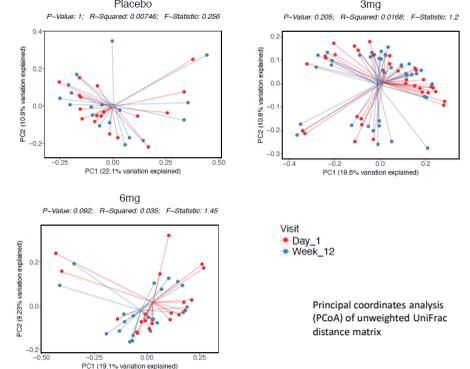
Stable Gut Microbiome with Alpha Diversity in Patients Treated with Aldafermin



Beta Diversity

- Differences among samples were measured by beta diversity
- UniFrac-based principal coordinates analysis did not reveal any clustering in treatment groups by time
- No clustering was observed among treatment groups at either Day 1 or Week 12

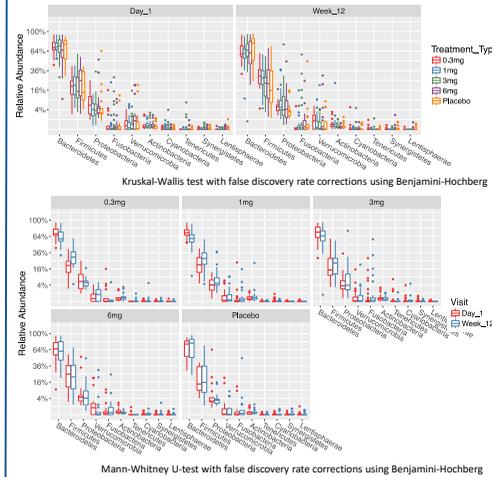
Stable Gut Microbiome by Beta Diversity in Patients Treated with Aldafermin



Phylum Level

- There were no significant differences in the abundances of main phyla over time or between aldafermin and placebo
- No change in the relative abundance of Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia, Fusobacteria, Actinobacteria, Tenericutes, Cyanobacteria, Lentisphaerae, Synergistetes, Euryarchaeota and Spirochaetae

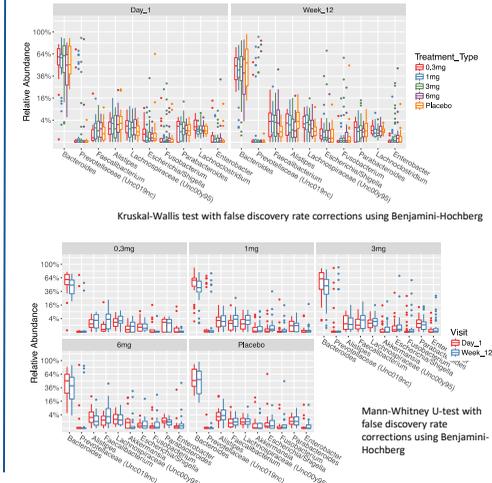
No Change in Phyla in Patients Treated with Aldafermin



Genus Level

- There were no significant differences in the abundances of the top 30 most abundant genera over time or between aldafermin and placebo
- GLM analysis revealed that age was not a factor in differences between time points

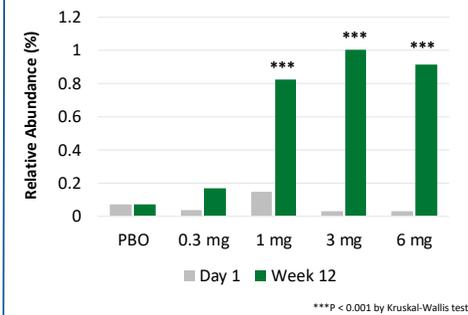
No Change in Genera in Patients Treated with Aldafermin



Veillonella

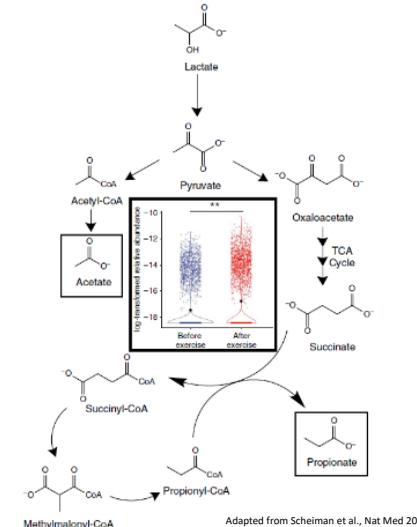
- Among all taxa in the study groups, a low abundance bacterial genus, *Veillonella*, was the only type exhibiting significant difference between aldafermin- and placebo-treated microbiomes
- Subjects who received aldafermin, but not placebo, had a statistically significant increase from baseline in the relative abundance of *Veillonella* at Week 12

Aldafermin Enriches *Veillonella* in Patients with NASH



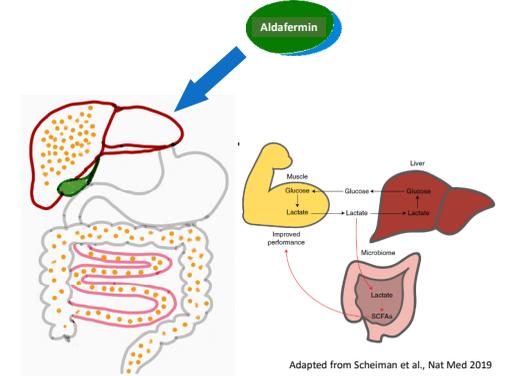
- Recent studies have identified a link between members of the genus *Veillonella* and exercise performance⁷
- An increase in *Veillonella* relative abundance was observed post-marathon in marathon runners⁷
- Veillonella* utilize lactate as their sole carbon source, and improve run time via metabolic conversion of exercise-induced lactate into propionate
- These findings suggest that the induction of *Veillonella* represents a natural, microbiome-encoded enzymatic process that enhances athletic performance

Veillonella is Enriched in "Athlete Gut Microbiome" And Functions in Lactate Metabolism



Summary

- Enrichment of *Veillonella* signifies an "Athlete Gut Microbiome"
- Aldafermin therapy increases the abundance of *Veillonella* in the gut microbiome in 12 weeks in patients with NASH



CONCLUSION

- Patients treated with NGM282 (aldafermin) had stable gut microbial composition and diversity
- No taxonomic differences were observed between baseline and Week 12 except for an enrichment in the low abundance genus *Veillonella*
- Through this large scale, hypothesis-free, stool microbiome profiling effort, we have identified *Veillonella* as a sensitive gut microbiome marker of aldafermin therapy in patients with NASH
- The role of *Veillonella* in lactate metabolism and its enrichment in "athlete gut microbiome" may have important implications for aldafermin therapy

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References:

- Gilbert et al., *Nat Med* 2018; 24: 392-400
- Zhou et al., *Cancer Res* 2014; 74:3306-3316
- Zhou et al., *Hepatal Commun* 2017; 1:1024-1042
- Harrison et al., *Lancet* 2018; 391:1174
- Rinella et al., *J Hepatol* 2019; 70:735-744
- Harrison et al., *Hepatology* 2019; doi: 10.1002/hep.30590
- Scheiman et al., *Nat Med* 2019; 25: 1104-1109

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Author disclosures on file at AASLD

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