

Marlyn J. Mayo<sup>1</sup>, Lei Ling<sup>2</sup>, Alex M. DePaoli<sup>2</sup>, Gideon M. Hirschfield<sup>3</sup>, Ulrich Beuers<sup>4</sup>

<sup>1</sup>University of Texas, Southwestern Medical Center, Dallas, United States; <sup>2</sup>NGM Biopharmaceuticals, South San Francisco, United States; <sup>3</sup>University Health Network, Toronto, Canada; <sup>4</sup>Academic Medical Center, Amsterdam, the Netherlands

## INTRODUCTION

- Pruritus is a common symptom in patients with cholestatic liver diseases, including primary sclerosing cholangitis (PSC), an inflammatory and progressively fibrotic liver disease devoid of effective medical interventions
- The pathogenesis of pruritus is poorly understood, and proposed pruritogens include bile acids and autotaxin/lysophosphatidic acid<sup>1-3</sup>
- Recently, bile acids have been shown to activate the MRGPRX4 receptor located in the sensory neurons to induce itch<sup>1-2</sup>
- Aldafermin (NGM282), a non-tumorigenic FGF19 analogue, potently inhibits bile acid synthesis, improves hepatic inflammation, and decreases fibrosis markers in patients with PSC<sup>4</sup>

## AIM

- To determine whether certain bile acid species may be related to pruritus, we correlated changes in individual serum bile acids with patient-reported outcome measures of pruritus from a phase 2 aldafermin trial in patients with PSC

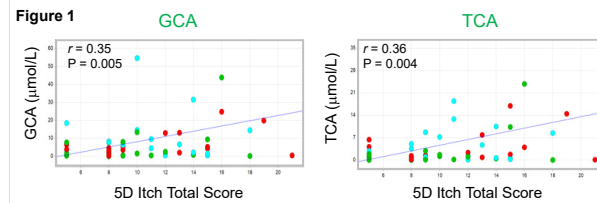
## METHOD

- 62 subjects, with PSC by EASL criteria and an elevated ALP > 1.5xULN at baseline (BL), were randomized to daily aldafermin 1mg, 3mg or placebo (PBO) for 12 weeks (W12)
- 5D-itch pruritus questionnaires (scores from 5 to 25) and fatigue severity numeric rating scale (NRS, from 0 to 10) were collected; higher numbers indicated more severe symptoms
- Serum concentrations of bile acid species were determined by mass spectrometry (Mayo Clinic)
- Scores were compared with the use of a mixed-effect model repeated measures analysis
- Correlations between pruritus and serum bile acids were assessed with a clinical anchor threshold of  $r > 0.30$  and  $P < 0.05$  as significant

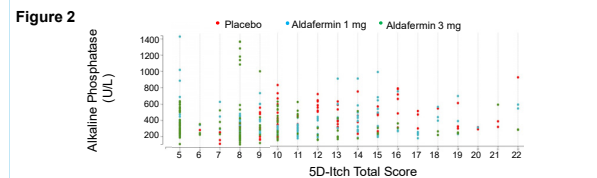
## RESULTS

- At baseline, pruritus severity by 5D-itch correlated with serum concentrations of GCA and TCA, but not ALP, ALT, AST, C4 or ELF

### Correlation Between 5D-Itch and Bile Acids at Baseline

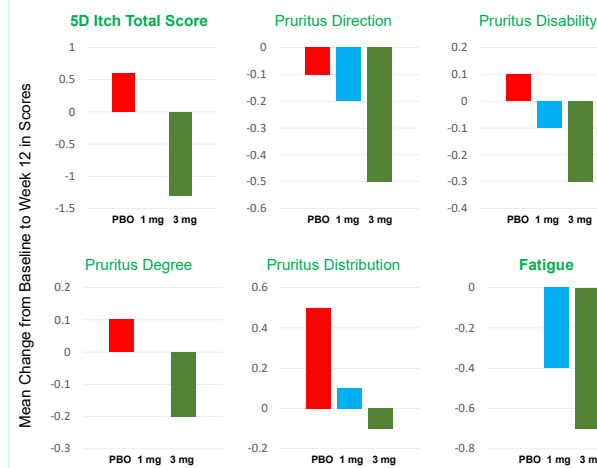


### Lack of Correlation Between 5D-itch and ALP at Baseline

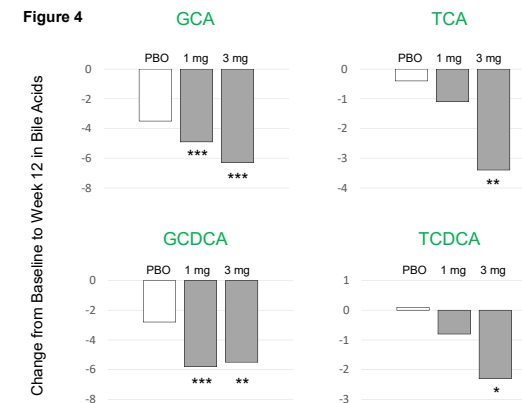


- At week 12, aldafermin treatment was associated with a trend of improvement in pruritus and fatigue, especially in the 3 mg group

### Effects of Aldafermin on Pruritus and Fatigue at Week 12

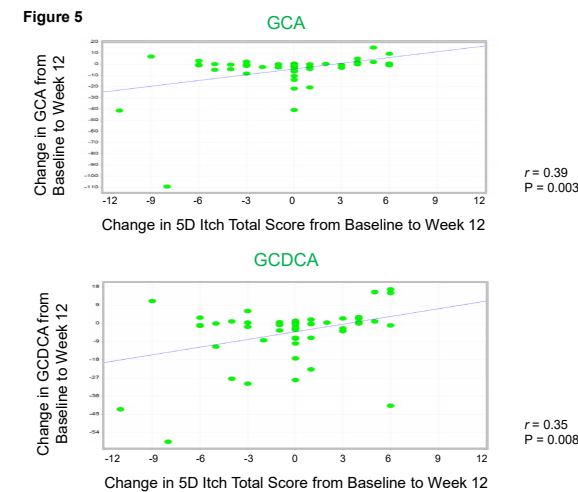


- Reductions from baseline in GCA and GCDCA were observed in the aldafermin groups, but not in the placebo group
- Aldafermin groups had less robust reductions in TCA and TCDC



- Change in pruritus severity from baseline to week 12 correlated with changes in GCA and GCDCA

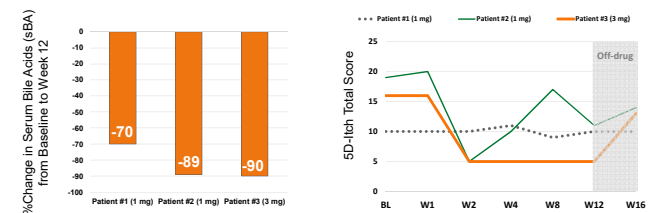
### Correlation Between Changes in 5D-Itch and Bile Acids



## Response to Aldafermin in Patients with Baseline sBA > 100 μM

Figure 6

- A few patients had serum bile acids > 100 μM at baseline, and they achieved 70-90% reduction in serum bile acids at week 12
- 5D-itch total scores were reduced and normalized in patient #3 (3 mg) at weeks 2, 4, 8, 12 (EOT), and back to baseline when off-drug



## CONCLUSIONS

- Aldafermin reduces serum bile acids, especially the more toxic, hydrophobic bile acids, in patients with PSC
- Treatment with aldafermin was associated with a trend of improvement in pruritus and fatigue, especially in the 3 mg group
- Reductions in serum GCA and GCDCA correlated with reductions in 5D-itch score
- These results indicate that specific bile acid species may serve as pruritogens and respond to aldafermin treatment

## ACKNOWLEDGEMENTS

We thank all of the patients who participated in this study, and the investigators, study coordinators and staff for their support.

## REFERENCES

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