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## INTRODUCTION

- Nonalcoholic steatohepatitis (NASH) represents an epidemic health crisis with broad impact on public health
- Developing therapeutics for NASH poses a vexing challenge, which requires invasive procedures such as liver biopsy
- Several inexpensive, simple, commonly used non-invasive tests (NITs), such as AST to platelet ratio index (APRI) and FIB-4 index, have been used to identify high-risk NASH patients from primary care settings<sup>1</sup>
- Ratio of triglyceride and HDL is a simple index that not only provides a rapid assessment of cardiovascular risk, but also correlates with histological improvement in NASH<sup>2</sup>
- Aldafermin (previously known as NGM282) is a non-tumorigenic FGF19 analogue that significantly inhibits bile acid synthesis, reduces steatosis, and ameliorates hepatic inflammation and fibrosis in patients with NASH<sup>3-6</sup>

## AIM

- Using well-characterized, prospective cohorts of patients with NASH enrolled in aldafermin phase 2 trials, we aimed to investigate the effects of aldafermin on several widely-used, inexpensive NITs

## METHOD

- In part 1 of the study, 82 subjects were randomized to aldafermin 3mg (n=27) or 6mg (n=28) vs. placebo (n=27) as a daily SC injection for 12 weeks<sup>4</sup>
- In part 2 of the study, 94 subjects received open-label aldafermin 0.3mg (n=23), 1mg (n=49) or 3mg (n=22) for 12 weeks for dose-range finding<sup>5-6</sup>
- Key inclusion criteria included biopsy-proven NASH with NAS ≥4 (at least 1 point in each component), Stage 1-3 fibrosis and absolute liver fat content (LFC) by MRI-PDFF ≥8%
- APRI, FIB-4, fatty liver index (FLI) and ratio of triglyceride and HDL (TG/HDL) were evaluated at baseline (BL) and week 12 (W12)
  - APRI: (AST / ULN [AST]) x 100 / platelets (10<sup>9</sup>/liter)
  - FIB-4: age x AST (IU/l) / platelets (10<sup>9</sup>/liter) x √ALT (IU/l)
  - FLI: (e<sup>0.953</sup> × loge(triglycerides) + 0.139 × BMI + 0.718 × loge(GGT) + 0.053 × waistcircumference - 15.745) / (1 + e<sup>0.953</sup> × loge(triglycerides) + 0.139 × BMI + 0.718 × loge(GGT) + 0.053 × waistcircumference - 15.745) × 100,
  - Ratio of triglyceride and HDL: TG/HDL

## RESULTS

- At baseline, mean APRI, FIB-4, FLI and TG/HDL values were similar across all groups

**Table 1** Baseline NITs Values

	APRI	FIB-4	FLI	TG/HDL
<i>Part 1: Double-Blind, Placebo-Controlled</i>				
PBO (n=27)	0.73 (0.40)	1.67 (0.79)	87.7 (13.7)	5.10 (5.50)
Aldafermin 3mg (n=27)	0.66 (0.49)	1.54 (0.78)	84.6 (11.6)	5.82 (5.31)
Aldafermin 6mg (n=28)	0.49 (0.28)	1.33 (0.55)	84.0 (23.2)	4.31 (2.65)
<i>Part 2: Open-Label</i>				
Aldafermin 0.3mg (n=23)	0.66 (0.41)	1.18 (0.49)	89.4 (13.4)	4.50 (4.03)
Aldafermin 1mg (n=49)	0.73 (0.42)	1.47 (0.65)	91.4 (8.7)	3.82 (1.82)
Aldafermin 3mg (n=22)	0.79 (0.39)	1.72 (0.68)	95.2 (7.5)	4.00 (2.10)

Shown are mean (SD)

**Table 2** Change from baseline to week 12 in NITs

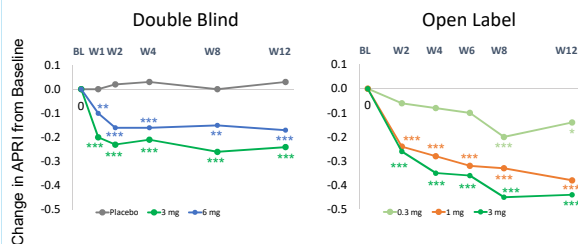
	APRI	FIB-4	FLI	TG/HDL
<i>Part 1: Double-Blind, Placebo-Controlled</i>				
PBO	0.03	0.08	0.3	-0.7
Aldafermin 3mg	-0.24***	-0.14	-1.2	-0.9
Aldafermin 6mg	-0.17***	-0.01	-2.2	-1.3**
<i>Part 2: Open-Label</i>				
Aldafermin 0.3mg	-0.14*	-0.04	-2.2	-0.9
Aldafermin 1mg	-0.38***	-0.22**	-3.1***	-1.4***
Aldafermin 3mg	-0.44***	-0.35**	-2.7	-1.7***

\*\*\*P<0.001, \*\*P<0.01, \*P<0.05 vs baseline

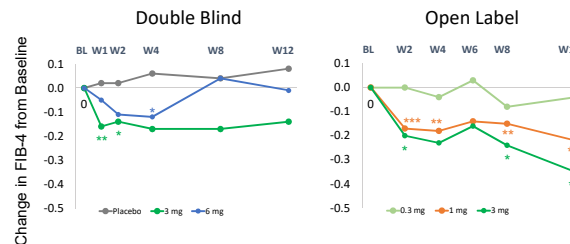
- At week 12, aldafermin-treated patients showed reductions in NITs of fibrosis (APRI and FIB-4), fatty liver (FLI) and cardiovascular risk (TG/HDL ratio); in contrast, no improvement was seen with placebo-treated subjects

- Improvements were observed as early as 2 weeks on aldafermin and were maintained throughout treatment duration

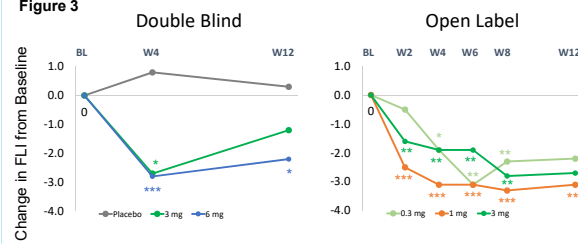
**Figure 1** APRI



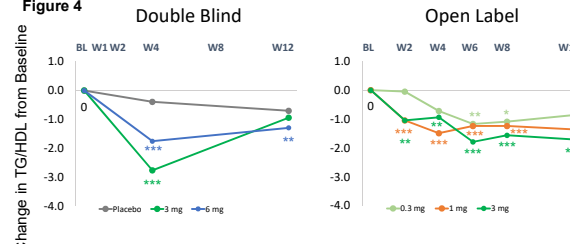
**Figure 2** FIB-4



**Figure 3** FLI



**Figure 4** TG/HDL Ratio



\*\*\*P<0.001, \*\*P<0.01, \*P<0.05 vs baseline

## CONCLUSIONS

- Although liver biopsy is considered the gold standard for the diagnosis of liver fibrosis and NASH, it is impractical to use for the estimated >25 million patients with NASH in the US and Europe
- There is an urgent need for non-invasive, easy-to-perform, cost-effective, and widely-available markers to assess disease severity and response to treatment
- Aldafermin therapy produced improvements in several simple and inexpensive NITs of liver fibrosis (APRI, FIB-4), steatosis (FLI) and cardiovascular risk (TG/HDL ratio)
- These NITs may be useful for monitoring early treatment response to aldafermin

## ACKNOWLEDGEMENTS

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