Positive topline results from a 24-week, randomized, double-blind, placebo-controlled, multicenter, phase 2 study of the FGF19 analogue aldafermin (NGM282) in patients with nonalcoholic steatohepatitis

August 29, 2020 (EASL/ILC 2020, London, UK)

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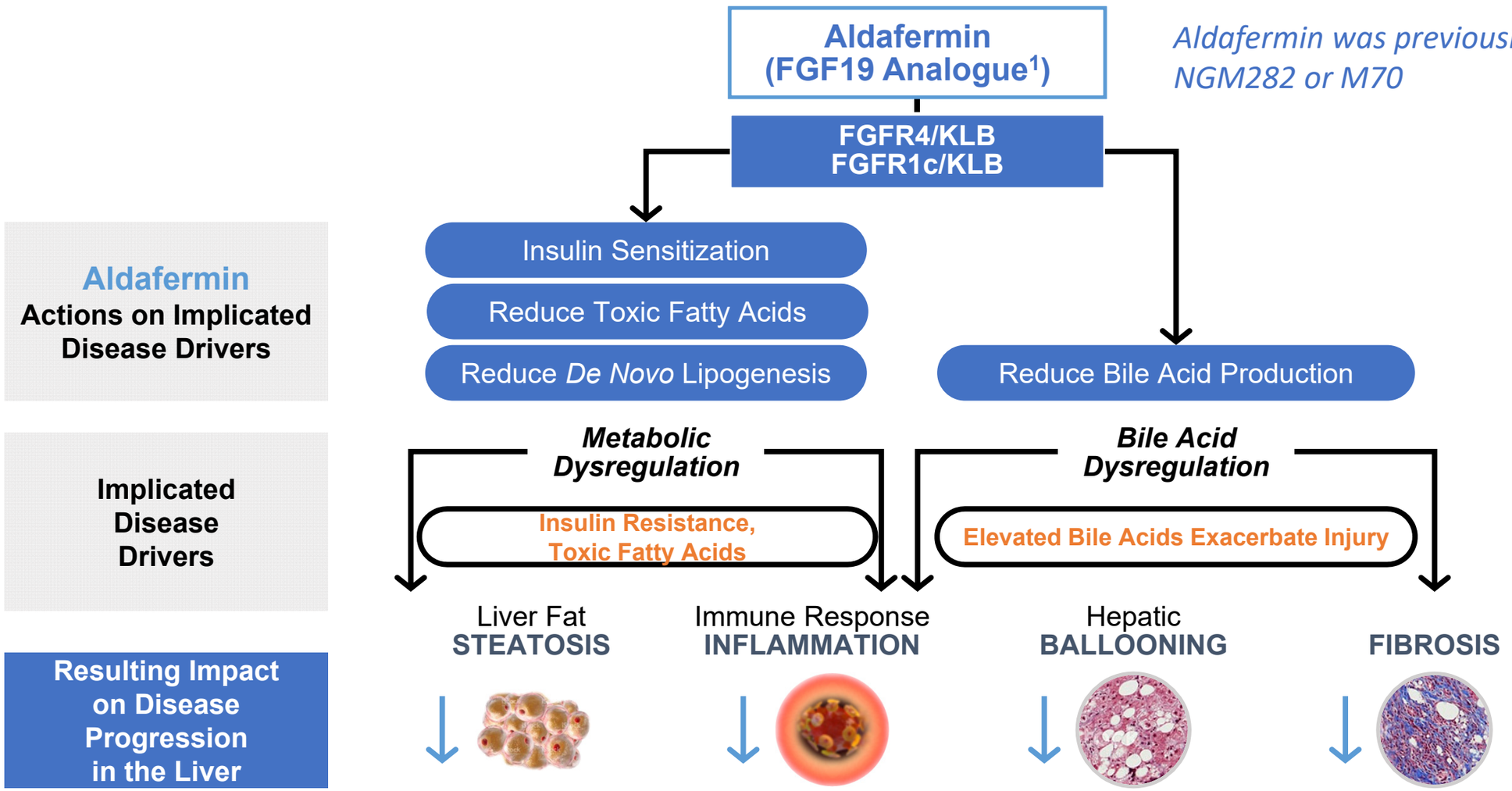
Disclosure Slide (Stephen A. Harrison)

- **Advisory Board/Consultant:** Akero, Altimmune, Arrowhead, Axcella, Cirius, Civi Biotherma, CLDF, Cymabay, Echosens, Foresite Labs, Fortress, Galectin, Gelesis, Genfit, Gilead, Hepion, Hightide Bio, Histoindex, Intercept, Kowa, Madrigal, Medpace, Metacrine, NGM Bio, Northsea, Novartis, Novo Nordisk, Poxel, Prometic, Ridgeline Therapeutics, Sagiment, Terns, Viking
- **Grant/Research Support:** Axcella, BMS, Cirius, Civi Biopharma, Conatus, Cymabay, Enyo, Galectin, Galmed, Genetech, Genfit, Gilead, Hepion, Hightide Bio, Immuron, Intercept, Madrigal, NGM Bio, Northsea, Novartis, Novo Nordisk, Pfizer, Sagiment, Second Genome, Tobira/Allergan, Viking
- **Stock/Shares (self-managed):** Akero, Cirius, Galectin, Genfit, Hepion, Histoindex, Metacrine, NGM Bio, Northsea

Aldafermin, FGF19 analogue, Impacts the Key Mechanisms of NASH Pathogenesis



[1] Kliewer et al., Dig Dis 2015;33:327-31; DePaoli et al., Diabetes 2019;68:1315-1328; Zhou et al., Hepatol Commun 2017;1:1024-1042; Zhou et al., Cancer Res 2014;74:3306-16; Zhou et al., Nat Commun 2017;8:15433; Zhou et al., J Lipid Res 2019;60:550-565; Luo et al., Sci Transl Med 2014;6:247ra100; Zhou et al., Hepatology 2016;63:914-29

Aldafermin Phase 2 NASH Program Overview

Clinical Data in Presentation

	COHORT 1	COHORT 2	COHORT 3	COHORT 4
Status	**Completed[1]**	**Completed[2]**	**Completed[3]**	**Completed**
Duration	**12 Weeks**			**24 Weeks**
Aldafermin Dose (# Patients)	Placebo (27) 3 mg (27) 6 mg (28)	0.3 mg (23) 1 mg (21) 3 mg (22)	1 mg (28)	Placebo (~25) 1 mg (~50)

KEY ENDPOINTS/ Assessment Measures

HISTOLOGY (Biopsy)

NON-INVASIVE MEASURES

STEATOSIS
% Liver Fat Content (LFC) (MRI-PDFF)

INFLAMMATION
ALT/AST (Biomarkers)

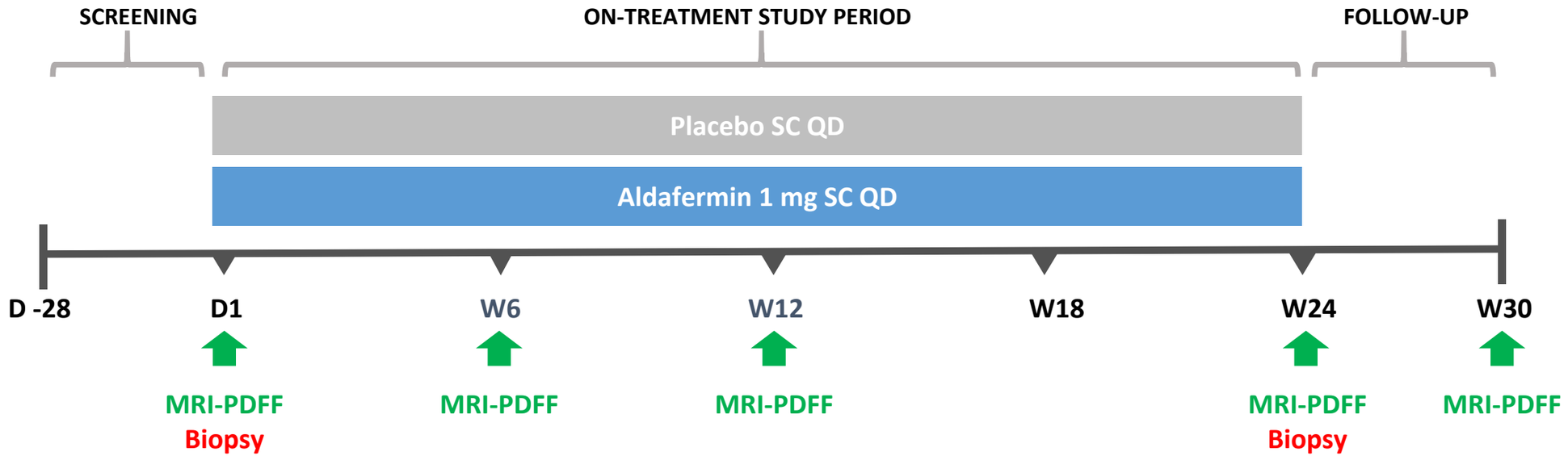
BALLOONING
ALT/AST (Biomarkers)

FIBROSIS
ELF/PRO-C3 (Biomarkers)

BILE ACIDS
C4[4] (Biomarker)

[1] Harrison et al., Lancet 2018;391:1174-1185; [2] Rinella et al., J Hepatol 2019;70:735-744; [3] Harrison et al., Hepatology. 2020;71:1198-1212; [4] C4: 7α-hydroxyl-4-cholesten-3-one

Cohort 4: A 24-Week Phase 2 Study of Aldafermin in Patients with Biopsy-Proven NASH



Safety population	N=78	Aldafermin : placebo (2:1)
Efficacy population	N=77	At least one dose and valid post-dose efficacy value
Liver histology population	N=72	Valid, non-missing biopsy at baseline and W24

- Key inclusion criteria include:
  - Biopsy-confirmed NASH with NAS ≥4 (1 point in each component); stage 2 or 3 liver fibrosis (F2 or F3 by NASH CRN criteria)
  - Absolute liver fat content (LFC) ≥8% by MRI-PDFF
  - ALT ≥ 19 IU/L in females, ALT ≥ 30 IU/L in males
- **Primary endpoint**: change from baseline in absolute LFC (as measured by MRI-PDFF) at W24
- **Secondary and exploratory endpoints** include liver histology, ALT, AST and biomarkers of fibrosis at W24
- Rosuvastatin (ROS 20 mg) started at W2 if low-density lipoprotein cholesterol (LDL-C) rise of 10 mg/dL observed

Patient Baseline Demographics and Characteristics

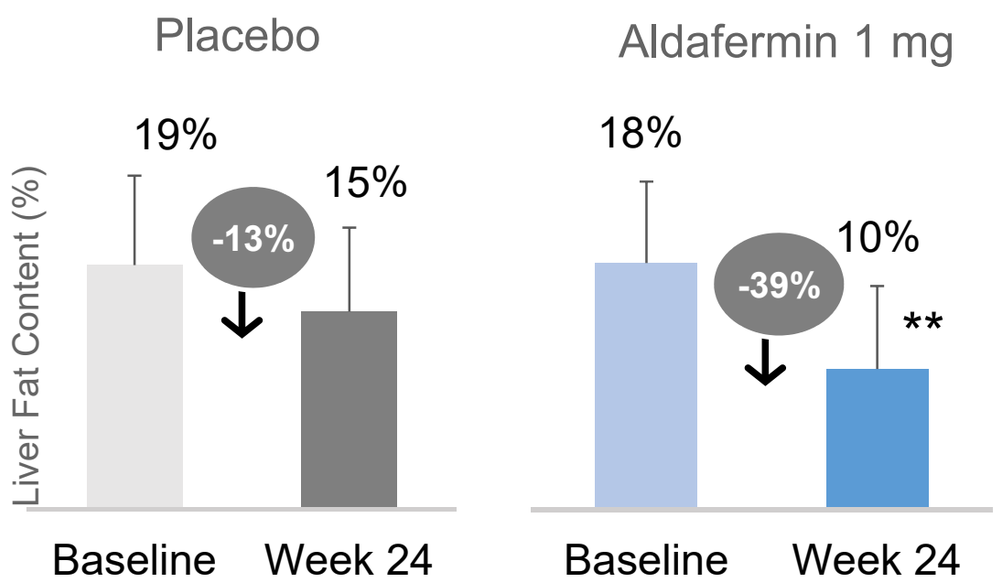
Parameters Mean (SD)	Placebo (N=25)	Aldafermin 1 mg (N=52)
Age (years)	54.1 (9.7)	53.0 (12.1)
Sex (Male/Female)	9 / 16	27 / 25
Weight (kg)	102.5 (29.7)	100.1 (21.0)
BMI (kg/m^2)	36.8 (9.0)	35.8 (6.4)
Waist (cm)	114.3 (17.0)	111.9 (15.4)
Type 2 Diabetes, n (%)	16 (64%)	31 (60%)
NAFLD Activity Score (NAS)	5.4 (1.1)	5.7 (1.1)
Fibrosis stage (F2 / F3)[1]	13 / 9	27 / 23
Liver Fat Content (% by MRI-PDFF)	18.5 (6.8)	18.0 (5.9)
Alanine aminotransferase, ALT (IU/L)	55.1 (29.6)	73.3 (39.6)
Aspartate aminotransferase, AST (IU/L)	44.3 (23.7)	54.5 (27.4)
HDL-C (mg/dL)	34.5 (16.7)	31.7 (12.5)
LDL-C (mg/dL)	95.0 (31.6)	95.1 (31.0)
Triglycerides (mg/dL)	167.7 (119.2)	194.2 (164.3)
Pro-C3 (ng/mL)	17.1 (7.0)	17.5 (8.4)

[1] Liver histology population (aldafermin n=50; placebo n=22)

Cohort 4 Primary Endpoint Met: Achieved Statistically Significant Reduction in Absolute Liver Fat Content Reduction

Cohort 4 (24W)

LFC by MRI-PDFF[1]



Liver Fat Content (LFC)

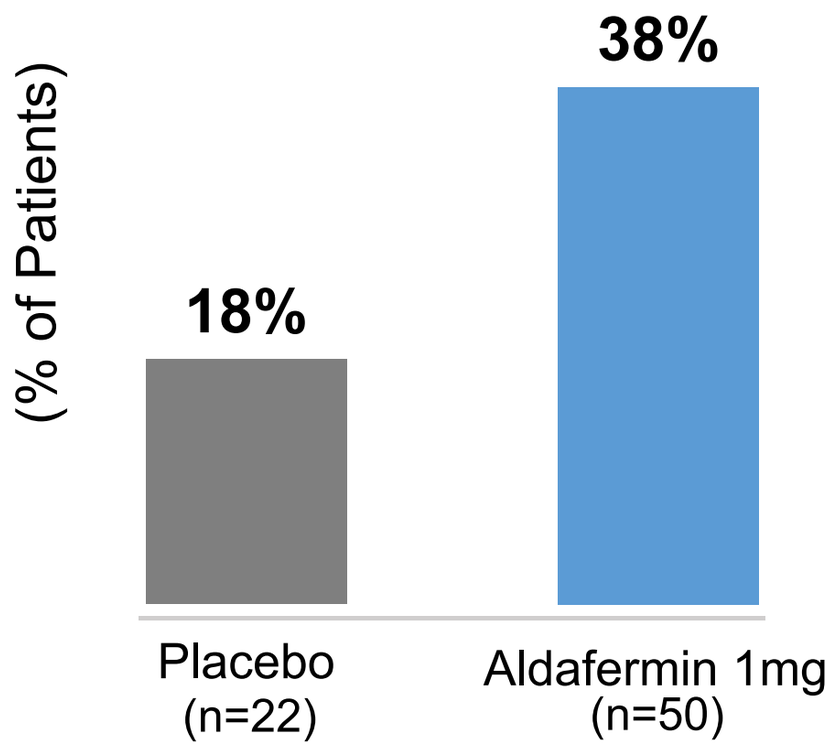
- 68% of aldafermin patients achieved ≥ 5% absolute LFC reduction *vs*. 24% placebo (P<0.001)
- 66% of aldafermin patients achieved ≥ 30% relative LFC reduction *vs*. 29% placebo (P=0.004)
- Consistent response on LFC across Cohorts 1-4

**P=0.002 *vs*. placebo

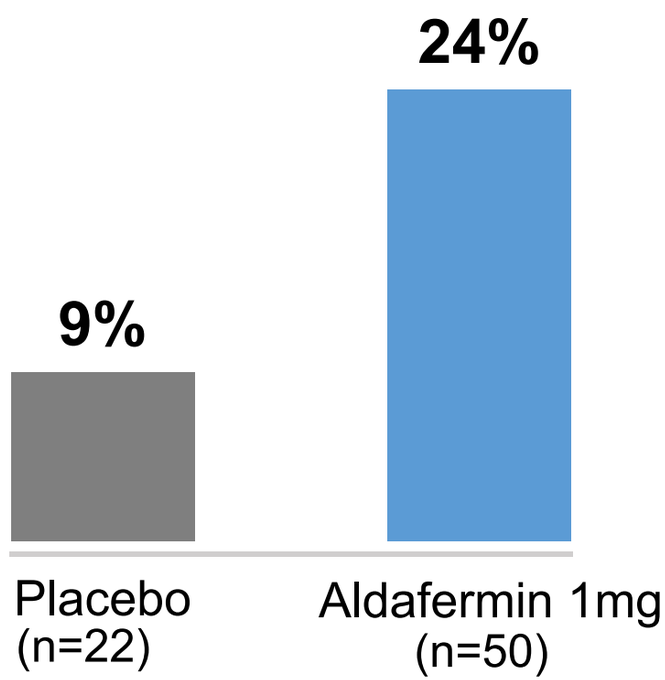
[1] Liver fat content (LFC) as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)

Cohort 4: Rapid and Consistent Improvement in Fibrosis or NASH Resolution at W24

Fibrosis Improvement ≥1 Stage with No Worsening of NASH[1]

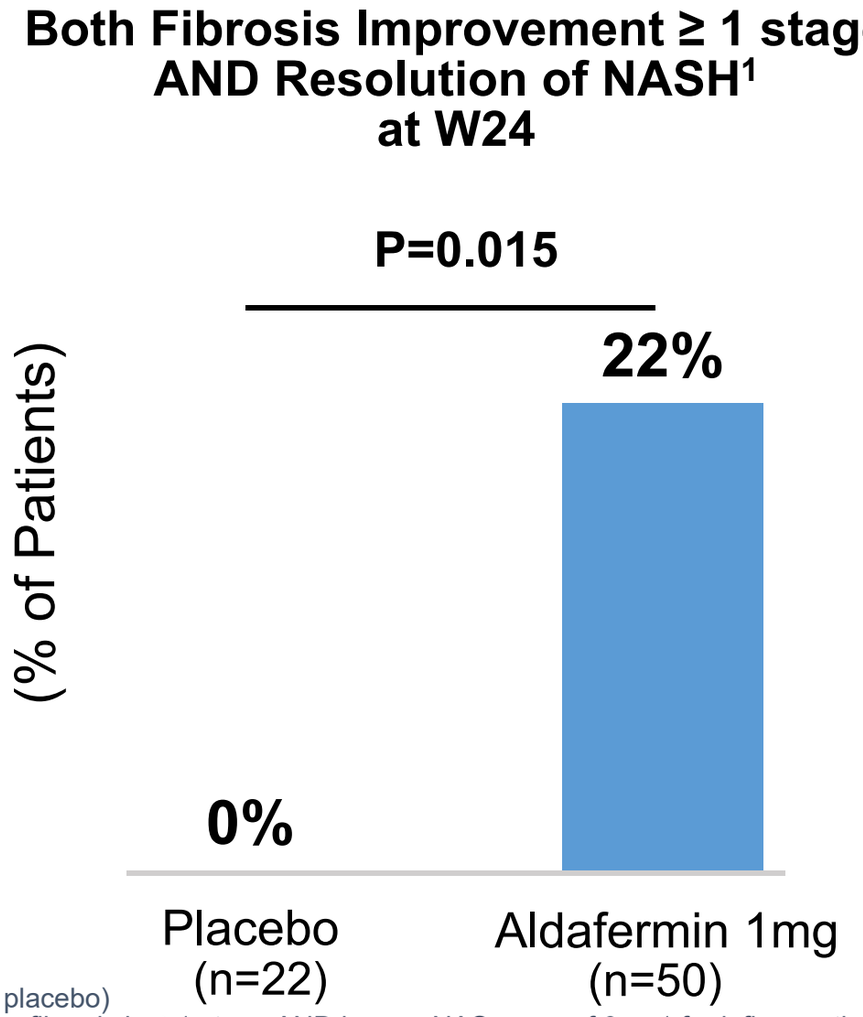


Resolution of NASH without Worsening of Fibrosis[1]



Liver Histology Population (n=50 aldafermin *vs*. n=22 placebo)
[1] Defined by CRN criteria: all biopsies were read blinded to treatment assignment and patient information

Cohort 4: Achieved Statistically Significance in Both Fibrosis Improvement AND Resolution of NASH

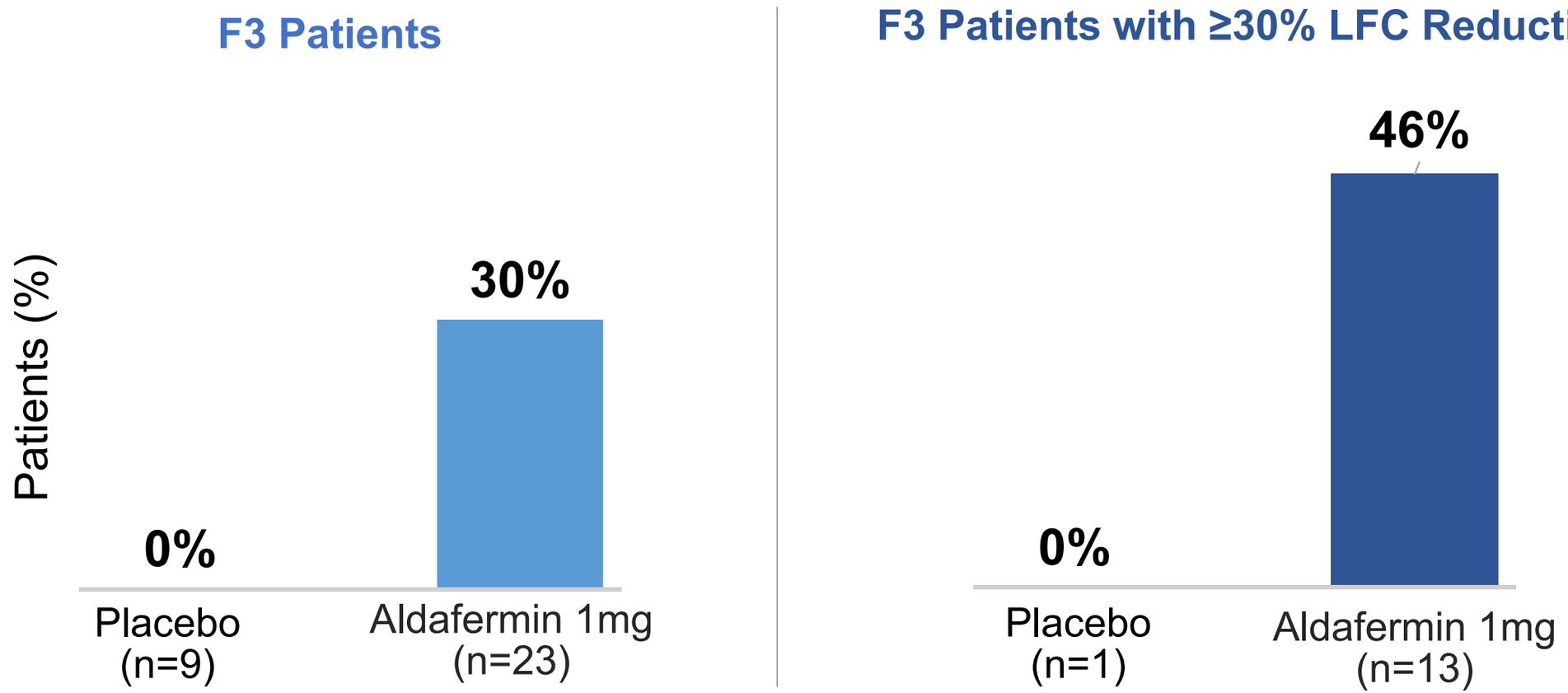


Liver Histology Population (n=50 aldafermin *vs*. n=22 placebo)

[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage AND have a NAS score of 0 or 1 for inflammation and 0 for ballooning at W24 (not powered for statistical significance);

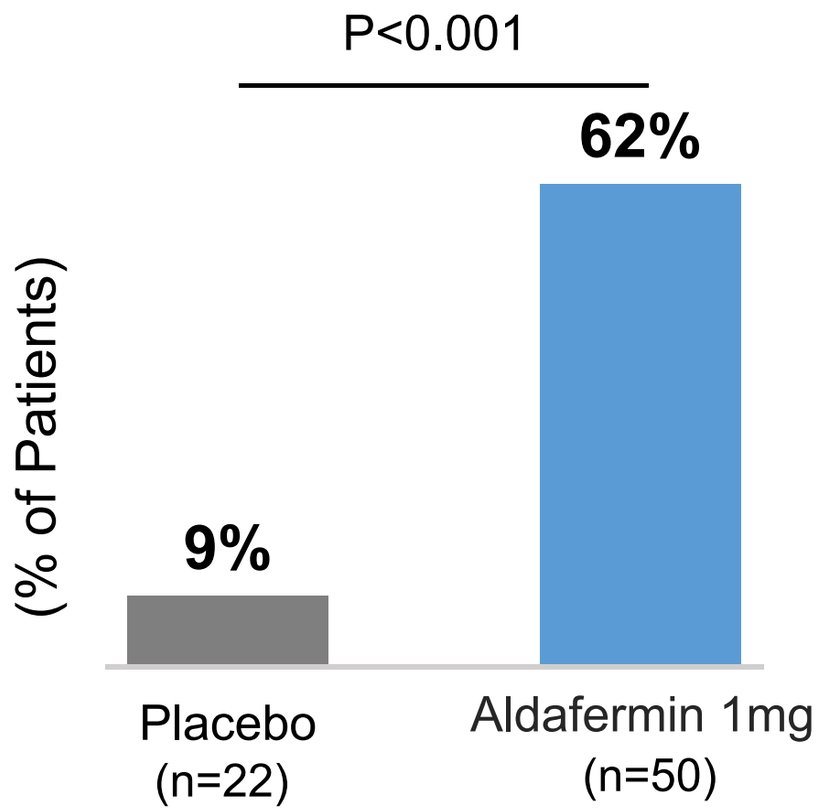
Cohort 4: Higher Fibrosis Improvement in Patients with Baseline Stage 3 Fibrosis and LFC reduction ≥ 30%

Fibrosis Improvement ≥1 Stage with No Worsening of NASH[1] at W24



[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening of NASH (no worsening of steatosis, lobular inflammation or hepatocyte ballooning grade) from baseline to W24 (not powered for statistical significance); LFC, liver fat content

Cohort 4: Statistically Significant Proportion of Patients Achieved NAS Reduction of ≥ 2 Points



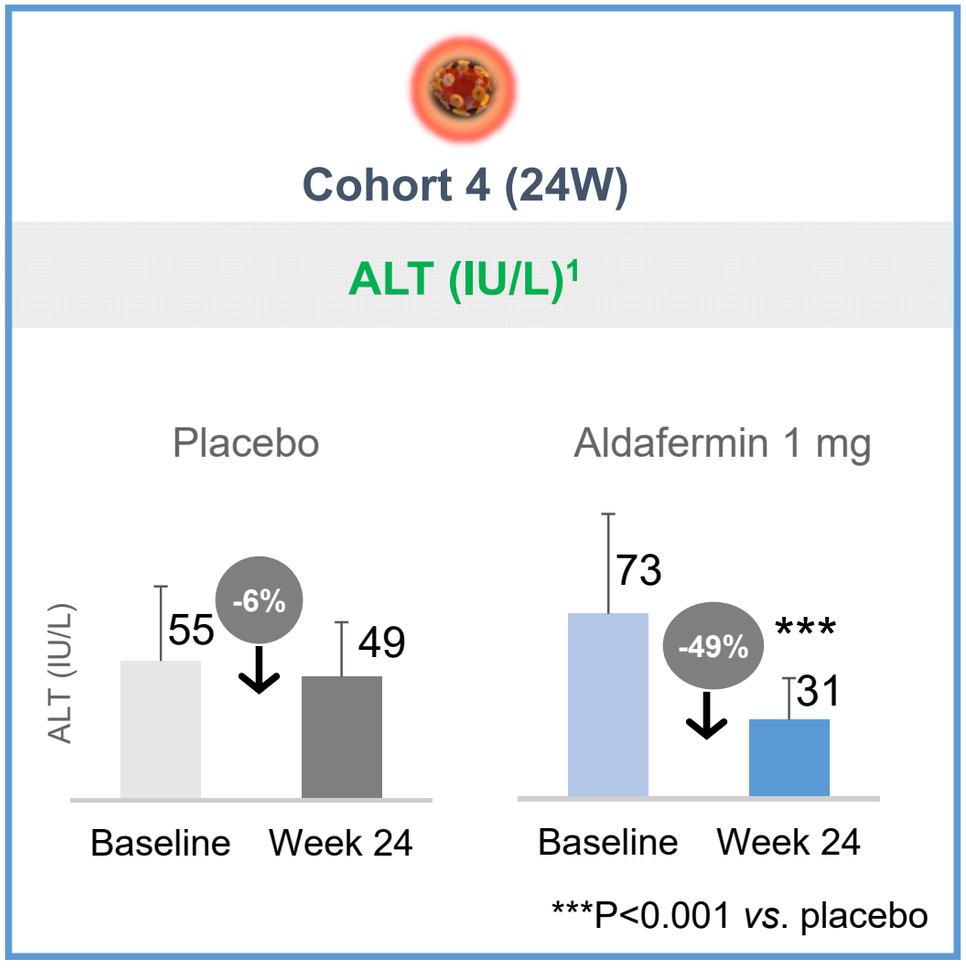
Improvement of NAS by ≥ 2 Points without Worsening of Fibrosis[1] at W24

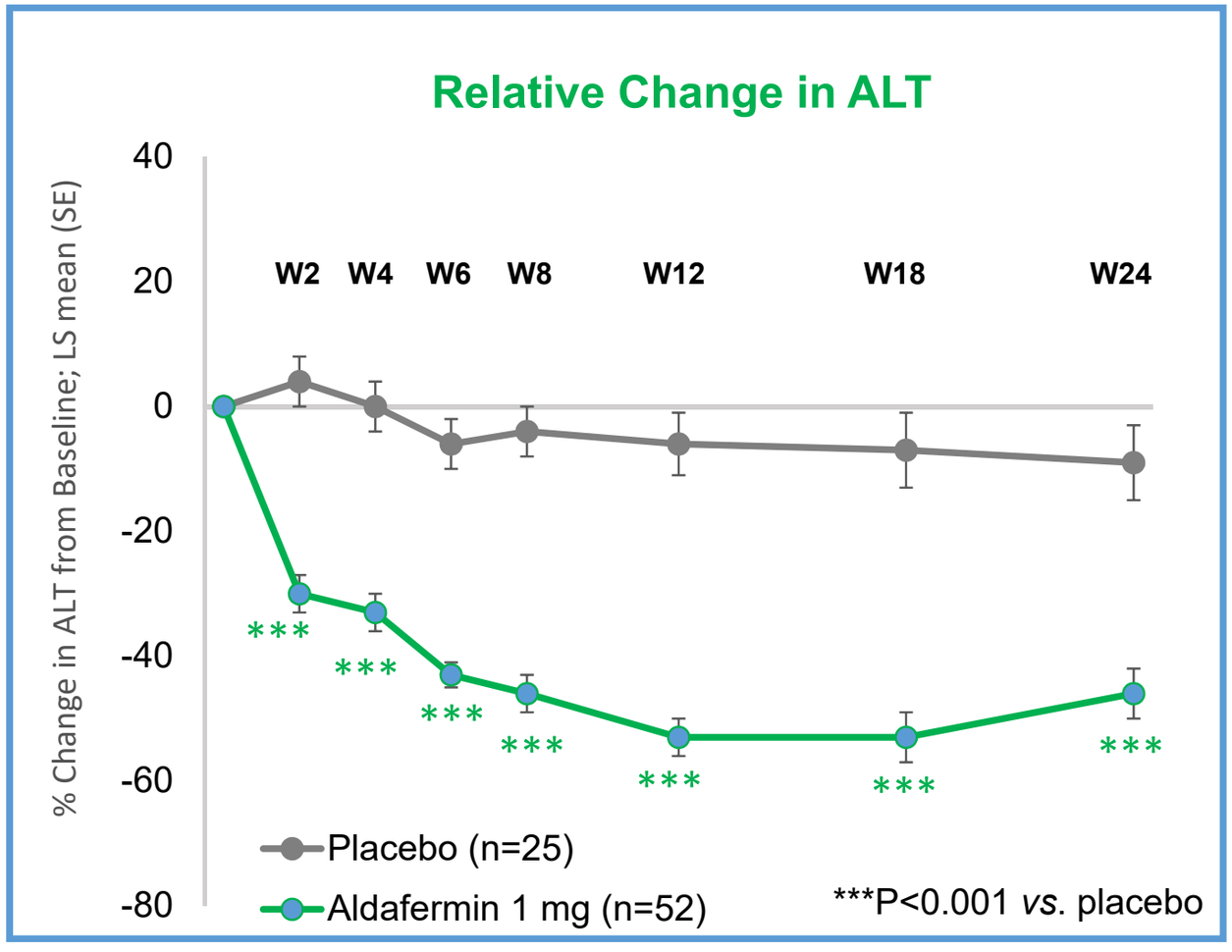
Statistically significant improvements in each NAS component of:

- Steatosis
- Lobular Inflammation
- Ballooning

Liver Histology Population (n=50 aldafermin *vs*. n=22 placebo)
[1] Defined as subjects having a NAS reduction of ≥2 points with no worsening of fibrosis (no progression of NASH CRN fibrosis stage) from baseline to W24 (endpoint not powered for statistical significance)

Cohort 4: Rapid and Sustained Decrease in ALT to Near Normal Levels with Aldafermin

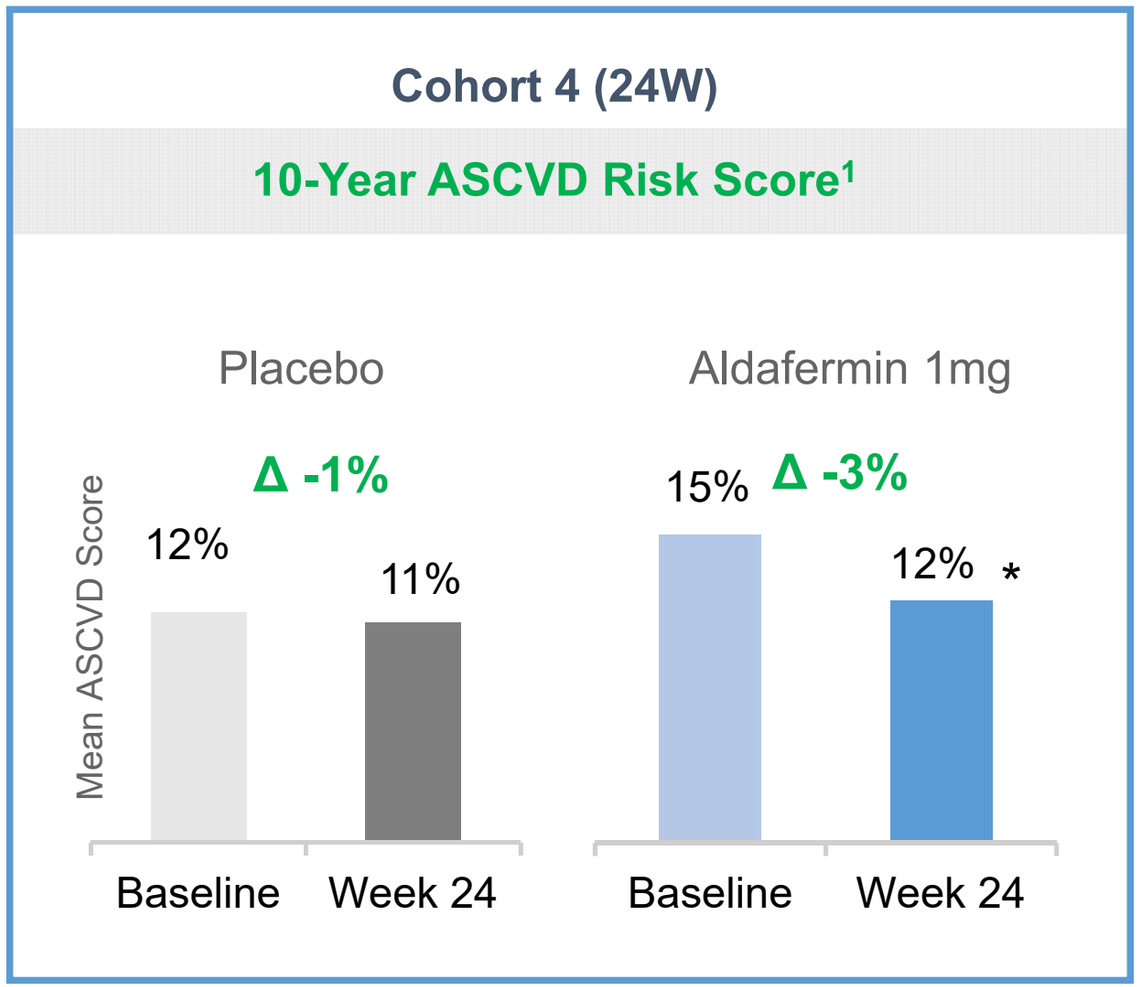




- Statistically significant reductions *vs.* placebo also observed with AST and PRO-C3

[1] Relative values are calculated as mean percent change from baseline

Cohort 4: Reduction in 10-Year ASCVD Risk Score and Optimized Lipid Management in NASH Patients



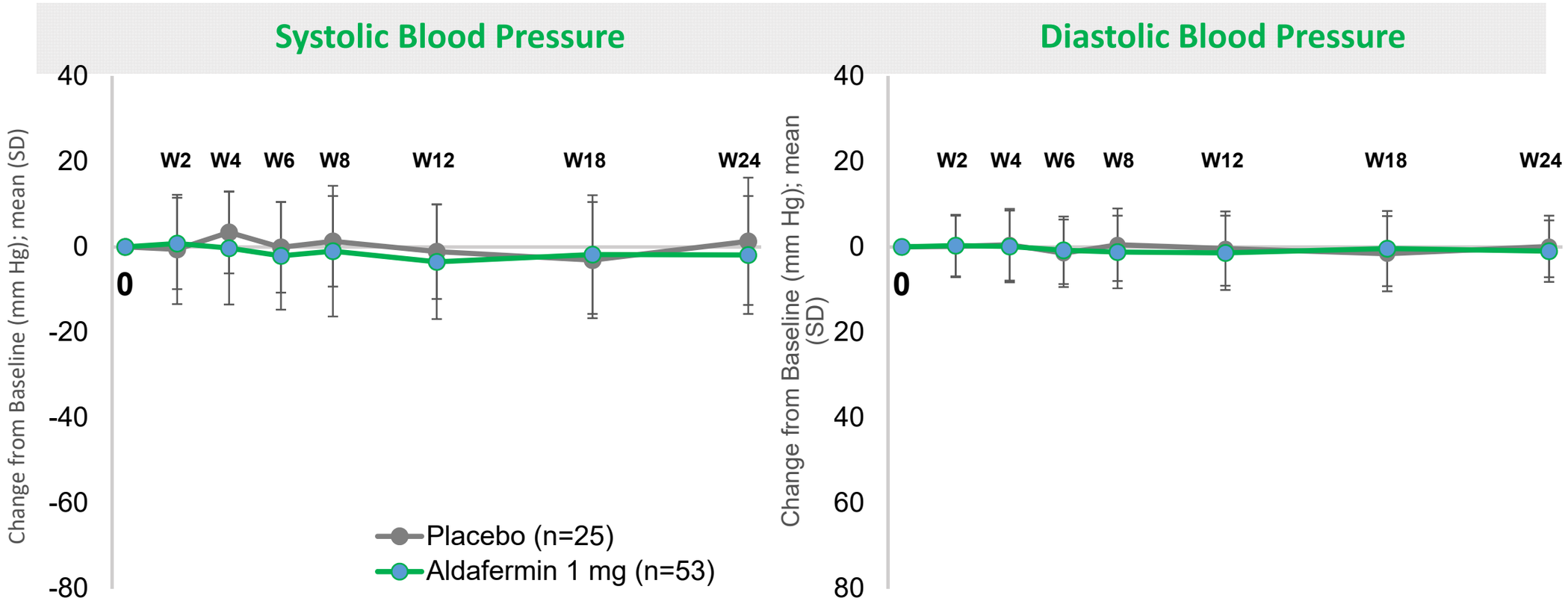
ASCVD Risk

- Optimal lipid management and reduction of ASCVD risk with rosuvastatin in this trial, including mitigating LDL increase from aldafermin
- At baseline, approx. 61% of NASH subjects had diabetes and qualified for statin use based on guidelines
- Only 32% of subjects on a statin at baseline
- In-trial lipid optimization with rosuvastatin at week 2 if LDL-C rise >10 mg/dL from baseline

*P=0.032 *vs.* placebo

[1] 10-year atherosclerotic cardiovascular disease (ASCVD) risk calculator at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

Cohort 4: No Changes in Blood Pressure or Heart Rate with Aldafermin



- No increase in heart rate with aldafermin throughout the study

Cohort 4: Aldafermin Well Tolerated and Adverse Events Generally Comparable to Placebo

TEAE Classification	Placebo (N=25)	Aldafermin 1 mg (N=53)
Any TEAE	22 (88.0%)	46 (86.8%)
TEAE Leading to Drug Withdrawal	1 (4.0%)	0
Serious Adverse Event (SAE)[1]	3 (12.0%)	2 (3.8%)
Drug-Related TEAE	11 (44.0%)	27 (50.9%)
TEAE Leading to Death	0	0

Most Common (>10%) Adverse Events	Placebo (N=25)	Aldafermin 1 mg (N=53)
Diarrhea	6 (24.0%)	15 (28.3%)
Nausea	6 (24.0%)	5 (9.4.%)
Headache	9 (36.0%)	7 (13.2%)
Fatigue	4 (16%)	3 (5.7%)
Abdominal Distension	3 (12.0%)	7 (13.2%)
Diabetes Mellitus	5 (20.0%)	2 (3.8%)
Peripheral Edema	3 (12.0%)	2 (3.8%)

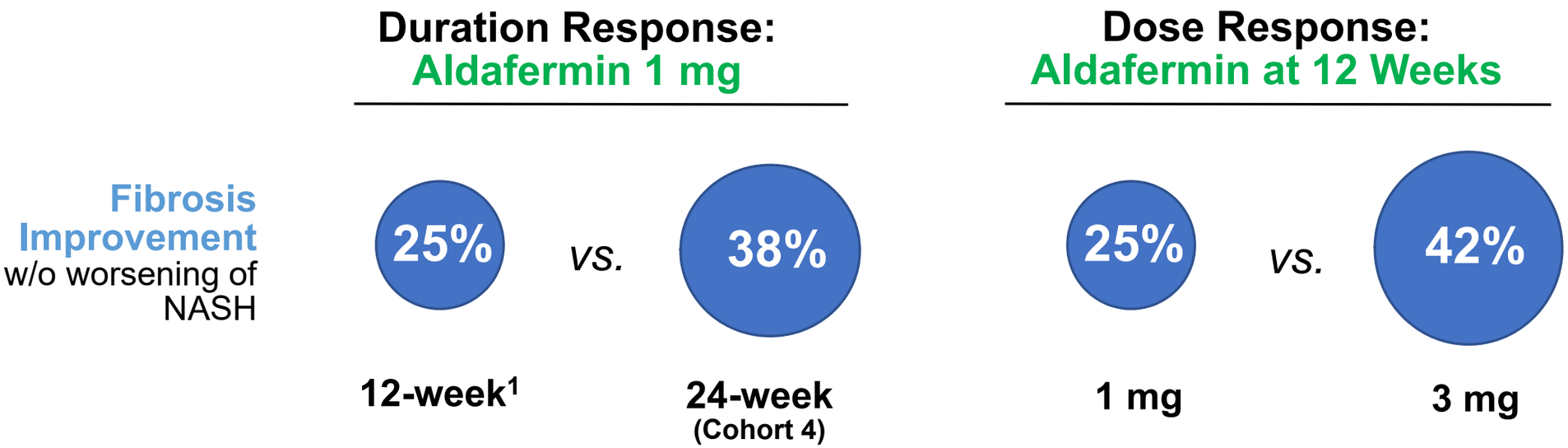
- All SAEs were deemed to be not related to treatment by site investigator

Aldafermin Safety

- No increase in gastrointestinal adverse events
- No increase in pruritus (4% aldafermin *vs*. 8% placebo)

[1] SAEs: Placebo (mental status changes; appendicitis; anxiety); Aldafermin (rectal bleeding; liver biopsy procedure-related complication)

Consistently Higher Efficacy Response Rates with Aldafermin in Both Duration and Dose Response Demonstrated in Phase 2 Trial Cohorts



Understanding of dose and duration relationship from NGM Phase 2 Trial (N=251) improves the chance of success in Phase 3

Awaiting ALPINE 2/3 trial results to understand aldafermin 3 mg response at 24 weeks (expected in first half of 2021)

Shown are % of patients achieving endpoint; [1] Harrison et al., Hepatology. 2020;71:1198-1212; Phase 2, N=251 (Aldafermin 199, Placebo 52)

Summary of Aldafermin (NGM282) Cohort 4 Results

24 Week Study of 1 mg Aldafermin *vs*. Placebo

- **Primary endpoint met**: significant reduction in liver fat content *vs.* placebo
- **Clinically significant improvements in histology regulatory endpoints**: fibrosis improvement, resolution of NASH and the composite endpoint requiring achievement of both
- Cohort 4 data suggest that the histological effects previously observed at 12 weeks are **durable and potentially amplified with extended treatment**
- **Favorable tolerability profile**: well tolerated and appears to be safe up to 24 weeks
  - ➢ most common adverse events occurred with similar frequency in placebo and aldafermin arms

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