Supplementary Appendix

Supplement to: Rinella ME, Lieu HD et al., A Randomized, Double-Blind, Placebo-Controlled Trial of Aldafermin in Patients with Nonalcoholic Steatohepatitis and Compensated Cirrhosis

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Supplementary Methods

ALPINE-4 investigators. The following investigators participated in the ALPINE-4 study and randomized at least one subject: **Australia**: Dr. Jacob George, Dr. Marc LeMire, Dr. Kate Muller, Dr. Stephen Pianko, Dr. Stuart Roberts, Dr. Marno Ryan, Dr. Marie Sinclair, Dr. Simone Strasser; **Belgium**: Dr. Christophe Moreno; **China (Hong Kong)**: Dr. Vincent Wai-Sun Wong; **France**: Dr. Victor De Ledinghen, Dr. Vlad Ratziu, Dr. Albert Tran; **Germany**: Dr. Ingolf Schiefke, Dr. Johannes Wiegand; **Poland**: Dr. Malgorzata Inglot, Dr. Krzysztof Simon; **Puerto Rico**: Dr. Grisell Ortiz-Lasanta; **United Kingdom**: Dr. Michael Heneghan; **United States**: Dr. Manal Abdelmalek, Dr. Naim Alkhouri, Dr. Victor Ankoma-Sey, Dr. Brian Borg, Dr. Donald Brannan, Dr. Michael Charlton, Dr. Kathleen Corey, Dr. Bradley Freilich, Dr. Michael Fuchs, Dr. Nadege Gunn, Dr. Stephen Harrison, Dr. Robert Jenders, Dr. Zeid Kayali, Dr. Whitfield Knapple, Dr. Anita Kohli, Dr. Kris Kowdley, Dr. Eric Lawitz, Dr. Mark Leibowitz, Dr. Cynthia Levy, Dr. Raza Malik, Dr. Fernando Membreno, Dr. Ann Moore, Dr. Guy Neff, Dr. Rashmee Patil, Dr. Mary Rinella, Dr, Aasim Sheikh, Dr. Muhammad Sheikh, Dr. Mohammad Siddiqui, Dr. Paul Thuluvath, Dr. Ziad Younes.

Liver biopsy. Liver biopsies were obtained during screening (baseline) and at week 48 (end of treatment), processed onto negatively charged slides, and stained with H&E and trichrome. 16-gauge needle or larger bore diameter were used for biopsy. The length of the liver biopsy core was > 15 mm. If the liver biopsy sample was insufficient, a repeat liver core biopsy was requested. Historical liver biopsy must be performed within 12 months of screening in order to serve as the baseline biopsy. The study central pathologist used the NASH CRN classification and assessed slides for degree of steatosis (0–3), lobular inflammation (0–3), hepatocellular ballooning (0–2), and fibrosis (0-4). The first three components were added together to determine the NAS that ranges from 0 to 8. The central pathologist conducted centralized evaluation and scoring for both baseline (for eligibility) and week 48 liver biopsies. Any unusual features were immediately reported. Biopsies were read unpaired and blinded to treatment, subject, clinical, laboratory and imaging information.

Lipid management. LDL-C levels were managed with over-encapsulated rosuvastatin/placebo by an independent medical monitor (blinded to treatment assignment) according to protocol-specified algorithm (Supplementary Figure S4). Over-encapsulated rosuvastatin or placebo were initiated at week 2, starting at 5 mg QD in statin-naïve (*i.e.,* not on statin at baseline) subjects whose ASCVD 10-year risk score is ≥7.5% (US) or ≥ moderate level risk (Europe). In subjects who are statin-naïve with diabetes or a history of myocardial infarction or stroke, or other ASCVD risk-enhancing diagnoses, rosuvastatin was initiated at 5 mg at week 2 if LDL-C is not already at the goal of ≤70 mg/dL (1.8 mmol/L). Subjects who are statin-experienced (*i.e.,* on statin at baseline), will be switched to an equivalent intensity rosuvastatin dose at Week 2. For self-identified Asians, 10 mg is considered a high intensity dose, and 5 mg is considered a moderate intensity dose. Matched placebo will be given to statin-naive study subjects who do not meet initiation criteria at Week 2 or subsequent visits. LDL-C values were further evaluated at study visit week 6, 12, 18, 24, 30, 36, and 42, in order to identify subjects who required rosuvastatin initiation or dose-escalation. Patients were allowed incremental dose titration to a maximum of 40 mg rosuvastatin daily. Subjects who do not meet rosuvastatin increase criteria will continue their prior assigned dose of over-encapsulated rosuvastatin/placebo.

Cardiovascular event definitions. An independent Cardiovascular Event Adjudication Committee comprised of experienced cardiologists adjudicated cardiovascular events in this study. Cardiovascular death includes death resulting from acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other cardiovascular causes. Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Myocardial infarction must meet one of the following criteria: 1. Detection of a rise and/or fall of cardiac biomarker values (preferable cardiac troponin [cTn]) with at least one value about the upper reference limit and with at least one of the following: symptoms of myocardial ischemia, new or presumed new significant ST-segment-T wave (ST-T) changes or new LBBB on the ECG, development of pathological Q waves on the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, identification of an intracoronary thrombus by angiography or autopsy. 2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new

ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased. 3. Percutaneous Coronary Intervention (PCI) related MI is arbitrarily defined by elevation of cTn values in subjects with normal baseline values or a rise of cTn values > 20% if the baseline values are elevated and are stable or falling. 4. Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values in subjects with normal baseline cTn values. 5. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values. Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Strokes were classified as ischemic, hemorrhagic, or undetermined. Transient ischemic attack (TIA) is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction and with symptoms that do not persist >24 hours. Coronary revascularization includes all coronary revascularization procedures ([Percutaneous Coronary Intervention] and/or Coronary Artery Bypass Grafting [CABG]) performed during the study.

Liver-related event definitions. An independent Liver-related Event Adjudication Committee comprised of experienced hepatologists adjudicated liver-related events in this study. Non-liver related death is defined as any death that is not determined to be due to a liver related cause. Liver-related death includes death resulting from a primary liver-related diagnosis, including but not limited to: liver cirrhosis, decompensated liver disease, acute liver failure, NASH-related sequela, drug-induced liver injury, death related to primary liver cancer and hepatitis. Laboratory findings, imaging results, clinical examination, hospital/clinic records, and autopsy or pathology results that are available should be consistent with the specific liver-related mode of death. Acute on chronic liver failure is defined as the rapid development of severe acute liver injury with impaired liver synthesis function and hepatic encephalopathy. Liver decompensation is defined as bleeding from gastro-esophageal varices, development of ascites and development of ascites requiring treatment (paracentesis and/or diuretic initiation), diuretic-resistant ascites (refractory ascites), spontaneous bacterial peritonitis, hepato-renal syndrome, or hepatic encephalopathy.

Hepatocellular carcinoma event definitions. An independent Hepatocellular Carcinoma Event Adjudication Committee adjudicated hepatocellular carcinoma (HCC) events in this study. HCC diagnosis is based on the 2018 Guidelines for the Clinical Management of HCC of the American Association for the Study of Liver Diseases [1]. Patients with cirrhosis and a liver nodule will be diagnosed with HCC if the nodule fulfills non-invasive radiological criteria of definitive HCC or if there is a histological confirmation of HCC after biopsy/resection. Any event that is determined by the adjudication to not meet the pre-specified definitions will be classified as a non-event.

Supplementary Tables

Supplementary Table S1. Inclusion criteria

Inclusion Criteria
1. Males and females between 18 and 75 years of age, inclusive, who are able to comprehend and willing to sign an Informed Consent Form. 2. Liver biopsy consistent with a diagnosis of NASH cirrhosis according to NASH CRN criteria and per the central pathologist evaluation. a. A historical biopsy is acceptable if tissue slides are available from within 12 months prior to Screening and are acceptable for the central pathologist evaluation. b. Liver biopsies must be consistent with cirrhosis according to the NASH CRN classification (NASH CRN fibrosis score of 4), as assessed by the central reader (see also Inclusion Criterion 4). c. NASH must be the etiology of cirrhosis (i.e., no other causes of cirrhosis; see also Inclusion Criterion 4). d. A limited number of subjects (capped at 10% of planned enrollment) with clinical diagnosis of NASH cirrhosis may be enrolled despite a NASH CRN fibrosis score of 3. Clinical diagnosis of NASH cirrhosis must meet at least one of the following: Agile 4 score ≥0.57 [2, 3], Platelet count ≤140,000/mm3 and Liver Stiffness Measure (LSM) by FibroScan® ≥13.6 kPA [4], or FIB-4 ≥3.25. 3. Criterion removed. 4. Subjects must have Definitive NASH cirrhosis as defined in Noureddin 2020 [5] as follows: a. Current biopsy shows cirrhosis with steatohepatitis. There is no evidence for a competing etiology. b. Previous biopsy showed steatohepatitis, but now with cirrhosis either by clinical history or current features, imaging, noninvasive tests, or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis, as these histological findings may have disappeared (burn-out). There is no evidence for a competing etiology. There is at least 1 coexisting or history of metabolic comorbidity to corroborate a diagnosis of NAFLD. c. Current biopsy shows cirrhosis with steatosis. There is no evidence for competing etiology. There are at least 2 coexisting or history of metabolic comorbidities, including obesity and/or T2DM to corroborate a diagnosis of NAFLD. 5. Have AFP ≤20 ng/mL at Screening. 6. Negative for hepatic lesions/nodules indicating HCC risk. 7. Subjects with T2D or insulin resistance are permitted as long as diabetic medications are reasonably stable within 3 months prior to Screening. 8. Other concomitant medications/therapies used for the treatment of coexisting conditions are acceptable, if on a stable regimen for at least 3 months prior to the Screening, except for non-statin lipid lowering agents, which can be used until Day 1 of Screening. 9. Statin use is acceptable based on the following criteria, as assessed by the investigator at Screening: a. Statin-naïve is defined as no administration of statins within 3 months prior to Screening. b. Statin-Experienced is defined as currently receiving ≤50% of the maximal approved dose of statin therapy. 10. The following additional laboratory parameters must be met at Screening a. Total bilirubin ≤1.3 mg/dL b. HbA1c ≤9.5% c. Platelet count ≥120,000/mm3 Subjects who meet the Baveno VI criteria with a platelet count >110,000/mm3 and <120,000/mm3 may be enrolled if they meet the expanded Baveno VI criteria [6] (Note: No more than 30% of the remaining population will be enrolled using the Baveno VI criteria). d. Creatinine clearance ≥60 mL/min as calculated by Cockcroft Gault equation e. Serum alanine amino transferase (ALT) levels ≤5 x ULN f. Serum aspartate amino transferase (AST) levels ≤5 x ULN g. Alkaline phosphatase ≤1.5 x ULN h. Serum albumin ≥3.5 g/dL i. International normalized ratio (INR) ≤1.7. 11. Female subjects must be either of a) non childbearing potential, OR b) if of childbearing potential, then have a negative serum pregnancy test at Screening and urine pregnancy test at the Day 1 visit prior to first dose of study drug, and must be non-lactating and non-breastfeeding. 12. Female subjects of childbearing potential and male subjects with a female partner of childbearing potential must agree to consistent and adequate birth control from Screening to End of Study (Week 54). 13. Able and willing to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

Supplementary Table S2. Exclusion criteria

Exclusion Criteria
1. Other causes of liver disease that are primary, secondary, or otherwise causes of cirrhosis or which may confound the intended patient population according to the investigator, including but not limited to alcoholic liver disease, hepatitis B, hepatitis C, autoimmune disorders, primary biliary cirrhosis, drug-induced hepatotoxicity, Wilson's disease, hemochromatosis, and alpha 1 anti-trypsin deficiency based on medical history and/or centralized read of liver histology. 2. Evidence of drug induced steatohepatitis secondary to amiodarone, corticosteroids, estrogens, methotrexate, tetracycline, or other medications known to cause hepatic steatosis. 3. History of hepatic decompensation, including variceal bleeding, ascites, or hepatic encephalopathy. 4. Prior or pending liver transplantation. 5. Child Pugh class B and C status. 6. Model of end stage liver disease (MELD) score >12. 7. Evidence of worsening liver disease (defined below) between screening visits (i.e., Day -56 and Day -42) including measures of AST, ALT, alkaline phosphatase (ALP) or total bilirubin (TBL): a. For subjects with TBL, AST, ALT, or ALP baseline levels >ULN, the second assessment should not exceed an increase of 35% over the first assessment. 8. History of porto-systemic shunt procedure 9. No evidence of gastroesophageal varices as documented by one of the following assessments: a. A historical and locally evaluated EGD obtained within 365 days of screening or b. A locally evaluated EGD conducted during the screening period. If no EGD is available, the latest EGD assessment guidelines during a global pandemic for patients with compensated cirrhosis (i.e., the expanded Baveno VI criteria, Petta 2018) [6] can be used as a replacement for the EGD to determine eligibility. Note: No more than 30% of the remaining population will be enrolled with the expanded Baveno VI criteria 10. Clinically significant cardiovascular or cerebrovascular event or new diagnosis within 6 months of Screening, including but not limited to congestive heart failure, myocardial infarction, acute coronary syndrome, revascularization, stroke (hemorrhagic or ischemic), transient ischemic attack (TIA), or implanted defibrillator or pacemaker (for uncomplicated elective, non-biventricular pacemaker procedure, 3 months post procedure will be allowed). 11. Gastric bypass or bariatric surgery in the past 5 years or planned procedure during the study period. 12. History of clinically significant unstable or untreated illness or any other major medical disorder that may interfere with subject treatment, assessment, or compliance with the protocol. 13. Documented significant weight change (± 5%) <3 months prior to Screening. 14. Screening ECG with clinically significant abnormalities that in the investigator's opinion, require evaluation and possible treatment. 15. Positive for HBsAg, anti-HIV Ab, or anti-HCV Ab plus HCV RNA. Subjects who are anti-HCV Ab-positive but HCV RNA-negative (secondary to treatment or viral clearance) are eligible with at least a 1-year period since documented sustained viral response at Week 12 post-treatment. 16. History of malignancy diagnosed or treated within 2 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ or breast ductular carcinoma in situ is allowed if appropriately treated within 2 years prior to Screening); subjects under evaluation for suspected malignancy are not eligible. History of hepatocellular carcinoma at any point regardless of treatment or treatment success will be excluded. 17. A positive drug screen (e.g., morphine, heroin, cocaine) will exclude subjects unless it can be clearly explained by a prescribed medication. 18. Significant alcohol intake as measured by a phosphatidylethanol (PEth) level ≥200 ng/mL AND significant alcohol use, as determined by the Alcohol Use Disorders Identification Test (AUDIT-C) alcohol consumption questionnaire. 19. Criterion deleted. 20. Consumption of ≥21 units of alcohol per week in males and ≥14 units of alcohol per week in females for two years prior to screening, where a "unit" of alcohol is equivalent to a 12-ounce beer, 4-ounce glass of wine, or 1 ounce shot of hard liquor. 21. Use of any prohibited concomitant medications within 3 months prior to screening. 22. History of statin intolerance, as defined by presence of significant side effects while on statins and/or inability to take or use statins for treatment. 23. Prior participation in a clinical trial of aldafermin unless previously enrolled into a placebo arm of the trial. 24. History of severe allergic or anaphylactic reactions to recombinant therapeutic proteins, fusion proteins, or chimeric, human, or humanized antibodies. 25. Participation in a study of another investigational agent within 28 days or five half-lives of the drug (whichever is longer) prior to Screening. 26. Any acute or chronic condition that, in the opinion of the investigator, would limit the subject's ability to participate, complete, and/or would confound data interpretation in this clinical study.

Supplementary Table S3. Key study endpoints

Study Endpoints
Primary endpoint: • The primary efficacy endpoint is the change in Enhanced Liver Fibrosis (ELF) score from baseline to Week 48 with aldafermin vs matched placebo. **Secondary endpoints:** • Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) • Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis • Changes from baseline in C4 and serum bile acids • Changes from baseline in Pro-C3 • Changes from baseline in ALT and AST • Changes from baseline in LSM by FibroScan® **Exploratory endpoints:** • Outcome events • NAS reduction of ≥2-point • Changes from baseline in lipids: total cholesterol, LDL-C, HDL-C, triglycerides • Changes from baseline in FIB-4

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7alpha-hydroxy-4-cholesten-3-one; ELF, enhanced liver fibrosis; FIB-4, fibrosis index-4; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measure; NAS, nonalcoholic fatty liver disease activity score; NASH CRN, nonalcoholic steatohepatitis clinical research network; Pro-C3, neoepitope-specific N-terminal pro-peptide of type III collagen.

Supplementary Table S4. Sensitivity analysis on change from baseline in ELF at week 48 in the ITT population

	Placebo (n=56)	Aldafermin 1 mg (n=42)	Aldafermin 3 mg (n=55)
Missing-at-random assumption			
ELF score	0.3 (0.1)	0.2 (0.1)	−0.1 (0.1)
Difference vs placebo		−0.1 (0.1)	−0.5 (0.1)
p value vs placebo		0.31	0.0003
Missing-not-at-random assumption			
ELF score	0.3 (0.1)	0.2 (0.1)	−0.1 (0.1)
Difference vs placebo		−0.1 (0.1)	−0.4 (0.1)
p value vs placebo		0.34	0.0022

Values are LS mean (SE).

Abbreviations: ELF, enhanced liver fibrosis; ITT, intention-to-treat; LS, least-squares; SE, standard error.

Supplementary Table S5. Sensitivity analysis on histologic fibrosis endpoint at week 48

	Placebo (n=56)	Aldafermin 1 mg (n=42)	Aldafermin 3 mg (n=55)
Missing-at-random assumption			
Fibrosis improvement of ≥ 1-stage (NASH CRN criteria)	15%	21%	23%
Difference vs placebo (95% CI)		7% (−10 to 24)	8% (−8 to 23)
p value vs placebo		*0.39*	*0.36*
Fibrosis improvement of ≥ 1-stage without NASH worsening	13%	16%	20%
Difference vs placebo (95% CI)		4% (−11 to 20)	7% (−8 to 22)
p value vs placebo		*0.54*	*0.37*
Missing-not-at-random assumption			
Fibrosis improvement of ≥ 1-stage (NASH CRN criteria)	16%	21%	21%
Difference vs placebo (95% CI)		7% (−10 to 24)	6% (−10 to 21)
p value vs placebo		*0.42*	*0.47*
Fibrosis improvement of ≥ 1-stage without NASH worsening	13%	16%	19%
Difference vs placebo (95% CI)		4% (−11 to 19)	6% (−9 to 20)
p value vs placebo		*0.56*	*0.45*
Patients who had both baseline and end-of-treatment biopsies (completers)			
Fibrosis improvement of ≥ 1-stage (NASH CRN criteria)	15%	20%	23%
Difference vs placebo (95% CI)		8% (−9 to 24)	8% (−9 to 24)
p value vs placebo		*0.38*	*0.36*
Fibrosis improvement of ≥ 1-stage without NASH worsening	13%	14%	21%
Difference vs placebo (95% CI)		5% (−10 to 19)	8% (−8 to 23)
p value vs placebo		*0.55*	*0.33*

Values are proportions of patients (%).

Fibrosis improvement was defined as ≥1-stage decrease in NASH CRN fibrosis score; no worsening of NASH was defined as no increase in NAS for ballooning, no increase in inflammation, and no increase in steatosis.

Abbreviations: CI, confidence interval; NASH CRN, nonalcoholic steatohepatitis clinical research network.

Supplementary Table S6. Change from baseline in lipids and metabolic parameters at week 48

	Placebo (n=56)	Aldafermin 1 mg (n=42)	Aldafermin 3 mg (n=55)
Lipids			
Total cholesterol, mmol/L	−0.91 (1.13)	−0.35 (0.87)	0.05 (1.27)
HDL-C, mmol/L	0.07 (0.22)	0.13 (0.23)	0.10 (0.25)
LDL-C, mmol/L	−0.99 (0.90)	−0.34 (0.79)	−0.01 (1.15)
Triglycerides, mmol/L	0.09 (1.07)	−0.30 (0.52)	−0.09 (0.79)
Metabolic parameters			
Weight, kg	−0.6 (4.9)	−2.1 (5.8)	−4.1 (7.1)
BMI, kg/m^2	−0.3 (1.9)	−0.8 (2.0)	−1.4 (2.5)
Glucose, mmol/mL	0.8 (2.7)	−0.2 (2.2)	−0.1 (3.0)
Insulin, μIU/mL	−0.1 (23.7)	6.2 (34.5)	−19.0 (50.6)
HOMA-IR	3.1 (15.7)	1.9 (16.8)	−9.4 (28.5)
HbA1c, %	0.3 (0.8)	−0.2 (1.0)	−0.1 (1.0)
Other parameters			
ALP, U/L	4.6 (18.0)	0.7 (13.0)	5.7 (19.8)
Total bilirubin, μmol/L	−0.8 (4.4)	0.2 (2.4)	−0.5 (2.8)

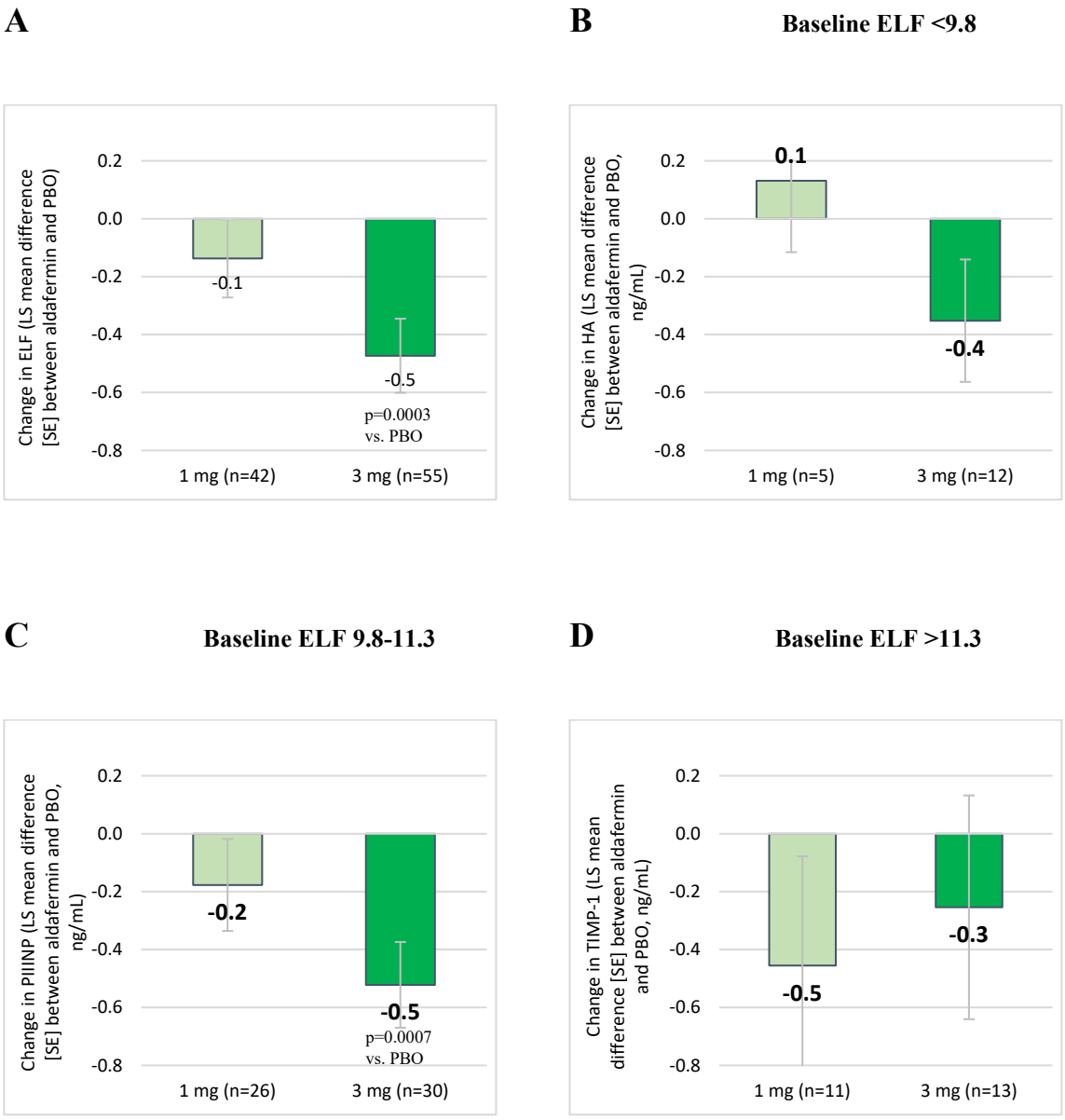
Values are mean (SD). To convert the values for cholesterol to milligram per deciliter, multiply by 38.67; to convert the values for triglycerides to milligram per deciliter, multiply by 88.57.

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment–estimated insulin resistance; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

Supplementary Table S7. Patients who had serious adverse events during the study

	Serious Adverse Event	Relatedness to Study Drug
Placebo		
Patient #1	The patient had a rectal adenocarcinoma removed endoscopically on day 311	Not related
Patient #2	The patient was hospitalized due to motor vehicle accident	Not related
Patient #3	The patient was hospitalized due to chest pain and shortness of breath	Not related
Aldafermin 0.3 mg		
None		
Aldafermin 1 mg		
Patient #1	The patient had lower respiratory tract infection	Not related
Patient #2	The patient had Covid-19 and was hospitalized	Not related
Patient #3	The patient had a fractured femur due to a fall	Not related
Patient #4	The patient had a knee surgery	Not related
Patient #5	The patient had bacterial kidney infection after treatment completion during the follow-up period	Not related
Patient #6	The patient had emesis due to arteriovenous malformation	Not related
Patient #7	The patient was diagnosed with pulmonary embolism	Not related
Patient #8	The patient had a right great toe swelling and infection following a treadmill stress test	Not related
Patient #9	The patient with a history of type 2 diabetes, hypertension and kidney stone was hospitalized for acute kidney injury after prolonged exposure to heat and dehydration	Not related
Patient #10	The patient had a four-vessel coronary artery bypass grafting procedure (adjudicated cardiovascular event)	Not related
Patient #11	The patient had a sudden cardiac death on a golf course after receiving study drug for one week (adjudicated cardiovascular event)	Not related
Aldafermin 3 mg		
Patient #1	The patient had musculoskeletal back pain and was admitted to the hospital	Not related
Patient #2	The patient had surgery to remove skin cancer	Not related
Patient #3	The patient was diagnosed with signet ring adenocarcinoma	Not related
Patient #4	The patient with a medical history of arterial hypertension experienced an event of arterial hypertension rises	Not related
Patient #5	The patient had a laparoscopic cholecystectomy	Not related

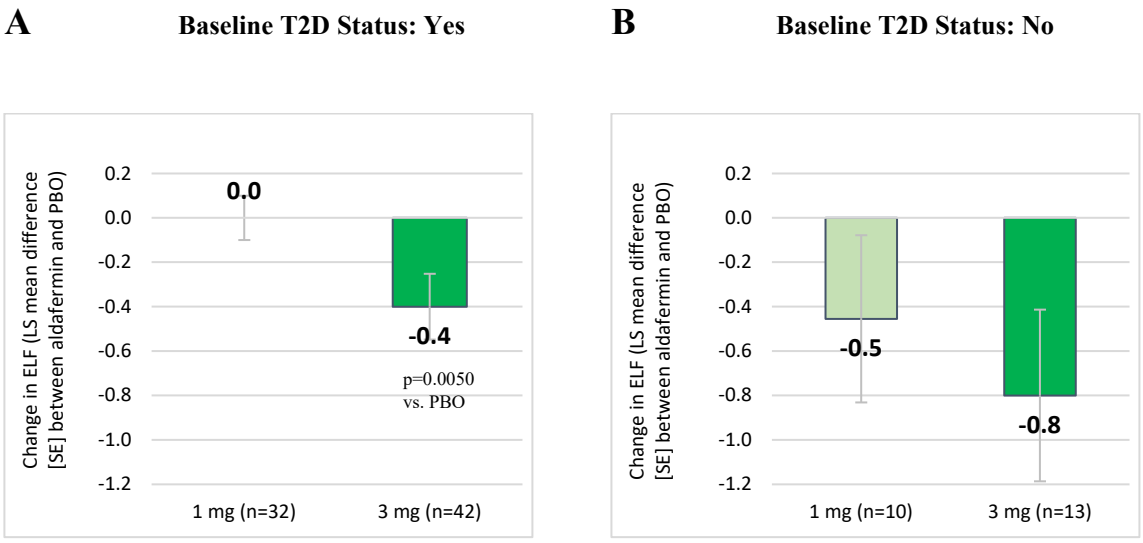
Supplementary Figures



Supplementary Figure S1. Subgroup analysis of change from baseline in ELF at week 48 by baseline ELF values

(A) Change from baseline in ELF score at week 48 in the ITT population. (B) Change from baseline in ELF score at week 48 in the subgroup of patients who had ELF<9.8 at baseline. (C) Change from baseline in ELF score at week 48 in the subgroup of patients who had 9.8≤ELF≤11.3 at baseline. (D) Change from baseline in ELF score at week 48 in the subgroup of patients who had ELF>11.3 at baseline.

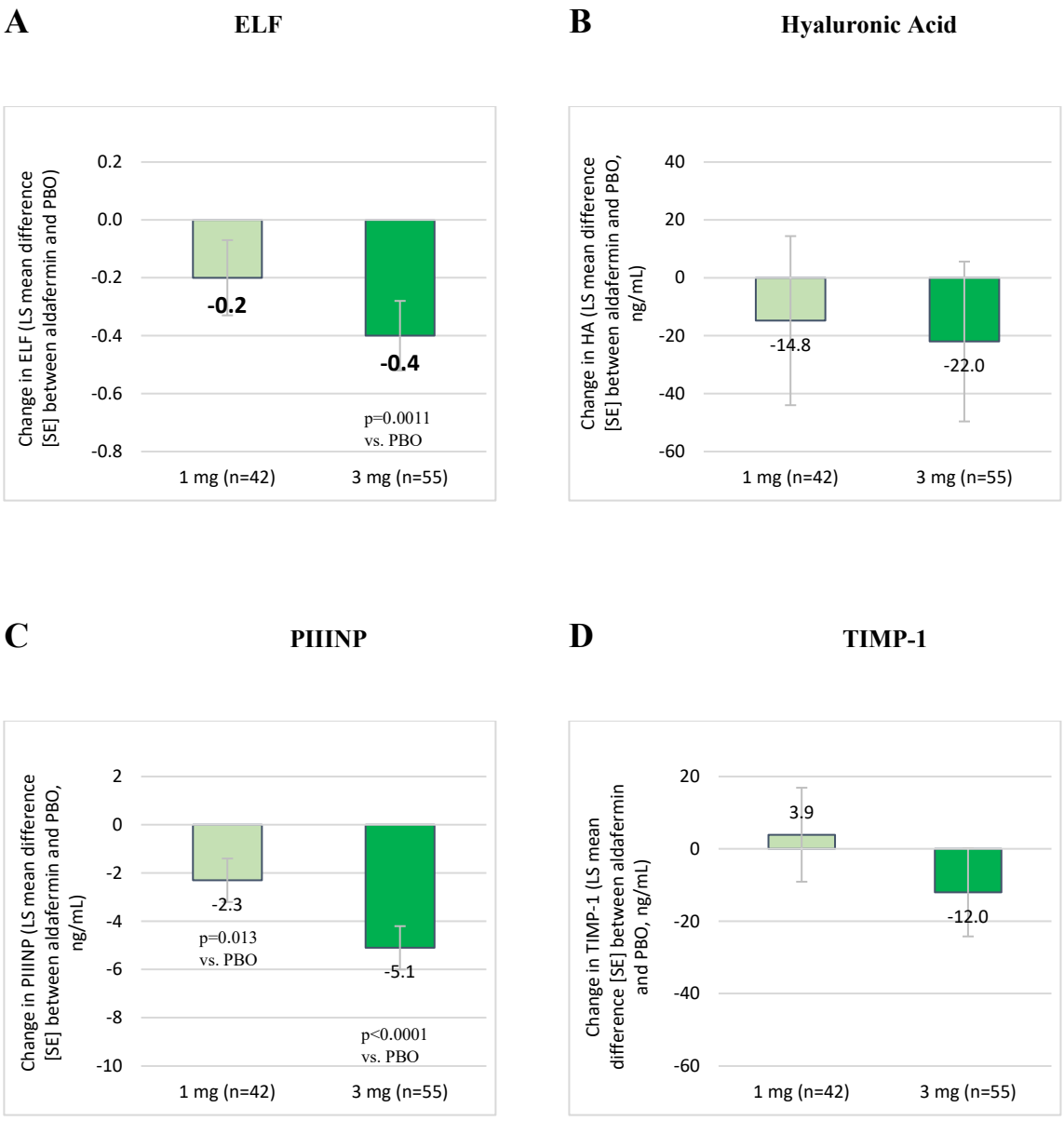
Abbreviations: ELF, enhanced liver fibrosis; ITT, intention-to-treat; LS, least squares; PBO, placebo; SE, standard error.



Supplementary Figure S2. Subgroup analysis of change from baseline in ELF at week 48 by baseline diabetes status

(A) Change from baseline in ELF score at week 48 in the subgroup of patients who had T2D at baseline. (B) Change from baseline in ELF score at week 48 in the subgroup of patients who did not have T2D at baseline.

Abbreviations: ELF, enhanced liver fibrosis; LS, least squares; PBO, placebo; SE, standard error; T2D, type 2 diabetes.

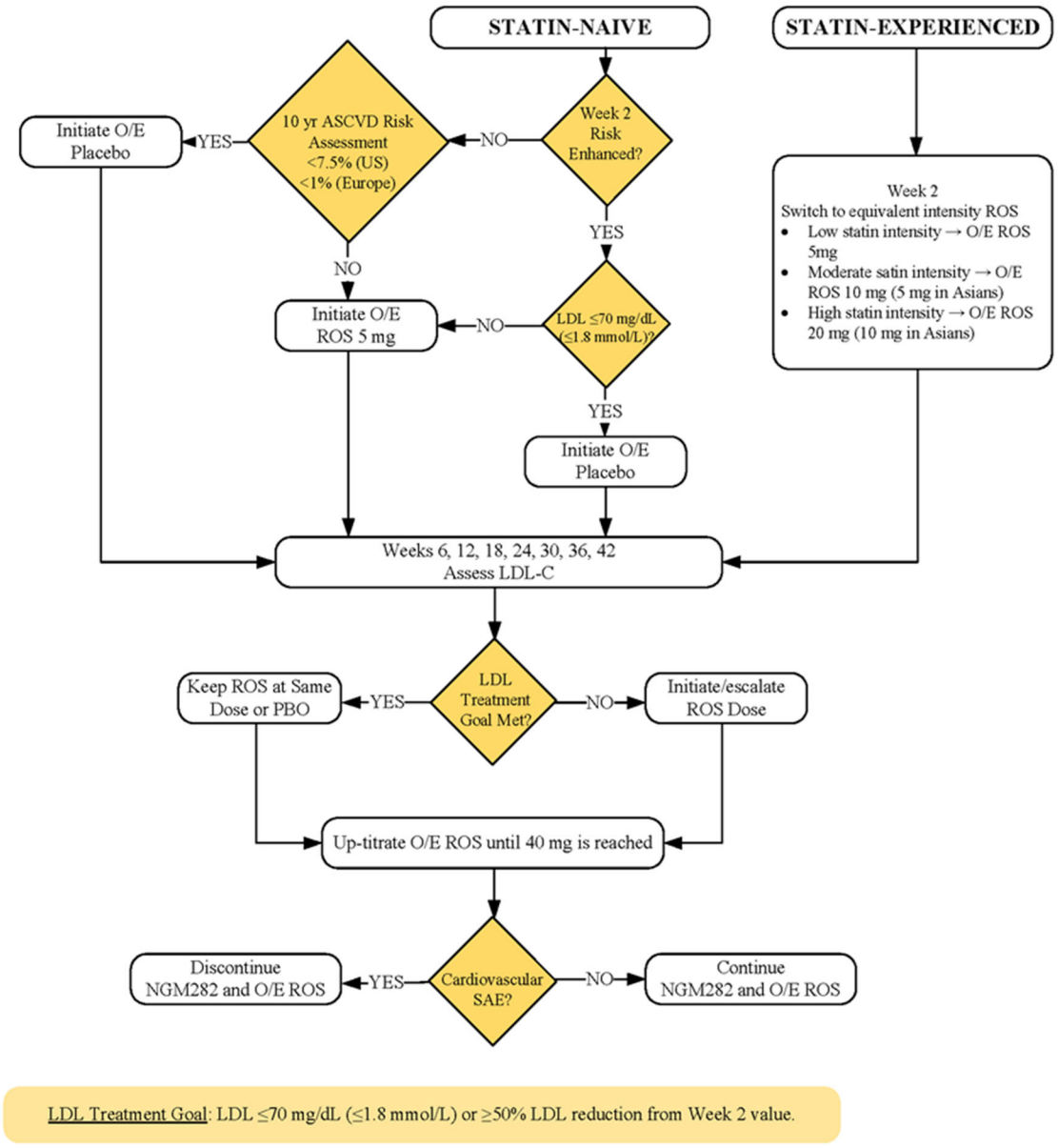


Supplementary Figure S3. Change from baseline in ELF and individual components at week 24

(A) Change from baseline in ELF score at week 24. (B-D) Change from baseline to week 24 in the individual components of ELF: HA (B), PIIINP (C) and TIMP-1 (D).

Shown are LS mean differences between the aldafermin group (1 mg or 3 mg) and the placebo group. Enrollment in the aldafermin 0.3 mg group was discontinued during trial.

ELF, enhanced liver fibrosis; HA, hyaluronic acid; LS, least squares; PBO, placebo; PIIINP, amino-terminal propeptide of type III procollagen; SE, standard error; TIMP-1, tissue inhibitor of metalloproteinase 1.



Supplementary Figure S4. Lipid management algorithm

LDL-C levels were managed with over-encapsulated rosuvastatin/placebo by an independent medical monitor (blinded to treatment assignment) according to protocol-specified algorithm.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low density lipoprotein cholesterol; O/E, over-encapsulated; ROS, rosuvastatin.

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