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Efficacy and Safety of Belapectin for the Prevention of Esophageal Varices in Patients with MASH Cirrhosis: The Randomized, Placebo-Controlled NAVIGATE Trial

Naga Chalasani[1] Raj Vuppalanchi[1], Mazen Noureddin,[2] Mitchell L. Shiffman[3], Eric Lawitz[4], Edward Mena[5] Nadege T. Gunn[6], Laura Ladron de Guevara[7], Hesham Elgouhari[8], Rifaat Safadi[9], Khurram Jamil[10], Stephen A. Harrison[11†], Naim Alkhouri[12]

[1] Indiana University School of Medicine, Indianapolis, Indiana, USA

[2] Houston Methodist Hospital and Houston Research Institute, Houston, Texas, USA

[3] Liver Institute of Virginia, Richmond, Virginia, USA

[4] Texas Liver Institute, University of Texas Health San Antonio, Texas, USA

[5] California Liver Research Institute, Pasadena, California, USA

[6] Coryell Health Medical Clinic, Waco, Texas, USA

[7] Center of Research and Gastroenterology, Mexico City, Mexico

[8] Texoma Liver Center, Denison, Texas, USA

[9] Hadassah Medical Centers of Hebrew University, Jerusalem, Israel

[10] Galectin Therapeutics, Atlanta, Georgia, USA

[11] Summit Clinical Research, San Antonio, Texas, USA

[12] Summit Clinical Research and North Shore Gastroenterology, Cleveland, Ohio, USA

[†]Deceased April 23, 2024

Address correspondence to: Naga Chalasani, MD, Indiana University School of Medicine, 702 Rotary Circle, Suite 225, Indianapolis, IN 46202. Phone: 317-274-8157; Email: nchalasa@iu.edu

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Conflicts of Interest:

Naga Chalasani consults for and received grants from Madrigal and Zydus. He consults for GSK, Altimmune, Eccogene, Akero, Chugai, Johnson & Johnson, Janssen, and insitro. He received grants from Boehringer Ingelheim. He owns stock in Heligenics and Avant Sante. Raj Vuppalanchi consults for, advises, and received grants from GSK and Takeda. He consults for and advises Cogent, Agios, Madrigal, 89bio, and Hanmi. He consults for Fortrea, Medpace, Thermo Fisher, Intercept, Ipsen, Akero, and Regeneron. He received grants from Galectin, Lilly, and Zydus. Mazen Noureddin consults for, advises, is on the speakers' bureau for, and received grants from Novo Nordisk. He consults for, advises, and is on the speakers' bureau for Madrigal and Boehringer Ingelheim. He consults for, advises, and received grants from Merck, Takeda, Terns, and Lilly. He consults for, advises, and owns stock in Akero, CytoDyn, and Altimmune. He consults for, received grants from, and owns stock in Rivus. He consults for and advises Sagimet, Aligos, AstraZeneca, Boston Pharma, and GSK. He consults for and owns stock in OPKO and HepaTx. He consults for Curve Biosciences, Daiichi Sankyo, Hepanova, HistoIndex,

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Author Contributions

Conceptualization: NC, SA trial design

Writing-original draft: NC, KJ worked with medical writer

Writing-review and editing: All authors were involved in reviewing and editing of the manuscript.

Data Sharing Statement

All relevant data from this study are reported in the manuscript or Data Supplement including protocol and statistical analysis plan. Requests for additional data should be provided to the corresponding author who will make sure that they are available and consistent with participant privacy and informed consent.

Abbreviations

AE – adverse event

CTP – Child-Turcotte-Pugh

DILI – drug-induced liver injury

EGD – esophagogastroduodenoscopy

MACE – major adverse cardiac events

MASH – metabolic dysfunction-associated steatohepatitis

MAFLD - metabolic dysfunction-associated steatotic liver disease

MELD – Model for End-Stage Liver Disease

NCI-CTCEA –National Cancer Institute-Common Terminology Criteria for Adverse Events

TEAE – treatment-emergent adverse event

TIPS – prior trans-jugular intrahepatic portal-systemic

Graphical Abstract

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ABSTRACT

Background and aims: Belapectin reduced variceal development in a subgroup of patients with MASH cirrhosis. We report the efficacy and safety of belapectin in patients with MASH cirrhosis and portal hypertension without varices at baseline.

Approach and Results: NAVIGATE was a global Phase 2b trial. Patients were randomized to intravenous (IV) belapectin 2 or 4 mg/kg lean body weight or placebo for 18 months stratified by type 2 diabetes. The primary endpoint was the incidence of varices with esophagogastroduodenoscopy (EGD) or a composite endpoint (new varices, intercurrent events or discontinuation) at 18 months with belapectin vs. placebo in the Full Analysis Set (FAS). In a pre-specified analysis, new varices were evaluated in all patients who underwent EGD at baseline and 18 months. Per Protocol population was patients treated for 18 months with EGD at 18 months. Of 357 randomized patients, 291 completed treatment. Baseline characteristics were comparable across cohorts. In the FAS, 17.8% with placebo vs. 10.1% with belapectin 2 mg/kg developed varices, a 43.2% reduction (p=0.13). In the per-protocol population (PP), varices occurred in 22.3% with placebo vs. 11.3% with belapectin 2 mg/kg, a 50% reduction (unadjusted p=0.04). Belapectin 4 mg/kg had no significant effect on variceal development. For the composite endpoint at 18 months, no significant difference was observed between belapectin 2 mg/kg (p=0.14) or 4 mg/kg (p=0.261) and placebo in the FAS. Belapectin was well tolerated with no safety signals.

Conclusion: Belapectin 2 mg/kg lowered development of new varices in MASH cirrhosis and portal hypertension.

Registered at clinicaltrials.gov: NCT04365868

INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is the progressive form of metabolic dysfunction-associated steatotic liver disease (MASLD) that is associated with obesity, type 2 diabetes, and other cardiac and metabolic disorders.[1] MASH is characterized by hepatic steatosis with inflammation and hepatocyte injury, often with progressive fibrosis that can lead to cirrhosis with its associated complications of hepatocellular cancer, end-stage liver disease, liver transplant, and death.[2] Worldwide, the prevalence of MASLD and MASH is estimated to be 30% and 5%, respectively, and the prevalence is increasing.[3-6]

Decompensated cirrhosis occurring secondary to MASH has become a leading cause of liver transplantation in the United States and worldwide.[7-9] Cirrhosis is associated with portal hypertension, which in conjunction with increased intrahepatic resistance, maintains the portal hypertensive state and leads to hepatic decompensation events, particularly esophageal varices, variceal bleeding, and clinically significant ascites and overt hepatic encephalopathy.[10] In the US population, the prevalence of clinically significant portal hypertension (CSPH) in chronic liver disease was 2.0% in MASLD, 1.3% in MASLD with alcohol consumption, and 0.35% in controls.[11] The prevention of varices and variceal bleeding is a significant unmet need in patients with MASH cirrhosis and portal hypertension.[12] The aim of treatment in patients with compensated cirrhosis is to prevent complications which define decompensation, particularly in patients with CSPH or varices. Among patients with severe cirrhosis and portal hypertension, the most common outcome within 2 years is variceal hemorrhage.[13,14] Once varices develop, the 1-year bleeding rate is about 12%, and 6-week mortality rates range from 15% to 20% for each bleeding episode.[15,16] No approved pharmacotherapies are available for treating MASH cirrhosis.

Belapectin is a complex carbohydrate, which contains oligosaccharide chains and binds to galectin-3 and to galectin-1.[17] Belapectin targets inflammatory hepatic macrophages and inhibits the galectin-3 protein, which has a role in the pathogenesis of MASH and liver fibrosis.[17-19] In animal models of liver fibrosis, belapectin consistently reduced NASH activity, fibrosis, and expression of galectin-3 in liver macrophages to reverse cirrhosis and portal hypertension.[18,19] In a Phase 1 trial in patients with advanced hepatic fibrosis without cirrhosis, belapectin was safe and well-tolerated, with evidence of a pharmacodynamic effect.[20] In a Phase 2 study of patients with portal hypertension and compensated MASH cirrhosis, belapectin 2 or 8 mg/kg lean body mass (LBM) was generally well tolerated, and produced a trend toward improved hepatic venous pressure gradient (HVPG).[21] In a subgroup of patients without esophageal varices at baseline, belapectin 2 mg/kg lean body mass (LBM) significantly reduced absolute and percent change in HVPG and reduced the incidence of new varices. In a phase 2b NAVIGATE trial, we investigated the efficacy and safety of belapectin in patients with MASH cirrhosis and portal hypertension without esophageal varices at baseline.

METHODS

Trial design

The NAVIGATE trial was a global, multicenter, randomized, double-blind, placebo-controlled study of patients with MASH cirrhosis and clinical signs of portal hypertension but without esophageal varices on endoscopy at baseline (NCT04365868). NAVIGATE study was originally designed as an adaptive, two-stage Phase2b/3 trial with a planned interim analysis at Month 18 once at least 315 subjects are enrolled (105 in each arm). An independent Data Safety

Monitoring Board (DSMB) was established to review the interim results, and based on pre-specified criteria, select a single dose to continue through the full 36-month study duration. The adaptive design also allowed for the enrollment of an additional 210–500 participants, resulting in a potential total sample size of approximately 550–1,000 participants. Following discussions with, and feedback from, the regulatory agency regarding the prespecified criteria for the interim analysis, the sponsor elected to discontinue the adaptive Phase 3 expansion. Instead, the Month 18 interim analysis was designated as the primary efficacy analysis, with the full alpha allocated to this analysis.

This study was conducted between June 2020 and December 2024 at 130 study sites in the United States, Australia, Canada, Korea, Israel, Mexico, and United Kingdom. Eligible patients were randomized 1:1:1 to belapectin 2mg/kg LBM, belapectin 4 mg/kg/LBM or placebo administered by intravenous (IV) injection over 60 minutes via a peripheral vein every other week for 18 months. Randomization was stratified by the presence of type 2 diabetes. An interactive web response system (IWRS) was used to administer the randomization schedule using SAS® software version 9.4 (SAS Institute Inc., Cary, North Carolina). Study patients, Investigators, and medical personnel were blinded to study treatment. The trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Ethical Guidelines of the Council for International Organizations of Medical Sciences, Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable laws and regulations. The trial protocol and amendments were approved by the institutional review board or independent ethics committee for each site. All patients provided written informed consent prior to any study procedures.

Participants

Men or women ages 18 to 75 years inclusive were eligible if they had evidence of portal hypertension with one of the following: 1) platelet count <150,000/mm^3; OR 2) documented hepatic venous pressure gradient (HVPG) measurement >6 mmHg; OR 3) at least two of the following: spleen size ≥14 cm (documented by ultrasound, MRI or CT scan); abdominal collateral circulation (documented by ultrasound, MRI, or CT scan or physical examination, i.e., caput medusae); documented liver transient elastography (e.g., FibroScan) ≥20 kPa or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio >1. All eligibility assessments related to portal hypertension were required to be completed within 2.5 months prior to randomization. Patients also had a history of MASH cirrhosis based on a historical liver biopsy showing cirrhosis with steatohepatitis and no evidence of hepatocellular carcinoma by imaging. Patients with type 2 diabetes were eligible if they were taking stable antidiabetic medication for at least 3 months and a screening glycated hemoglobin ≤9.5%; patients on stable regimens of vitamin E, pioglitazone or statins also were eligible. Women were eligible if they were of non-childbearing potential or not pregnant; men or women agreed to use two acceptable methods of contraception throughout and for 90 days after the study.

Key exclusion criteria included (a) esophageal, gastroesophageal or isolated gastric varices, based on an esophagogastroduodenoscopy (EGD) conducted during screening, although patients with portal hypertensive gastropathy could be enrolled; (b) history of any decompensation events including any episode of variceal bleeding, ascites, spontaneous bacterial peritonitis or overt hepatic encephalopathy; (c) prior trans-jugular intrahepatic portal-systemic (TIPS) shunt

procedure; (d) Model for End-Stage Liver Disease (MELD) score >12; (e) Child-Turcotte-Pugh (CTP) score ≥7; (f) estimated glomerular filtration rate <45 mL/min; or (g) use of non-selective beta-blockers. A complete list of inclusion and exclusion criteria is provided in the **Supplement**. http://links.lww.com/HEP/K465

Procedures

At a screening visit within 10 weeks before randomization, eligible patients underwent a complete history with vital signs (heart and respiratory rate, blood pressure, and body temperature) and physical examination, ECG, and clinical laboratory evaluations (hematology, chemistry, coagulation profile, urinalysis, specialized tests for specific liver diseases, and pregnancy test [for women of childbearing potential]). Patients were assessed for the presence of portal hypertension based on aforementioned criteria. Esophagogastroduodenoscopy (EGD) with video recording was performed to confirm the presence or absence of esophageal varices. A liver and abdomen ultrasound exam was performed to screen for hepatocellular carcinoma (HCC) and for ascites. Liver biopsy, while not required, could confirm the diagnosis of MASH cirrhosis by the central study pathologist, if necessary. The diagnosis of cirrhosis was based on Liver Forum NASH Cirrhosis Working Group criteria.[22]

Following randomization, patients underwent an EGD with video recording to assess varices at the end of Month 18 or upon early discontinuation. An independent endoscopy review expert panel reviewed all EGD records and adjudicated all assessments. Transient elastography to assess liver stiffness measurement (LSM) was done at approximately 6-month intervals. Blood samples for liver enzymes (e.g., ALT, AST, ALP, GGT), liver function and inflammatory markers (e.g., bilirubin, albumin, international normalized ratio, Pro-C3, Pro-C4, YLK-40), and

platelet count were drawn at scheduled intervals, along with routine central clinical laboratory tests for safety monitoring. Patients who discontinued early (prior to Month 18) had an Early Termination Visit (14 to 28 days after their last dose) and a final visit (End of Study Visit) 14 days after the Early Termination Visit.

All cirrhosis-related complications, as well as all-cause mortality, including major adverse cardiac events (MACE: myocardial infarction, hospitalization for unstable angina, stroke/transient ischemic attack or heart failure, drug-induced liver disease, hepatocellular carcinoma) were adjudicated by the Clinical Events Committee (CEC).

Endpoints

The primary endpoint was the proportion of patients who developed esophageal varices (composite of varices, intercurrent event, and discontinuation without an EGD/intercurrent event) at 18 months with belapectin compared to placebo in the Full Analysis Set (FAS) population. A key secondary endpoint was the proportion of patients who developed composite clinical outcomes, which was any of the following: 1) varices (esophageal or gastric) requiring treatment, 2) variceal bleed requiring hospitalization, 3) clinically significant ascites requiring hospitalization, 4) spontaneous bacterial peritonitis, 5) overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization), 6) mortality (all-cause), 7) liver transplant, 8) MELD score ≥15 on 2 consecutive occasions for belapectin compared to placebo.

Other secondary endpoints included the proportion of patients with belapectin vs. placebo who progressed to large esophageal varices or developed red wales; event-free survival by time to

first cirrhosis related clinical event, including: 1) progression to large varices or red wale markings; 2) esophageal variceal hemorrhage requiring hospitalization; 3) clinically significant ascites requiring hospitalization; 4) spontaneous bacterial peritonitis; 5) overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization); 6) CTP score increase of ≥2 points (from baseline) on 2 consecutive occasions; increase in MELD score to ≥15 on 2 consecutive occasions; 7) liver transplant; and 8) liver-related death. Agile scores were calculated from Fibroscan and clinical laboratory testing.[23-25] Improvement of portal hypertension risk category was determined using Baveno VII Guidelines where CSPH LSM ≥ 25 kPa; Probable CSPH LSM ≥20 and platelet <150 or LSM 15-20 and platelet <110; no/low CSPH LSM≤ 15 and platelet≥ 150.[27]

The key secondary efficacy endpoint (composite endpoint: any esophageal varices or intercurrent events of liver related clinical events, AE leading to discontinuation, TIPS or >12 month use of GLP-1 or NSBB) was analyzed in the FAS as a main analysis, and in the PP as supportive analyses. The cumulative incidence rate at 18 months for a treatment group was calculated as number of patients with the event / total time at risk in weeks over all patients times 18 months. The risk duration was from the first dosing date to the date of the first event. For patients with no events reported, the risk duration was from the first dosing date to the end of follow-up. The difference of the cumulative incidence rate at 18 months between 2 groups, associated 95% CI, and p-value were calculated.[26] Other secondary endpoints were analyzed descriptively.

Safety assessments included treatment-emergent adverse events (TEAEs), physical examination, vital signs (heart rate, blood pressure), 12-lead electrocardiogram (ECG), clinical laboratory testing (hematology, chemistry, urinalysis, coagulation), including assessment of drug-induced liver injury (DILI) and MACE. The safety analyses will include evaluation of the incidence of TEAEs, Grade 3 or greater AEs, serious AEs (SAEs), and TEAEs leading to discontinuation of study treatment. AEs grading will use the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Statistical analysis

Based on the Phase 2 belapectin trial,[21] the estimated annual incidence rate to develop new esophageal varices was 18% for placebo and 9% for belapectin (i.e., 50% reduction in the incidence rate compared to placebo). Thus, the anticipated proportion of patients developing new esophageal varices at 18 months was 25.7% for placebo and 13.2% for belapectin. The relative risk reduction from placebo at 18 months was anticipated to be at least 48.6% with a one-sided significance level (Type I error) of alpha=0.025. A sample size for the final analysis of 357 patients would provide approximately 70% power to demonstrate that belapectin was superior to placebo for the primary efficacy endpoint (proportion of new varices at 18 months. Evaluation of the primary efficacy endpoint utilized a composite strategy that included EGD assessments and a predetermined list of intercurrent events as the primary estimand.

The FAS population included all randomized patients; the PP/completer population included all patients who received at least one dose of study drug, completed 18 months of treatment, and had EGD at baseline and at 18 months. The safety population was all randomized patients who

received at least one dose of study drug. Key populations of interest were analyzed as pre-specified subgroup analyses, this included gender, age, BMI categories, type II diabetes, baseline LSM, and baseline platelet categories. Statistical tests were 2-sided at $\alpha = 0.05$. Two-sided 95% confidence intervals (CIs) were produced. Categorical endpoints were summarized counts as number and percentages, with 95% CI for the percentage. Time-to-event endpoints were summarized using the Kaplan-Meier (KM) method to estimate the median and 25th and 75th percentiles. Continuous endpoints with more than one post-baseline measurement were analyzed using a mixed effects model for repeated measures (MMRM) model. Unadjusted p-values comparing the proportions between each belapectin group and placebo were based on the Cochran-Mantel-Haenszel (CMH) test controlling for the stratification variable at randomization of type 2 diabetes. For the primary analysis of the primary endpoint in the FAS population, p-values were adjusted for multiple comparisons using the Step-Down Bonferroni Holm procedure, which controlled for the overall Type I error at the one-sided 0.025 significance level. All other p-values reported for subsequent analyses were unadjusted. The number and percentage of patients in the FAS who met the composite endpoint (i.e., developed esophageal varices or had intercurrent events) at 18 months were calculated by treatment group. The two-sided 95% exact binomial CIs of the proportions was calculated using the Pearson-Clopper method. The difference in proportions between treatment groups and the associated 95% CIs were estimated using the CMH method controlling for type 2 diabetes. Supportive estimands were similar to the primary estimand and included the proportion of patients who developed new esophageal varices in the FAS regardless of intercurrent events.

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This study was designed with the authors' agreement and financial support from Galectin Therapeutics. Data were collected, validated, and analyzed by Galectin Therapeutics, working with the authors. All authors were involved in the review and revisions of the manuscript. All authors had full access to the data, made final decisions about content and submission for publication, and guarantee the accuracy and completeness of the analyses. The corresponding author had full access to all data and the final responsibility to submit for publication. All authors reviewed and approved the final manuscript.

RESULTS

One thousand sixty-seven individuals were screened for participation in this study and 357 individuals meeting the eligibility were randomized to placebo (n=118), belapectin 2mg/kg (n-119), or belapectin 4 mg/kg (n=118) **(Figure 1)**. The FAS population consisted of 355 randomized participants (two patients were randomized but had baseline varices), and the PP/completer population included 287 individuals who completed 18 months of treatment. Two hundred and ninety-one randomized participants completed the study (77.6%), and the completion rate was comparable across three treatment groups **(Figure 1)**. The primary reasons for study discontinuation were adverse events in 20 (5.6%) patients and study withdrawal in 34 (9.5%) patients (**Figure 1**). Baseline characteristics were generally similar among treatment groups (**Table 1**). In the overall population, mean age was approximately 60 years, two-thirds were female, 91% were white, and 67.0% had type 2 diabetes and 72.4% had hypertension.

Efficacy

In the FAS Population, the proportion of patients with the composite primary endpoint was 47.5%, 37.8%, and 43.2% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively (**Table 2**). In the FAS Population, the incidence of new varices at 18 months was 17.8% (95% CI 10.9 % to 24.7%) with placebo, 10.1% (95% CI 4.7 % to 15.5%) with belapectin 2 mg/kg (p=0.08 vs. placebo), and 12.7% (95% CI 6.7 % to 18.7%) with belapectin 4 mg/kg (p=0.27 vs. placebo) (**Figure 2**). In the PP/completers population at 18 months, a significant reduction in new varices was observed with belapectin 2 mg/kg vs. placebo (11.3% [95% CI 5.0% to 17.7%] vs. 22.3% [95% CI 13.9% to 30.8%], p=0.04), but the difference was not statistically significant for belapectin 4 mg/kg vs. placebo (13.5% [95% CI 6.7% to 20.4%] vs. 22.3% [95% CI 13.9% to 30.8%], p=0.13) (**Figure 2**). Further, in the PP population, non-diabetic patients showed a greater reduction in new varices (belapectin 2 mg/kg: 12.1%, belapectin 4 mg/kg 19.4% vs. placebo: 29.4%, n=70), although interpretation is limited.

For the key secondary endpoint (new varices, intercurrent events, or discontinuation), no significant difference was observed at 18 months between belapectin 2 mg/kg (p=0.14) or belapectin 4 mg/kg (p=0.261) and placebo in the FAS Population (**Table 3; Supplemental Figure 1, http://links.lww.com/HEP/K465**). Furthermore, no significant differences were observed between belapectin and placebo in the incidence of intercurrent events (**Supplemental Figure 1; http://links.lww.com/HEP/K465 Table 3**). In the PP population at 18 months, the incidence of adjudicated events was generally comparable among treatment groups, although 7 (7.1%) of those on belapectin 4 mg/kg vs. 3 (3.1%) on belapectin 2 mg/kg, and 4 (4.2%) on placebo experienced any event (**Supplemental Table 2, http://links.lww.com/HEP/K465**).

In the FAS population, the incidence of medium varices (>5 mm diameter, <one-third of lumen) was 33.3%, 8.3%, and 33.3% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively. The majority were small varices, 61.9%, 83.3%, and 66.7% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively. In the PP/completers population, the incidence of medium varices (>5 mm diameter, <one-third of lumen) was 7.4%, 1.0%, and 4.2% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively (**Supplemental Figure 2, http://links.lww.com/HEP/K465**). Among those with new varices at 18 months, no large varices were observed with belapectin, and 10 of 11 (90.9%) patients treated with belapectin 2 mg/kg had small varices. Thus, the difference in overall incidence of new varices was driven by a clinically meaningful reduction in medium and large varices.

Evaluation of Key Markers of Fibrosis

In the FAS population, mean (SD) percent change from baseline at 18 months for liver stiffness (kPa) was 1.8 (47.3) for placebo and -6.3 (39.1) and -4.5 (37.3) for belapectin 2 mg/kg and 4 mg/kg, respectively (**Figure 3**). Similar findings were observed in the PP/completers population with a mean (SD) percent change from baseline 1.7 (46.8), -8.4 (38.3), and -5.0 (38.1) with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively. Fewer patients in the PP/completers population with belapectin had worsening of LSM (≥30% increase from baseline [p=0.03] or ≥5 increase [p=0.09] in kPa) with belapectin compared with placebo (**Figure 3**). Categorical analysis of LSM in the FAS and PP/completers populations showed improvement with belapectin vs. placebo overall and mean change and categorical analysis by region of study.

After 18 months, belapectin 2 mg/kg shifted patients toward lower-risk Baveno VII categories (**Figure 4**).[27] In the portal hypertension group, rates declined from 33.3% to 25.9% with belapectin versus 34.2% to 32.9% with placebo. Importantly, the no/low-risk category increased from 42.0% to 56.8% with belapectin versus 44.7% to 51.3% with placebo. At 18 months compared to baseline, a greater proportion of belapectin-treated patients improved to the no/low-risk category vs. placebo (p=0.0073). In the FAS and PP populations, a slightly lower number of belapectin-treated patients compared to placebo had ≥0.5 increase in ELF at 18 months, but in high risk patients i.e. those with clinically significant portal hypertension at baseline, greater number of subjects had an increase in ELF at 18 month, 42.9% with placebo and 31.0% with belapectin 2 mg/kg (**Figure 4**). AGILE-4 also favored belapectin: in the PP/completers population, 47% more patients experienced ≥20% progression with placebo (16.9%) compared with belapectin 2 mg/kg (11.5%) after 18 months (**Supplemental Figure 3, http://links.lww.com/HEP/K465**).

Safety and Tolerability

The incidence of TEAEs was 94.9%, 97.5%, and 96.7% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively and of drug-related TEAEs was 23.7%, 23.5%, and 26.7% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg, respectively (**Table 4**). Infusion procedure-related TEAEs occurred in 44 (12.3%) patients, and TEAEs caused study drug discontinuation in 30 (8.4%) patients, although the incidence was 10% with belapectin 4 mg/kg. The incidence of Grade 3 or greater TEAEs was 21.2%, 31.1%, and 30.8% with placebo, belapectin 2 mg/kg, and belapectin 4 mg/kg. The most common TEAEs were gastrointestinal disorders in 227 (63.6%) patients, infections in 272 (76.2%) patients, and musculoskeletal in 156

(43.7%) patients. The most common treatment-related AEs were diarrhea (19 patients, 5.3%), fatigue (14 patients, 3.9%), headache (10 patients, 2.8%), and pruritus (11 patients (3.1%). No drug-related or infusion-related serious AEs occurred.

The incidence of treatment-emergent serious AEs was similar across treatment arms, and one patient in each treatment group discontinued the study due to death. MACE occurred in one patient with placebo, one patient with belapectin 2 mg/kg, and three patients with belapectin 4 mg/kg arm at 18 months. A prolonged QT interval was recorded in 2 (1.7%) patients in each treatment group.

No adjudicated events of drug-induced liver injury occurred. An evaluation of drug-induced serious hepatotoxicity (eDISH) plot of peak total bilirubin vs. peak ALT showed the majority of patients remained within the normal range (**Supplemental Figure 4, http://links.lww.com/HEP/K465**). One (0.8%) patient in each treatment group experienced a myocardial infarction or hospitalization for unstable angina, and two (1.7%) patients in the belapectin 4 mg/kg group experienced a stroke or transient ischemic attack.

DISCUSSION

While a numerically lower incidence of varices was observed in belapectin 2 mg/kg compared to placebo in the FAS population, no statistically significant differences were observed for the overall composite primary endpoint, although significant differences between belapectin and placebo were observed for other endpoints. In the PP population, belapectin 2 mg/kg

demonstrated a significant and meaningful reduction in the development of new esophageal varices in patients with MASH cirrhosis and portal hypertension, confirming prior findings.[21]

Among completers in the PP population, a statistically significant reduction in the incidence of varices at 18 months was observed with belapectin 2 mg/kg. In addition, significantly more patients in the placebo group showed progression in liver stiffness based on an increase in of greater than 30% or greater than 10 kPa increase from baseline, although the clinical significance of a 6.3% relative reduction is uncertain. Improvement in non-invasive markers, i.e., liver stiffness and ELF provide supportive evidence showing a lower incidence of disease progression with belapectin 2 mg/kg compared to placebo. Liver stiffness is recognized as an independent predictor of complications and mortality in patients with chronic liver disease.[28-31] A >10 kPa increase from baseline in LSM was a marker of increased risk for liver-related events,[28,31] and others have identified >30% increase from baseline in LSM as a predictor of disease progression in chronic liver disease.[29,32] Results from this study demonstrated lower rates of worsening in liver stiffness using these thresholds. Each incremental increase in ELF predicted an increased rate of hepatic decompensation and liver-related mortality.[33] Increased all-cause mortality and decompensation were associated with an ELF ≥13. An ELF score ≥9.8 was independently associated with progression of advanced fibrosis, and a 4.3-fold increased risk of progression occurred with each incremental increase in ELF score.[34] Similarly, the ELF score strongly correlated with the risk of liver-related events, and a 5-fold higher risk of developing a liver-related outcome occurred at a threshold score ≥11.3.[35,36] Improvements from baseline were observed in the risk of portal hypertension at Week 78.

Belapectin 2 mg/kg and 4 mg/kg were safe and well tolerated. No suspected unexpected serious adverse reactions (SUSARs) and no drug-related serious AEs were reported. No cases of adjudicated drug-induced liver injury (DILI) were observed, and no patients met criteria for Hy's Law. A numerically higher proportion of patients in the placebo arm than in each of the belapectin arms had ALT/AST levels outside the normal range. No difference between placebo and belapectin was noted in the incidence of major cardiovascular adverse events (MACE). No cases of anaphylactic reactions were reported, and no differences in the incidence of TEAEs from QT prolongation were observed.

This study failed to show a statistically significant difference between belapectin and placebo for the primary endpoint. Since the study did not meet its primary endpoint, all per-protocol analyses are reported using nominal p-values. This could be attributed to fewer recorded varices than expected. A mid-study sample size re-estimation was based on the composite endpoint rather than the incidence of varices. The study also had a shorter treatment duration, with the primary analysis at 18 months rather than the planned 36 months. NAVIGATE enrolled sicker patients with a higher baseline rate of CSPH than some of the other recent MASH cirrhosis trials, yet the duration of treatment was shorter, i.e., 18 months instead of 2 years, as observed in other studies, suggesting that a longer duration of treatment is required to show meaningful efficacy in this population. A higher study discontinuation rate (18.3% observed vs. 10% expected) occurred, which mostly occurred during first 4 months of the study and was attributed to COVID. Notably, discontinuations were more frequent with placebo compared to belapectin.

Based on findings from preclinical and clinical trials to date, belapectin likely demonstrates target-mediated drug disposition.[21] Once galectin-3 binding sites within macrophages are saturated, additional drug molecules do not enhance efficacy. Higher doses may exceed the macrophage-specific uptake mechanisms, resulting in altered drug distribution and clearance. Higher drug concentrations were associated with reduced efficacy,[21] where patients receiving belapectin 8 mg/kg achieved a higher exposure but exhibited lower pharmacodynamic effects. Belapectin 2 mg/kg demonstrated the most consistent and optimum efficacy response. Similar PK-PD effects were observed in the current trial as well as the earlier trial with belapectin.[21]

Variceal bleeding is major cause of morbidity and mortality in those with cirrhosis, and each subsequent episode of variceal bleeding is associated with a mortality rate of up to 20%. Patients who experience active variceal bleeding have a 60% to 70% risk of a recurrent episode within 1 year.[37] The highest mortality rate occurs among patients with decompensating complications (95.2%), variceal bleeding (83.2%) and ascites (44.9%).[38] The mortality rate from acute variceal hemorrhage ranges from 15% to 25% at 6 weeks.[39]

The MASH-related cirrhosis clinical development program for belapectin targets a population characterized by compensated liver cirrhosis with clinical signs of portal hypertension but excluding patients with CSPH and esophageal varices. Focusing on the prevention of esophageal varices in the early stage of portal hypertension allows for a relevant clinical endpoint that is already integrated in clinical practice as part of the routine surveillance of patients with cirrhosis. This strategy also is consistent with the mechanism of action of belapectin, which targets activated liver parenchymal macrophages but is not expected to have an effect on the splanchnic

veinous dynamic tone. While the benefit of belapectin was most apparent in the numerically lower number of medium or larger varices compared to placebo, prevention of small varices was also clinically relevant, and these patients may benefit from treatment with non-selective beta-blockers to prevent future episodes of decompensation, which is important in managing patients with portal hypertension.[40,41] The presence of small esophageal varices was associated with a higher risk of decompensation than no varices over a median of 36 months (hazard ratio 4.7, p=0.015), even with no short-term difference in the risk of variceal bleeding.[42] These data demonstrate that small esophageal varices are a key factor in disease progression and decompensation events, and is an important clinically meaningful endpoint in the management of patients with CSPH.

In summary, while the primary endpoint was not achieved, the observed reduction in the incidence of new esophageal varices suggest a benefit of belapectin in preventing progression of liver disease. Treatments for variceal bleeding include endoscopic procedures and medications, but no medications are specifically approved for preventing varices or reducing the risk of bleeding in MASH cirrhosis.[12] The distinct mechanism of action along with favorable safety profile further strengthen case for future development of belapectin as treatment options for patients with MASH cirrhosis and portal hypertension. Findings from this trial will be used in the design of future studies of belapectin for MASH cirrhosis and portal hypertension.

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Figure 1. Patient disposition

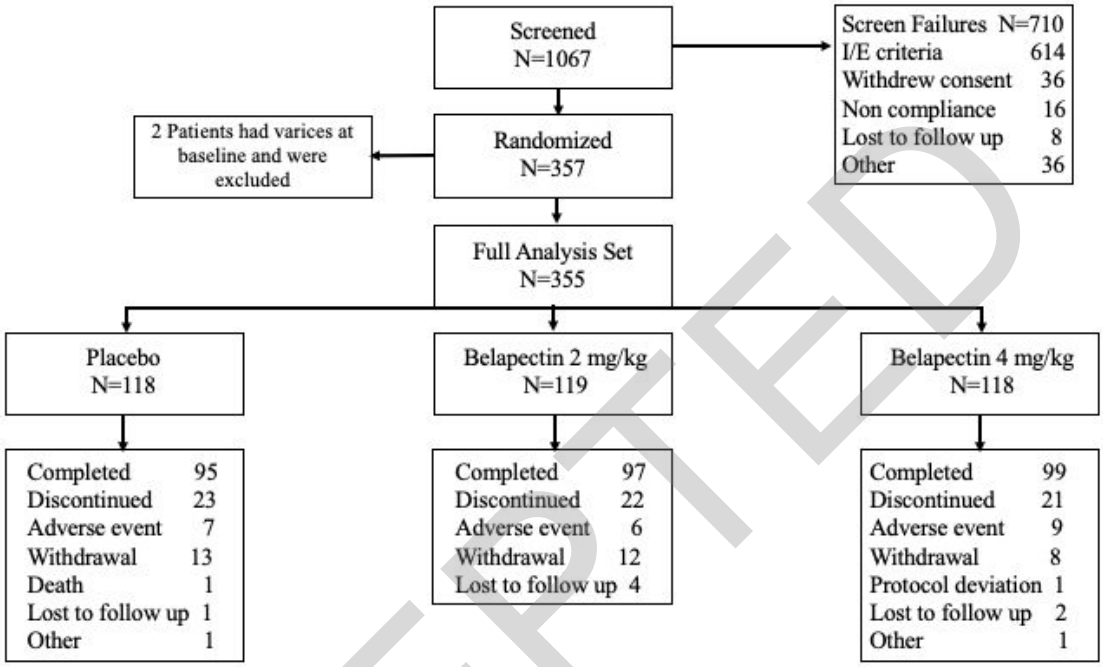
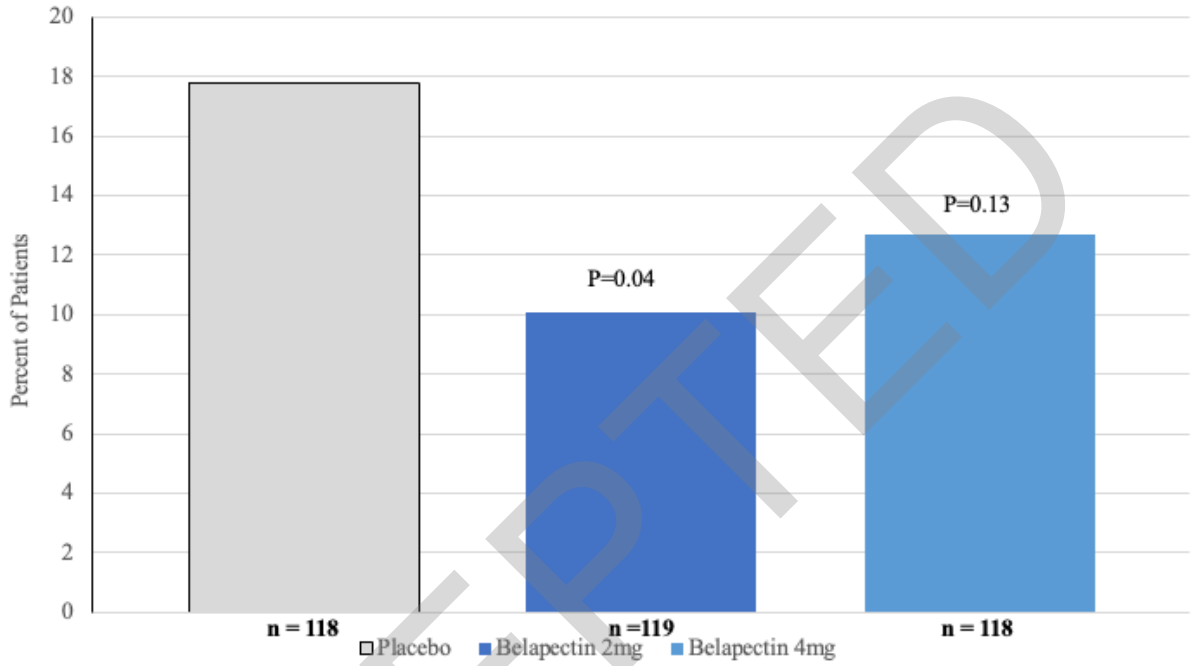


Figure 2. Proportion of patients developing new varices at 18 months for FAS Population, N=355 (Panel A) and for Per Protocol/completers Population, N=287 (Panel B). P-value from Mantel-Haenszel test.

Panel A



Panel B

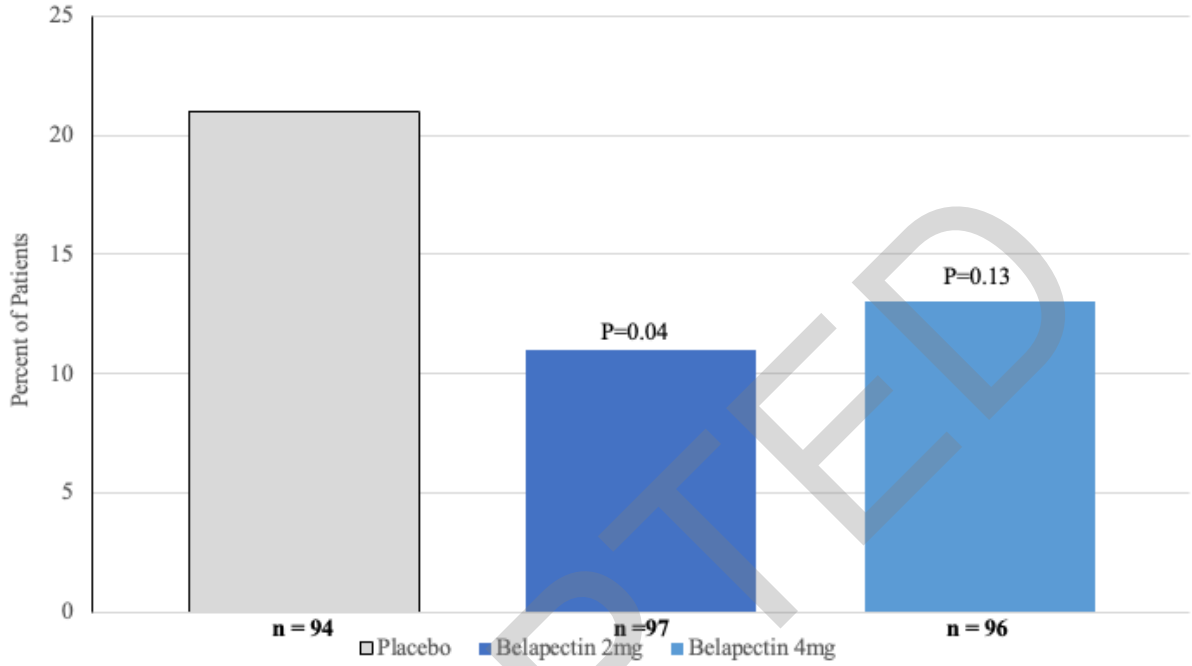
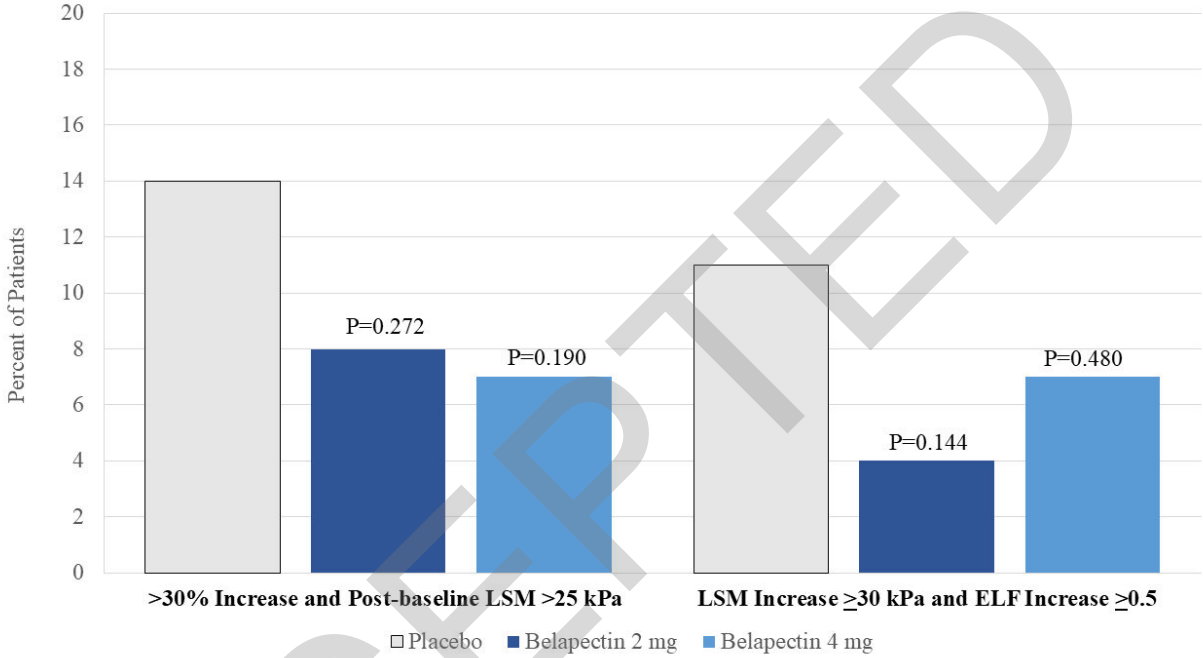
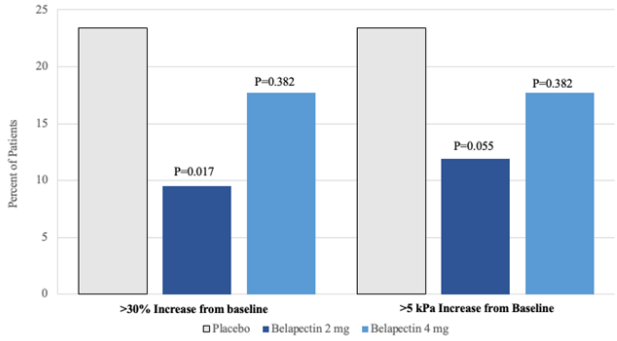
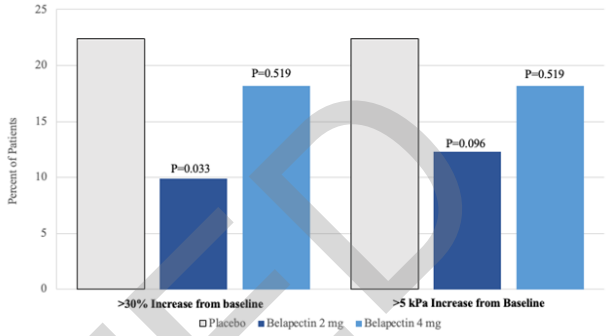


Figure 3. Percent change from baseline to 18 months for LSM (kPa) in FAS (N=315) and PP/completer (N=234) populations (top). Proportion of patients with worsening liver stiffness measure at 18 months for FAS populations, N=240 and PP/completer population populations, N=234 (middle), and worsening liver stiffness measure and ELF at 18 months (PP/completer population, N=199) (bottom). Treatment comparisons were with Chi-square test.




25
20
15
10
5
0
Percent of Patients
P=0.017
P=0.382
P=0.055
P=0.382
>30% Increase from baseline
>5 kPa Increase from Baseline
Placebo
Belapectin 2 mg
Belapectin 4 mg


25
20
15
10
5
0
Percent of Patients
P=0.033
P=0.519
P=0.096
P=0.519
>30% Increase from baseline
>5 kPa Increase from Baseline
Placebo
Belapectin 2 mg
Belapectin 4 mg

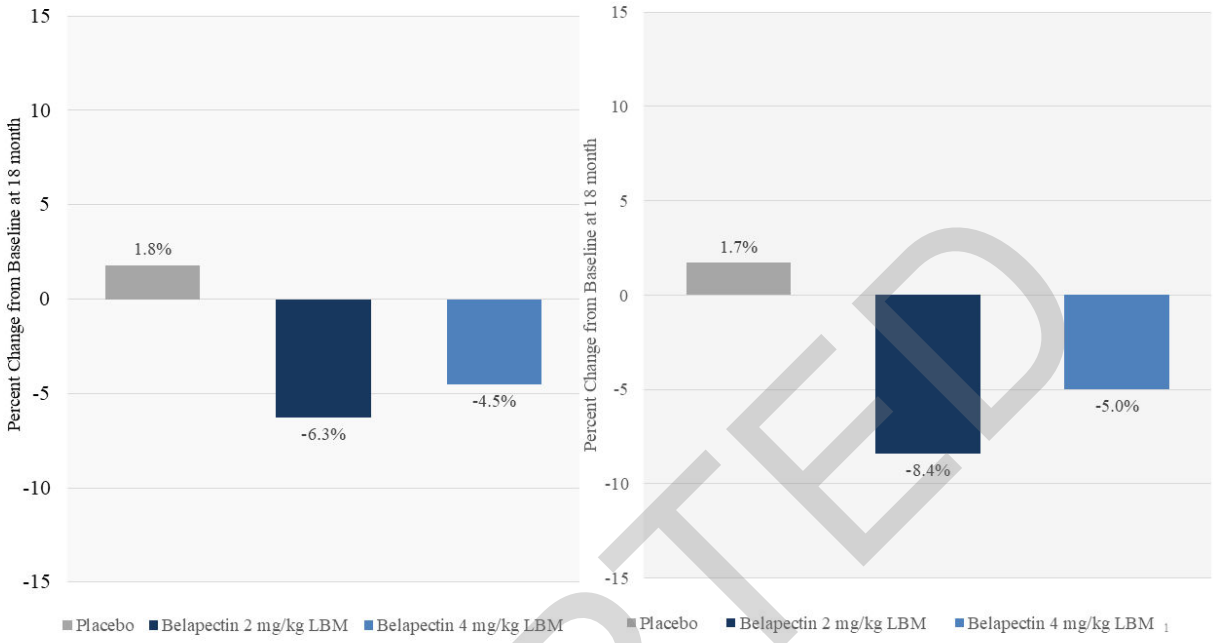
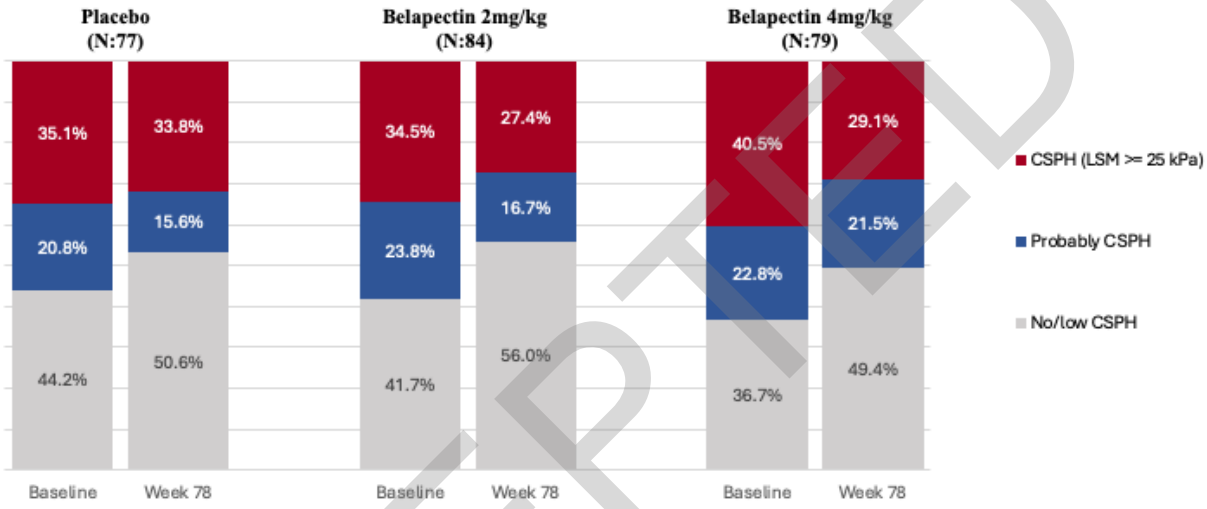

15
10
5
0
-5
-10
-15
Percent Change from Baseline at 18 month
1.8%
-6.3%
-4.5%
Placebo
Belapectin 2 mg/kg LBM
Belapectin 4 mg/kg LBM
15
10
5
0
-5
-10
-15
Percent Change from Baseline at 18 month
1.7%
-8.4%
-5.0%
Placebo
Belapectin 2 mg/kg LBM
Belapectin 4 mg/kg LBM

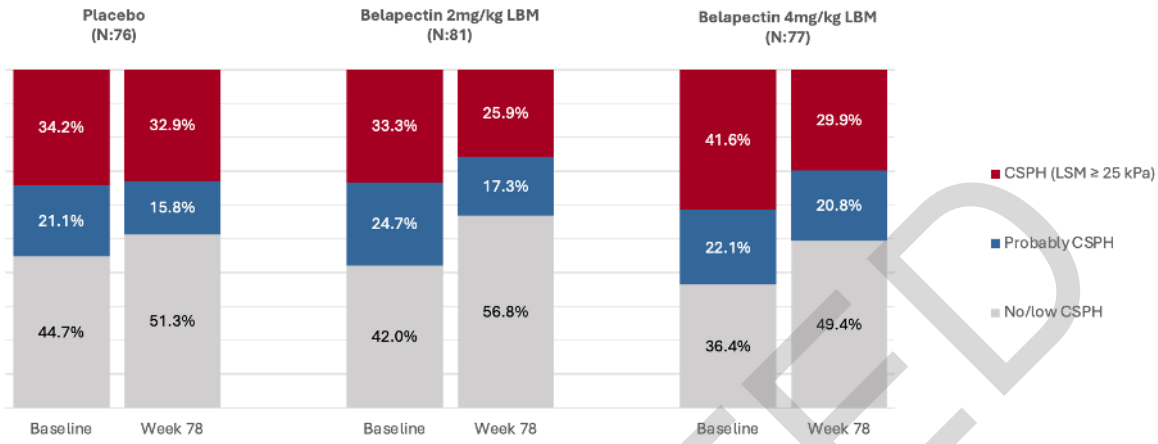
Figure 4. Improvement in Portal Hypertension Risk Category (FAS Population, N=240) top panel, (Per Protocol/completer Population, N=234) middle panel, using Baveno VII Guidelines,[27] proportion of patients with ELF score ≥0.5 at 18 months (bottom panel).

Top Panel



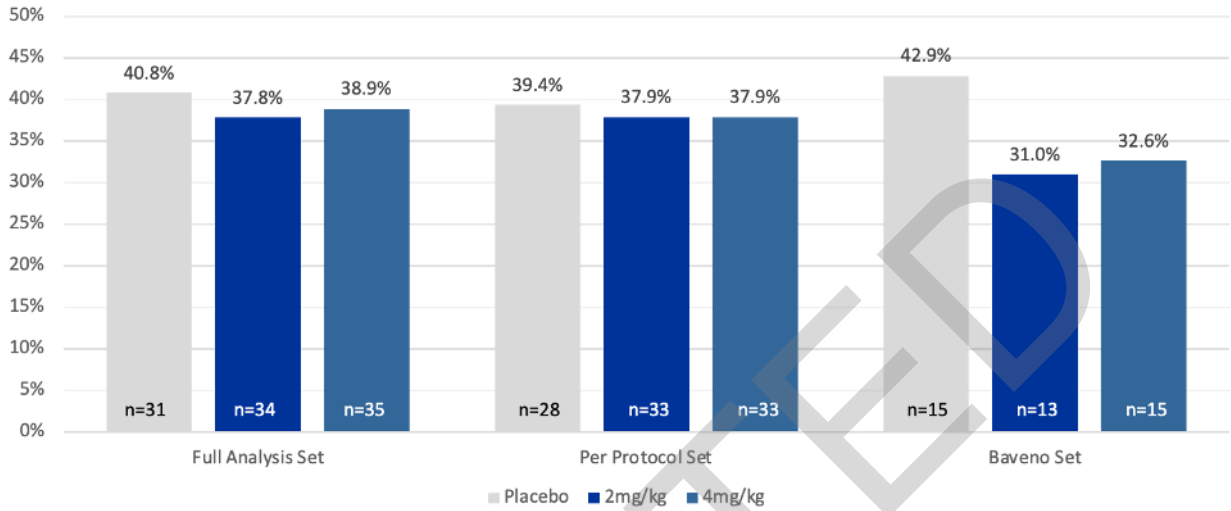
p=0.677 for 2 mg/kg vs placebo p=0.600 for 0.4 mg/kg vs. placebo

Middle Panel



p=0.631 for 2 mg/kg vs placebo p=0.718 for 0.4 mg/kg vs. placebo

Bottom Panel



p=0.743 for 2 mg/kg vs placebo p=0.902 for 2 mg/kg vs placebo p=0.280 for 2 mg/kg vs placebo

p=0.743 for 4 mg/kg vs. placebo p=0.785 for 4 mg/kg vs. placebo p=0.344 for 4 mg/kg vs. placebo

Table 1. Baseline characteristics (FAS Population)

	Placebo (N=118)	Belapectin 2 mg/kg LBM (N=119)	Belapectin 4 mg/kg LBM (N=118)
Age, years [a]	60.4 ± 8.5	60.6 ± 8.8	59.0 ± 9.1
Female, n (%)	72 (61.0)	75 (63.0)	83 (70.3)
Hispanic, n (%)	34 (28.8)	39 (32.8)	33 (28.0)
Race, n (%)			
American Indian/Alaska Native	6 (5.1)	6 (5.0)	3 (2.5)
Asian	5 (4.2)	2 (1.7)	2 (1.7)
Black or African American	1 (0.8)	2 (1.7)	0
White	104 (88.1)	107 (89.9)	111 (94.1)
Other	2 (1.7)	2 (1.7)	2 (1.7)
Weight, kg [a]	94.2 ± 21.7	98.1 24.3	94.6 ± 21.0
Body mass index, kg/m^2 [a]	33.8 ± 6.5	34.9 6.7	34.5 ± 6.2
Hypertension, n (%)	89 (75.4)	89 (74.8)	79 (66.9)
Type 2 diabetes, n (%)	80 (67.8)	79 (66.4)	79 (66.9)
Glycated hemoglobin, %	6.4 ± 1.3	6.3 ± 1.1	6.4 ± 1.1
Alanine aminotransferase, U/L [a]	46.3 ± 29.9	38.9 ± 26.9	39.7 ± 20.2
Aspartate aminotransferase, U/L [a]	46.7 ± 23.5	41.8 ± 24.4	43.6 ± 21.9
Platelets, ‖L [a]	130.1 ± 39.7	127.6 ± 48.4	136.4 ± 53.6
MASH cirrhosis diagnosis, n (%)*			
1A	48 (40.7)	48 (40.3)	54 (45.8)
1B	11 (9.3)	12 (10.1)	10 (8.5)
1C	17 (14.4)	15 (12.6)	14 (11.9)
2A	2 (1.7)	4 (3.4)	1 (0.8)
2B	38 (32.2)	38 (31.9)	37 (31.4)
Missing	2 (1.7)	2 (1.7)	2 (1.7)
Liver stiffness, kPa [a]	24.2 ± 12.2	24.6 ± 13.6	25.7 ± 13.2
Spleen, cm [a]	13.8 ± 2.8	14.0 ± 2.6	13.9 ± 2.4
MELD score [a]	7.6 ± 1.7	7.9 ± 2.5	7.5 ± 1.6
Child-Pugh score [a]	5.1 ± 0.3	5.1 ± 0.3	5.0 ± 0.2
Statins, n (%)	49 (41.5)	55 (46.2)	47 (39.8)
GLP-1 agonists, n (%)	24 (20.3)	24 (21.8)	27 (22.9)

[a] Mean ± standard deviation

GLP-1 = glucagon-like peptide-1; LBM = lean body mass; MELD = Model for End-Stage Liver Disease

* See Supplemental Appendix for definitions of MASH Cirrhosis.

Table 2. Proportion of patients with composite clinical outcomes at 18 months – primary estimand FAS Population

	Placebo	Belapectin 2 mg/kg	Belapectin 4 mg/kg
Composite endpoint FAS population	**N=118**	**N=119**	**N=118**
New varices, n (%)	**21 (17.8)**	**12 (10.1)**	**15 (12.7)**
Intercurrent events, n (%)	26 (22.0)	29 (24.4)	30 (25.4)
GLP-1 use≥12 months	15 (12.7)	20 (16.8)	16 (13.6)
Liver complications	6 (7.0)	6 (7.0)	4 (5.0)
Discontinuation for adverse events	8 (6.8)	6 (5.0)	9 (7.6)
No end-of-treatment EGD or ICE, n (%)	13 (11.0)	8 (6.7)	11 (9.3)
Total composite endpoint	56 (47.5)	45 (37.8)	51 (43.2)
Proportion with event, % (95% CI)	47.5 (38.2, 56.9)	37.8 (29.1, 47.2)	43.2 (34.1, 52.7)
Difference, % (95% CI)		-9.4 (-21.8, 3.0)	-4.1 (-16.8, 8.5)
2-sided p-value		0.278	0.522

CI = confidence interval; ICE = intercurrent events: liver related clinical events, adverse event leading to discontinuation, transjugular intrahepatic portosystemic shunt (TIPS); >12 months use of GLP-1 or non-selective beta-blocker; FAS = full analysis set population
P-value from 2-sided, Cochran-Mantel-Haenszel test, stratified by type 2 diabetes at randomization; P-values adjusted for multiplicity using the Step-Down Bonferroni Holm method
NOTE: The categories of new varices and intercurrent events were not mutually exclusive. Patients with no end of trial EGD or intercurrent event treatment were considered as non-responders and hence assumed to have developed varices. Not all patients were included in FAS including those who didn't have an EGD at 18 months.

Table 3. Cumulative incidence of patients who developed composite clinical outcome at 18 months – primary estimand (FAS population)

	Number (%) of Patients		
	Placebo N=118	Belapectin 2 mg/kg N=119	Belapectin 4 mg/kg N=118
Patients with composite clinical outcome	6 (5.1)	8 (6.7)	6 (5.1)
Varices requiring treatment	3 (2.5)	4 (3.4)	3 (2.5)
Variceal bleed requiring hospitalization	0	1 (0.8)	0
Clinically significant ascites requiring hospitalization	1 (0.8)	0	0
Overt hepatic encephalopathy (West Haven score ≥2 and requiring hospitalization)	2 (1.7)	1 (0.8)	1 (0.8)
Liver transplant	1 (0.8)	0	0
MELD score ≥15 on 2 consecutive occasions	0	0	1 (0.8)
All-cause death	1 (0.8)	2 (1.7)	1 (0.8)
Cumulative incidence rate [a]	0.28	0.32	0.32
Difference in cumulative incidence rate (95% CI)		0.04 (-0.12, 0.20)	0.05 (-0.11, 0.20)

CI = confidence interval; GLP = glucagon-like peptide; MELD = Model for End-Stage Liver Disease

[a] Exposure-adjusted cumulative incidence rate was calculated as (number of patients with the event / total time at risk in weeks over all patients) * 18 months.

Belapectin dosed at mg/kg lean body weight

Table 4. Summary of treatment-emergent adverse events (TEAE) (safety population)

	Number (%) of Patients			
	Placebo (N=118)	Belapectin 2 mg/kg LBM (N=119)	Belapectin 4 mg/kg LBM (N=120)	Total (N=357)
Any TEAE	112 (94.9)	116 (97.5)	116 (96.7)	344 (96.4)
Number of TEAEs	1207	1244	1334	3785
TEAEs of CTCAE grade ≥3	25 (21.2)	37 (31.1)	37 (30.8)	99 (27.7)
Drug-related TEAEs	28 (23.7)	28 (23.5)	32 (26.7)	88 (24.6)
Infusion procedure-related TEAEs	15 (12.7)	16 (13.4)	13 (10.8)	44 (12.3)
TEAE leading to drug discontinuation	8 (6.8)	10 (8.4)	12 (10.0)	30 (8.4)
Death from treatment-emergent serious AE	2 (1.7)	5 (4.2)	1 (0.8)	8 (2.2)
Most common TEAEs by system organ class				
Covid-19	32 (27.1)	35 (29.4)	37 (30.8)	104 (29.1)
Diarrhea	28 (23.7)	27 (22.7)	24 (20.0)	79 (22.1)
Urinary tract infection	26 (22.0)	27 (22.7)	24 (20.0)	77 (21.6)
Arthralgia	20 (16.9)	21 (17.6)	22 (18.3)	63 (17.7)
Nausea	23 (19.5)	17 (14.3)	17 (14.2)	57 (16.0)
Fatigue	17 (14.4)	20 (16.8)	16 (13.3)	53 (14.9)
Nasopharyngitis	16 (13.6)	22 (18.5)	14 (11.7)	52 (14.6)
Headache	16 (13.6)	13 (10.9)	21 (17.5)	50 (14.0)
Cough	16 (13.6)	14 (11.8)	14 (11.7)	44 (12.3)
Upper respiratory tract infection	12 (10.2)	12 (10.1)	19 (5.8)	43 (12.0)
Back pain	13 (11.0)	12 (10.1)	17 (14.2)	42 (11.8)
Dizziness	10 (8.5)	17 (14.3)	12 (10.0)	39 (10.9)
Edema peripheral	15 (12.7)	9 (7.6)	15 (12.5)	39 (10.9)
Abdominal pain upper	11 (9.3)	11 (9.2)	15 (12.5)	37 (10.4)
Pruritus	9 (7.6)	15 (12.6)	12 (10.0)	36 (10.1)
Abdominal pain	14 (11.9)	7 (5.9)	12 (10.0)	33 (9.2)
Sinusitis	14 (11.9)	8 (6.7)	10 (8.3)	32 (9.0)

CTCAE = Common Terminology Criteria for Adverse Events; LBM = lean body mass