Innovating in cirrhosis: NAVIGATE, a seamless, adaptive, phase 2b/3 of belapectin, a galectin-3 inhibitor, for the prevention of esophageal varices in NASH cirrhosis

Pol Boudes[1], Stephen A. Harrison[2], Naga Chalasani[3]

In NASH, most drug development target non-cirrhotic subjects and primarily use histopathology as an outcome.

NASH cirrhosis, however, is a challenge. The safety profile of candidate drugs is difficult to establish, particularly for liver-related side effects. Advanced cirrhotic patients are generally excluded from registration studies and primary efficacy outcomes that record decompensation events are too infrequent.

Contrary to other chronic diseases, no overall measure of liver function exists and there is no sensitive method to measure cirrhosis improvement on histology.

In a one-year phase 2 proof of concept study [1], belapectin, when compared to placebo, decreased portal hypertension and prevented esophageal varices in patients who have not yet developed them.

This led us to design and initiate NAVIGATE, an innovative phase 2b/3 confirmatory study (NCT04365868).

Because of challenges associated with liver biopsies, the primary efficacy outcome needs to be clinically relevant and integrated into clinical practice while respecting the spirit of regulatory guidance.

A seamless design allows to follow patients for extended periods to better inform the risk benefit profile.

An adaptive design is advantageous when few data on event rate are available. Adaptations are based on accumulating evidence and allow to adjust a sample size without amending the protocol.

The population chosen and the duration of the trial must balance the risk of decompensation events in cirrhotic patients with the ethical use of a placebo when no other therapeutic option exists.

NAVIGATE proceeds as a global phase 2b/3 (figure). Patients have NASH cirrhosis, clinical signs of portal hypertension, but no esophageal varices.

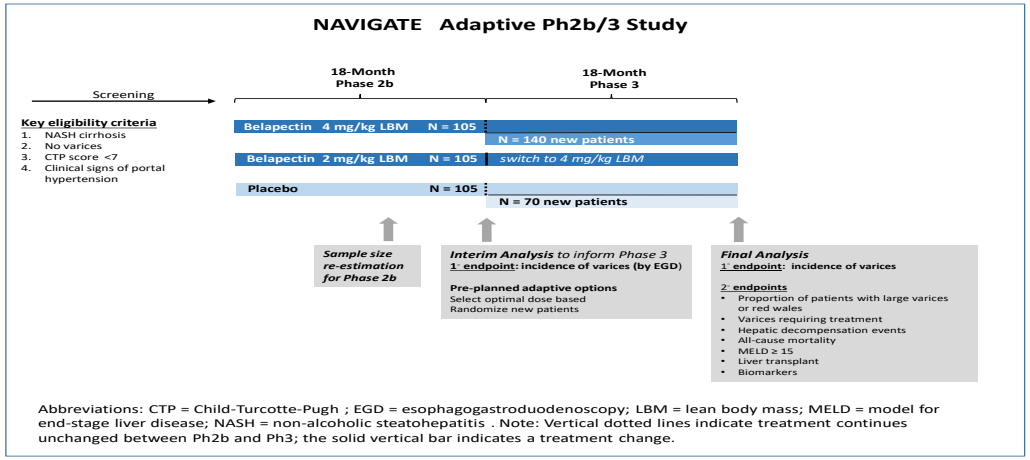
The primary outcome of efficacy is the development of esophageal varices after 18 months, adjudicated by an independent committee, comparing belapectin and placebo.

The 18-month phase 2b will confirm previous phase 2 results on a larger set of patients and select the optimal dose of belapectin. Phase 2b patients continue seamlessly into an extension for an additional 18 months to provide long term safety and efficacy data.

Following the phase 2b interim analysis, phase 3 will proceed with new patients, for a similar 18-month duration and outcome, and the optimal dose of belapectin.

For the final analysis, data from phase 2b and phase 3 will be combined with the appropriate statistical adjustments [2].

Two sample size adaptations are planned: a blinded reevaluation during the phase 2b to confirm the event rate of esophageal varices, and at the phase 2b interim analysis. Based on these, the study size may vary from 525 to 1,010 patients.



Abbreviations: CTP = Child-Turcotte-Pugh ; EGD = esophagogastroduodenoscopy; LBM = lean body mass; MELD = model for end-stage liver disease; NASH = non-alcoholic steatohepatitis . Note: Vertical dotted lines indicate treatment continues unchanged between Ph2b and Ph3; the solid vertical bar indicates a treatment change.

There is a need for innovative study designs in liver cirrhosis to bring potential new treatments for these patients.

Esophageal varices are a serious complication of portal hypertension and mark a progression in the severity of the disease. Preventing esophageal varices represents a relevant clinical benefit.

NAVIGATE is an ongoing, global phase 2b/3 study that evaluates the risk benefit of belapectin for patients with NASH cirrhosis. The risk benefit will be evaluated both at the end of phase 2b and at the end of phase 3.

[1] Chalasani N, Abdelmalek MF, Garcia-Tsao G, et al. Effects of belapectin, an inhibitor of galectin-3, in patients with nonalcoholic steatohepatitis with cirrhosis and portal hypertension. Gastroenterology. 2020 Apr;158(5):1334-1345.

[2] FDA. Adaptive Designs for Clinical Trials of Drugs and Biologics. Industry Guidance Nov 2019.

AUTHORS / AFFILIATIONS

[1] Galectin Therapeutics, Norcross, GA, USA boudes@galectinrx.com [2] Pinnacle Research, San Antonio, TX, USA [3] Indiana University, Indianapolis, IN, USA