Pharmacokinetic exposure and safety of belapectin, a candidate treatment for NASH-cirrhosis, in patients with hepatic insufficiency

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Galectin Therapeutics

Belapectin, a galectin-3 inhibitor, is currently in phase 2b/3 development for the prevention of esophageal varices in patients with NASH cirrhosis.

Belapectin is a large polysaccharidic molecule that is primarily captured by activated macrophages and thus inhibits galectin-3 at its main site of production. The residence time of belapectin in macrophages allows for a bi-weekly administration of the drug.

Galectin-3, a glycan binding protein, plays a central role to foster liver inflammation and fibrosis in NASH cirrhosis (the galectin-3 '*fibrosome*').

We report on an interim assessment of the pharmacokinetic (PK) and safety profiles of belapectin in patients with hepatic insufficiency NCT04332432.

An open-label, phase 1 study investigated a single IV infusion of belapectin 4 mg/kg lean body mass in patients with Mild (Child-Pugh A), Moderate (Child-Pugh B), and Severe (Child-Pugh C) hepatic insufficiency and healthy controls matched for sex and body mass Index.

Belapectin serum levels are determined pre-infusion, and at 3, 24, 36, 48, 72, 120, 210 (Day 10), and 336 hours (Day 15) post infusion. Primary PK parameters were maximum concentration (Cmax), time to Cmax (Tmax), and area under the curve (AUC).

Safety included adverse events, ECGs, biochemistry, and hematology. Safety-related stopping criteria were defined. An interim review was performed when two Severe patients had completed the study. The interim review's main objective is to review the data and decide if it is safe to enroll the remaining Child-Pugh C patients.

AASLD

Twenty-two subjects with a mean age of 59 years old have been enrolled and analyzed (6 healthy subjects, 6 Child-Pugh A patients, 8 Child-Pugh B patients, and 2 Child-Pugh C patients).

Belapectin is well tolerated and appeared safe. Three subjects had treatment-related headaches that were mild and transient. There were no infusion-related reactions, no treatment emergent SAE, no ECG findings, and no subject discontinuing the study or meeting a safety-related stopping criteria.

After the interim data review by the investigators and sponsor's staff, the dose of belapectin was confirmed and the recruitment of additional patients was authorized.

The Mean (SD) PK results are presented below:

	N	Cmax µg/mL (SD)	Tmax hours (SD)	AUC last µg.hr/mL (SD)
Healthy	6	154 (24)	29 (6)	10,580 (2,740)
Child-Pugh A	6	144 (31)	31 (7)	10,400 (2,670)
Child-Pugh B	8	134 (29)	33 (9)	9,148 (2,390)
Child-Pugh C	2	131 (21)	37 (17)	9,032 (570)

CONCLUSION

Belapectin, at 4 mg/kg lean body mass, the highest dose in the phase 2b/3 NAVIGATE program, was well tolerated and appeared safe.

The PK profile of belapectin was not modified in patients with Child-Pugh A (Mild) and Child-Pugh B (Moderate) hepatic impairment.

Preliminary data suggest the PK profile of belapectin is not modified in patients with Child-Pugh C (Severe) hepatic insufficiency.

The current PK profile suggests that no belapectin dose adjustment is necessary with advancing cirrhotic disease.

The PK profile of belapectin is consistent with the distribution of belapectin from the blood compartment to parenchymal activated macrophages.

In the cirrhotic liver, activated macrophages constitute both a reservoir for belapectin and the main site of action to inhibit galectin-3[1].

REFERENCES

[1] Boudes P, et al. "Mechanism of galectin-3 binding by belapectin, a galectin-3 inhibitor developed for NASH cirrhosis. #1924. The Liver Meeting 2021

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