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GULLIVER-2 is an Innovative, Hybrid, Hepatic Impairment Trial of the Oral Galectin-3 Inhibitor GB1211

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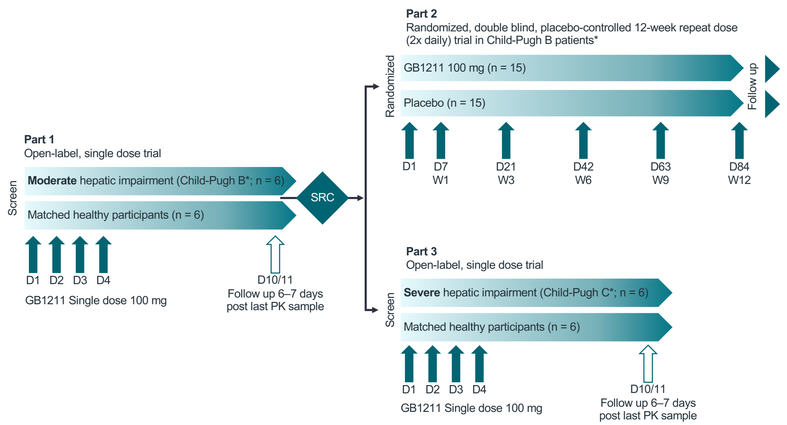
Background

- Cirrhosis is the final stage of liver fibrosis and is the leading cause of liver-related death, constituting 2.4% of the total number of deaths globally[1,2]
- Galectin-3 (Gal-3) is a beta-galactoside binding lectin which is a key regulator of inflammation and fibrosis in the liver[3]
- GB1211 is a novel, high affinity, selective and potent small molecule oral Gal-3 inhibitor: a type of molecule that has been shown to reduce fibrosis in mice, suggesting a potential role of Gal-3 inhibitors in the treatment of fibrotic disorders[4,5]
- The GULLIVER-2 (ClinicalTrials.gov identifier: NCT05009680) trial investigates the effect of hepatic impairment on the safety, tolerability and pharmacokinetics (PK) of GB1211, as well as the effect of GB1211 on liver function and fibrosis in patients with hepatic impairment and decompensated cirrhosis
- Here, we report the findings from Parts 1 and 3 of the trial; Part 2 will be presented separately as a late-breaker oral presentation and an ePoster

Methods

- GULLIVER-2 is a three-part trial assessing the safety, tolerability and PK of oral GB1211 in patients with hepatic impairment of Child-Pugh B or Child-Pugh C cirrhosis score
  - Part 1: A single dose, open-label safety and PK trial of GB1211 administered to patients with moderate hepatic impairment (Child-Pugh B) and to matched healthy participants
  - Part 2: A randomized, double-blind, placebo-controlled trial in patients with moderate hepatic impairment (Child-Pugh B)
  - Part 3: A single dose, open-label safety and PK trial of GB1211 administered to patients with severe hepatic impairment (Child-Pugh C) and to matched healthy participants
- Primary endpoints of all three parts include:
  - Safety and tolerability of GB1211
  - PK of GB1211

Figure 1. GULLIVER-2 (NCT05009680) trial design



*A measure of the severity of cirrhosis (Child-Pugh A: 5–6 points [good hepatic function]; Child-Pugh B: 7–9 points [moderately impaired hepatic function]; Child-Pugh C: 10–15 points [severe hepatic dysfunction]). D, day; PK, pharmacokinetics; SRC, safety review committee; W, week

Summary

- GB1211 is a novel, high affinity, selective and potent small molecule oral Gal-3 inhibitor
- GULLIVER-2 is a three-part trial investigating safety, PK and exploratory efficacy of oral GB1211 in patients with hepatic impairment and cirrhosis
- In a cohort of patients with decompensated cirrhosis, GB1211 was well tolerated, with no adverse events reported in Parts 1 and 3
- Preliminary data from Part 1 and Part 3 of GULLIVER-2 indicate that hepatic impairment had moderate effects on the GB1211 PK profile, compared with healthy participants:
  - $AUC_{0-\infty}$ increased by less than two-fold in Child-Pugh B and C patients, compared with matched healthy participants
  - C_{max} was unaffected in Child-Pugh B patients, and was increased in Child-Pugh C patients, compared with matched healthy participants
  - The average terminal half-life ($T_{1/2}$) increased in both Child-Pugh B and C patients, compared with matched healthy participants

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Results

Safety data

- Preliminary data from Parts 1 and 3 have shown GB1211 to have an acceptable safety profile, with no adverse events reported; data were supportive of patients proceeding to Part 2

PK data

- Hepatic impairment increases GB1211 exposure by less than two-fold after a single dose in Child-Pugh B and Child-Pugh C patients (Table 1 and Figure 2)
  - $AUC_{0-\infty}$ increased by 60% in Child-Pugh B and Child-Pugh C patients, versus matched healthy participants (Figure 3)
  - Compared with matched healthy participants, C_{max} was unaffected in Child-Pugh B patients, but there was an increase of 35% in Child-Pugh C patients (Figure 4)
  - Average $T_{1/2}$ was increased in patients with hepatic impairment versus matched healthy participants

Table 1. PK parameters of total GB1211 concentration in plasma

100 mg GB1211, geometric mean (range)	Part 1			Part 3		
	Healthy participants (n = 6)	Child-Pugh B patients (n = 6)	Ratio	Healthy participants (n = 6)	Child-Pugh C patients (n = 6)	Ratio
$AUC_{0-\infty}$, h.ng/mL	5954 [3404–13206]	9980 [6953–19864]	1.57	7420 [5005–13081]	10893 [5175–22584]	1.62
C_{max}, ng/mL	509 [297–1546]	491 [250–1421]	0.96	488 [257–1194]	656 [349–1227]	1.34
$T_{1/2}$, h	16.4 [9.8–27.7]	28.1 [16.6–90.0]	–	16.3 [13.6–21.6]	21.5 [11.3–42.7]	–

$AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 to infinity; C_{max}, maximum plasma concentration; h, hours; $T_{1/2}$, terminal half-life

Results ct'd

Figure 2. Arithmetic mean concentration-versus time profiles of total plasma GB1211 for Child-Pugh B patients in Part 1 (A) and Child-Pugh C patients in Part 3 (B) versus healthy matched participants, following a single oral dose of 100 mg

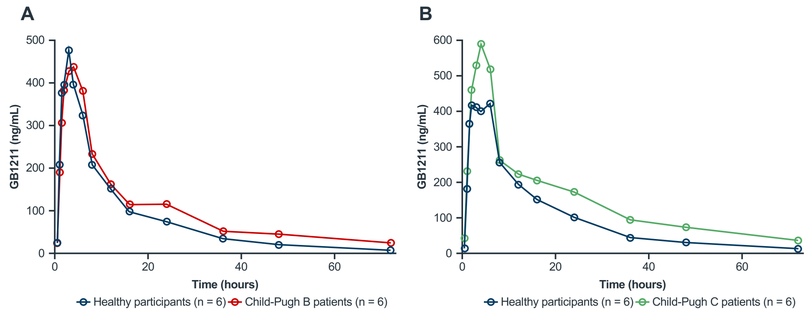
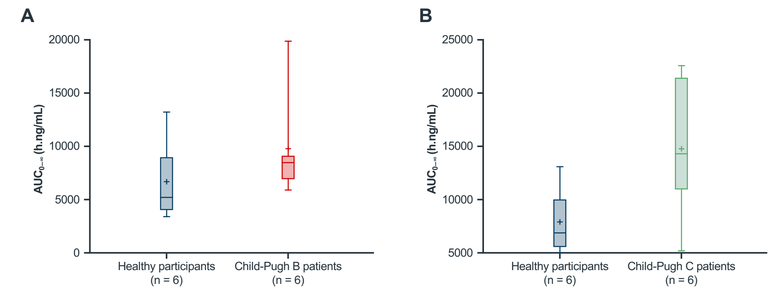
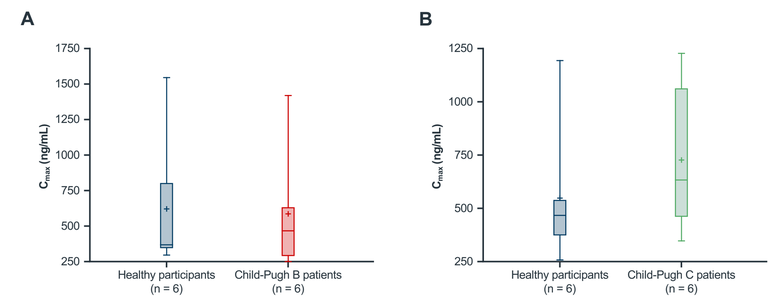


Figure 3. Boxplots of $AUC_{0-\infty}$ following a single oral dose of GB1211 for Child-Pugh B patients in Part 1 (A) and Child-Pugh C patients in Part 3 (B)



+ represents the arithmetic mean. $AUC_{0-\infty}$, area under the plasma concentration versus time curve from time 0 to infinity

Figure 4. Boxplots of C_{max} following a single oral dose of GB1211 for Child-Pugh B patients in Part 1 (A) and Child-Pugh C patients in Part 3 (B)



+ represents the arithmetic mean. C_{max}, maximum plasma concentration

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