GLEPAGLUTIDE, A NOVEL LONG-ACTING GLUCAGON-LIKE PEPTIDE-2 ANALOG, AMELIORATES DISTURBANCES IN GUT-LIVER AXIS BY TRIGGERING FARNESOID X RECEPTOR SIGNALING PATHWAYS IN PATIENTS WITH SHORT BOWEL SYNDROME

BACKGROUND & AIM
Activation of the farnesoid X receptor (FXR), a major regulator of bile acid biosynthesis, seems to play a role in the restoration of the disturbed homeostatic feedback in the gut-liver axis in patients with short bowel syndrome. Substantial ileal resections combined with accelerated gastrointestinal transit and hypersecretion as well as microbial dysbiosis result in reduced intestinal FXR activation leading to decreased circulating plasma levels of fibroblast growth factor 19 (FGF19) and increase in bile acid synthesis marked by elevated plasma levels of 7α-hydroxy-4-cholesten-3-one (C4).

We have previously presented that daily s.c. injections with 1 mg and 10 mg of glepaglutide, a novel long-acting glucagon-like peptide-2 (GLP-2) analog, resulted in significant reduction in fecal output (primary endpoint) and improvement in intestinal absorption (secondary endpoint) in patients with short bowel syndrome.

As exploratory endpoints, we assessed the effect of glepaglutide on FXR signaling pathways and bile acid biosynthesis biomarkers. This is the first trial addressing this issue in a GLP-2 short bowel syndrome setup.

This was a randomized, double-blind, dose-finding, single-center, phase 2 trial. In a crossover design, patients received two of three daily doses (0.1 mg, 1 mg, and 10 mg) of subcutaneous glepaglutide injections for 3 weeks.

Gut-liver axis was assessed before and at the end of each 3-week treatment period by:

1. FXR gene expression in intestinal mucosa biopsies
2. Plasma FGF19
3. Plasma C4
4. Total fecal bile acid concentration

- Gene expression of FXR by quantitative polymerase chain reaction.
- Fasting and postprandial (0-2 h) samples of FGF19 and C4. Plasma FGF19 was measured using a commercial ELISA kit, and plasma C4 was measured using liquid chromatography-mass spectrometry.
- Total fecal bile acid concentration was collected in relation to a standard test meal and measured by liquid chromatography-mass spectrometry.

STATISTICS
- Data are presented as median (min to max) for baseline characteristics.
- Endpoints are analyzed by Friedman’s test, which is a non-parametric test corresponding to a two-way ANOVA, with factors dosage and subject. The absolute changes from baseline in each dose group are presented as median, quartiles (25%- and 75%-percentiles) and p-values associated with Friedman’s test.
- Friedman’s test evaluates equality of effect parameters across all three dose groups.

CONCLUSION
The increase in FGF19 and the associated reduction in C4, as well as the decrease in total fecal bile acid concentration, suggest that glepaglutide may play a role in the restoration of the impaired homeostatic feedback in the FXR-FGF19-C4 gut-liver axis.

Since the intestinal FXR gene expression did not change, it is possible that the effect of glepaglutide on FXR-FGF19-C4 gut-liver axis is mediated either: 1) indirectly through the prolonged GI transit time (data already presented), which allows a longer contact between bile acid and the existing FXR, or 2) through the induction of an expanded absorptive surface area, leading to an increased stimulation of these receptors.