Post-bariatric hypoglycemia (PBH) is a rare disease characterized by recurrent episodes of severe, symptomatic hyperinsulinemic hypoglycemia (HH). The predominant form occurs after Roux-en-Y gastric bypass (RYGB). However, severe cases also present after other upper-gastrointestinal procedures. The mechanisms mediating PBH have long been debated, though a critical role for excessive postprandial secretion of glucagon-like peptide-1 (GLP-1) has been established. Avexitide (exendin 9-39) is a first-in-class GLP-1 receptor antagonist in development for treatment of PBH. Prior studies with avexitide administration have shown normalization of postprandial insulin concentrations and reductions in the occurrence of symptomatic hypoglycemia. In the Phase 2 multicenter PREVENT trial, avexitide administered to post-RYGB patients at a total daily dose of 60 mg [30mg twice daily (BID) or 60mg once daily (QD)] for 28 days was well-tolerated and demonstrated significant reductions in the rates of hypoglycemia, symptoms, and percent time in hypoglycemia. Based on the favorable safety and tolerability profile and dose-response relationship observed, we sought to evaluate whether higher doses of avexitide may further enhance the pharmacodynamic response. In addition, we sought to extend the evaluation to patients with HH after vertical sleeve gastrectomy, esophagectomy, gastrectomy or Nissen fundoplication. In this Phase 2b, open label, cross over study (NCT04652479), eligible patients included males and females (>18 years of age; BMI ≤40 kg/m²) with a history of recurrent hypoglycemia refractory to medical nutrition therapy (MNT) and exhibiting at least two severe hypoglycemia events while adhering to MNT over a 14-day period. Metabolic and symptomatic parameters were assessed by self-monitoring of blood glucose (SMBG), e-Diary, and blinded continuous glucose monitor (CGM) during 14 days of MNT as compared to 14 days of MNT + avexitide administered by subcutaneous injection at a dose of 45mg BID and 90mg QD in crossover design and random order, for a total of 28-days of treatment. An interim analysis (mixed-effect model) at ~50% completion was conducted (n=8). The primary and secondary endpoints were met with statistical significance. Compared with MNT alone, avexitide 45mg BID and 90mg QD reduced the rate of Level 1 hypoglycemia (SMBG<70 mg/dL) by 66% (p=0.022) and 74% (p=0.010); Level 2 hypoglycemia (SMBG <54 mg/dL) by 70% (p=0.003) and 93% (p=0.001); and Level 3 hypoglycemia (severe event characterized by altered mental and/or physical function requiring assistance) by 77% (p=0.002) and 93% (p=0.001), respectively. Objective: assessment by blinded CGM corroborated SMBG/e-Diary results, demonstrating significant reductions in the rates of hypoglycemia and improvements in percent time in hypoglycemia. Responses were comparable across surgical subtypes. Greater improvements were consistently observed with once daily (90 mg QD) than twice daily (45 mg BID) dosing and exceeded those reported in the PREVENT trial. Avexitide was well-tolerated, with no serious adverse events. Complete study results will be presented.

Presentation: Saturday, June 11, 2022 12:15 p.m. - 12:30 p.m.