Publication News 70 - 15 May 2023

Efficacy and safety of velusetrag on diabetic and idiopathic gastroparesis: a phase 2b study

Aim: The objective of this study is to evaluate efficacy and safety of velusetrag, a 5-HT4 agonist with pan-gastrointestinal prokinetic activity, for the management of gastroparesis symptoms and gastric emptying in subjects with diabetic or idiopathic gastroparesis.

Methods: In this multicentre, phase 2b, 12-week, randomized, double-blind, placebo-controlled study, subjects were randomized into 4 groups (using once-daily 5, 15, 30 mg of oral velusetrag or placebo). The primary outcome was the change in 7-day mean Gastroparesis Cardinal Symptom Index 24H composite score (GCSI-24H) from baseline to weeks of treatment. Subjects completed also proprietary Patient-Reported Outcome (PRO) over a 7-days baseline period, and the Gastroparesis Rating Scale (GRS). Gastric emptying was measured on day 28 by 4-h ^{99m}Tc Gastric Emptying Scintigraphy (GES) or 13C-spirulina Gastric Emptying Breath Test (GEBT). Secondary efficacy endpoints included 7-day GCSI-24H mean composite and individual domain subscores over weeks 1–12 of treatment.

Results: 232 subjects were randomized (183 female, 119 with diabetic gastroparesis, 50.3 years, HbA1c in the diabetic group 7.3%, GCSI-24H score 3.1) and 194 completed the study protocol. Least-squares mean improvement from baseline GCSI-24H (primary endpoint) at week 4 treatment was −1.5 following velusetrag 5 mg vs −1.1 following placebo (treatment difference, −0.4; 95% CI −0.75 to −0.03; nominal p=0.0327). This result was not significant after adjustment for multiple comparisons (Hochberg-adjusted p=0.0980). Symptom improvement was achieved only with velusetrag 5 mg and mainly in subjects with idiopathic gastroparesis. Improvement from baseline GE by GES was greater in subjects receiving velusetrag (all doses) vs placebo, with normalization of GE at 4 h in >70% of subjects receiving velusetrag 30 mg. Treatment-emergent adverse events were generally mild.

Conclusions: Velusetrag 5 mg decreased the day mean GCSI-24H after 4-weeks with nominal significance. Less symptoms improvement was observed using Velusetrag 15 or 30 mg despite Velusetrag at all doses improved gastric emptying measured by GES. Safety assessment was positive.

Comments. Although gastroparesis represents an important health burden also for its impact on morbidity and quality of life, treatments for symptomatic forms remain limited and suboptimal. This multicentre study at 60 sites in Europe and UK suggests velusetrag as a possible approach to manage symptoms of diabetic and non-diabetic gastroparesis. Despite these data are not conclusive and require confirming studies, velusetrag seems to have favourable efficacy and safety profile. Furthermore, other studies are considering velusetrag as a possible treatment of chronic constipation, so this medication could offer a possible approach to treat subjects with complex gastrointestinal manifestations of autonomic neuropathy.

Ilenia D'Ippolito

Reference. Abell TL, Kuo B, Esfandyari T, Pfeifer ND, Grimaldi M, Renzulli C, Tacchi R, Zhou K, Barnes CN, Nguyen DD, Nguyen L, Talley NJ, McCallum R. A randomized, double-blind, placebo-controlled, phase 2b study of the efficacy and safety of velusetrag in subjects with diabetic or idiopathic gastroparesis. Neurogastroenterol Motil. 2023 Apr;35(4):e14523. doi: 10.1111/nmo.14523. Epub 2023 Jan 9. PMID: 36624727.
https://onlinelibrary.wiley.com/doi/epdf/10.1111/nmo.14523