Efficacy Analysis of Tradipitant in Idiopathic and Diabetic Gastroparesis In Study VP-VLY-686-3301

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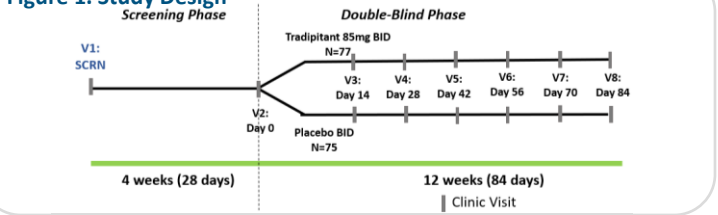
Background

- Gastroparesis is a serious medical condition characterized by delayed gastric emptying and symptoms of nausea, vomiting, bloating, fullness after meals, and abdominal pain (1)
- Substance P acts on NeuroKinin-1 Receptor (NK1R) and exerts a key role within the central emetic circuitry along with serotonin (2) and NK1R are also expressed in enteric neurons and interstitial cells of Cajal and stimulate smooth muscle contractions in the GI tract along with acetylcholine (3)
- Tradipitant is a potent and selective NK1R antagonist. NK1R antagonists have previously shown efficacy in chemotherapy induced nausea vomiting (4) and gastroparesis (5)
- Study VP-VLY-686-3301 was a multicenter, randomized, double-blind, placebo-controlled phase 3 study assessing the efficacy of tradipitant in relieving symptoms of gastroparesis
- The Intent-to-Treat (ITT) population included idiopathic and diabetic gastroparesis patients with delayed gastric emptying, moderate to severe nausea, and at least 1 vomiting episode.
- PK Compliance Population used a threshold of insufficient exposure of tradipitant concentration of less than 140ng/ml was used to create the
- No Rescue Medication Population analysis restricted the evaluation to a subpopulation of 30% of patients (61/201) who reported no use of concomitant rescue medication during the screening period or during the treatment period.

Methods

Figure 1. Study Design



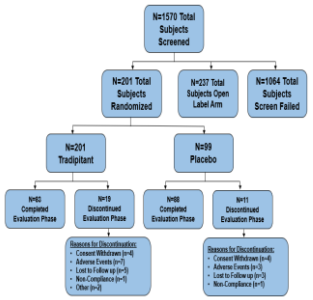
Inclusion Criteria

- Idiopathic or diabetic gastroparesis with moderate to severe nausea
- Delayed gastric emptying
- Adults aged 18-70 yrs. old
- Controlled blood glucose levels, HbA1c < 9%

Assessments

- Nausea was assessed with the 5-point Gastroparesis Core Symptom Daily Diary (GCSDD, 0=none, 5=very severe)
- Overall Gastroparesis symptom improvement was assessed with the Patient Global Impression of Change (PGI-C) and Overall Patient Benefit (OPB) Scales

Figure 2. Patient Disposition



Results

Table 1. Study Demographics – ITT

All Randomized Subjects	Tradipitant (N=102)	Placebo (N=99)	Total (N=201)
Sex, n (%)			
Female	77 (75.5)	84 (84.8)	161 (80.1)
Male	25 (24.5)	15 (15.2)	40 (19.9)
Age (years)			
Mean (SD)	49.5 (13.97)	48.8 (11.99)	49.1 (13.00)
Disease etiology, n (%)			
Idiopathic	52 (51.0)	51 (51.5)	103 (51.2)
Diabetic	50 (49.0)	48 (48.5)	98 (48.8)
Body Mass Index (kg/m^2)			
Mean (SD)	30.913 (5.9027)	30.625 (6.3405)	30.771 (6.1086)

Table 2. Nausea and Overall Gastroparesis Symptoms– ITT

ITT Population-Week 12	Tradipitant N=102	Placebo N=99	*p value*
DD-Nausea Severity	-1.55	-1.49	*0.741*
GCSI Total Score	-1.48	-1.39	*0.6283*

Figure 3. ITT Population PGI-C and OPB Responder Rates

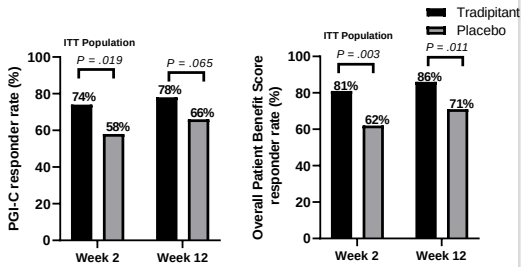


Figure 4. PK Compliance Population Change from Baseline in Average Nausea

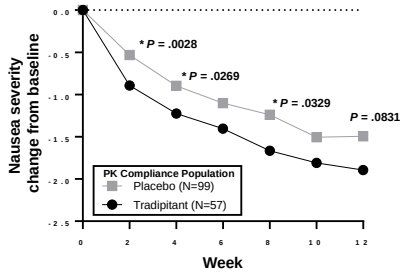


Figure 5. PK Compliance Population PGI-C and OPB Responder Rates

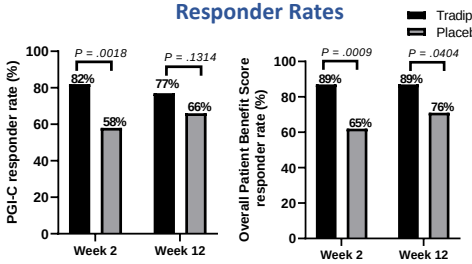


Figure 6. No Rescue Meds Population Change from Baseline in Average Nausea

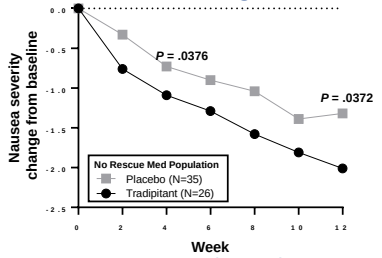
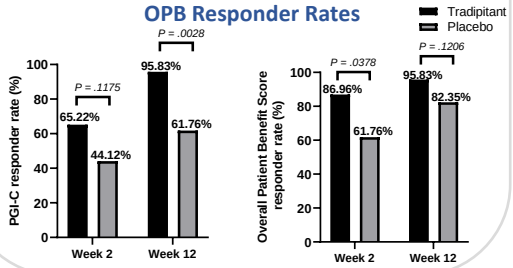


Figure 7. No Rescue Med Population PGI-C and OPB Responder Rates



Results Summary

- The study did not meet its prespecified primary endpoint which was the difference between drug and placebo on the change of the severity of nausea from baseline at week 12 of treatment. Both treatment arms showed significant improvements from baseline on nausea (-1.55 improvement for tradipitant and -1.49 for placebo) and for total GCSI score (-1.48 improvement for tradipitant and -1.39 for placebo). **(Table 2)**
- Responder rates in ITT population for PGI-C were 74% on tradipitant versus 58% on placebo at week 2 and 78% on tradipitant versus 66% on placebo at week 12 **(Figure 3).**
- For the Overall Patient Benefit, more patients improved on tradipitant versus placebo with 81% v. 62% at week 2 and 86% v. 71% at week 12 (**Figure 3**)
- Further analysis was performed to unmask the high placebo effect. PK Compliance and No Rescue Medication Populations controlled for study confounders and showed a larger rate of responders despite the smaller size. **(Figure 4- Figure 7)**

Conclusions

- Significant but similar improvements from baseline for tradipitant and placebo may have masked the true treatment effect size at the primary endpoint of the study of change in nausea severity, as measured by daily diary at week 12.
- Despite the large placebo effect, tradipitant was shown to be significantly better than placebo in global measures of patient improvement including the Patient Global Impression of Change (PGI-C) and the Overall Patient Benefit (OPB) scales.
- Sensitivity analysis adjusting for drug compliance and rescue medication use further confirmed the ITT findings in both the PGI-C and OPB analyses at week 2 and week 12.

Acknowledgements

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REFERENCES

1. M. Camilleri *et al.*, *Nat. Rev.*, pp. 145–150, 2018
2. R. A. Leslie, *Neurochem. Int.*, vol. 7, no. 2, pp. 191–211, 1985
3. L. Quartara and C. A. Maggi, *Neuropeptides*, vol. 32, no. 0143–4179, pp. 1–49, Feb. 1998
4. J. Herrstedt *et al.*, *J. Clin. Oncol.*, vol. 27, no. 32, pp. 5363–5369, 2009.
5. Carlin et al., Gastroenterology; Vol. 160, no. 1, P76-87.E4, Jan 2021