Pooled Efficacy Analysis of Tradipitant in Idiopathic and Diabetic Gastroparesis: Study VP-VLY-686-3301 and VP-VLY-686-2301

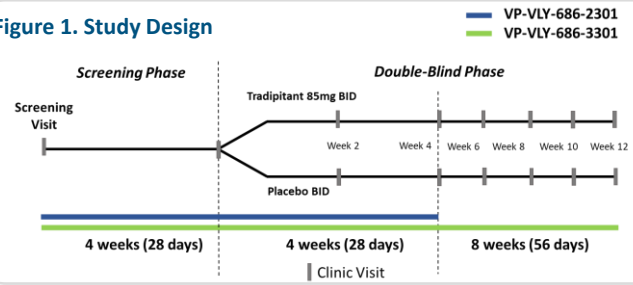
Jesse L. Carlin, Ph.D.; Christos Polymeropoulos, M.D.; Michaela Fisher, Darby Madonick, Caleigh Kupersmith, Paula Moszczynski, Changfu Xiao, Ph.D.; Gunther Birznieks, M.S.; Mihael H. Polymeropoulos, M.D. – *Vanda Pharmaceuticals Inc., Washington, DC*

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)
- Substance P 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)
- Study VP-VLY-686-3301 and VP-VLY-686-2301 were multicenter, randomized, double-blind, placebo-controlled studies assessing the efficacy of tradipitant in relieving symptoms of gastroparesis
- Data from the first 4 weeks of treatment in study VP-VLY-686-3301 and study VP-VLY-686-2301 were pooled

Methods

Figure 1. Study Design



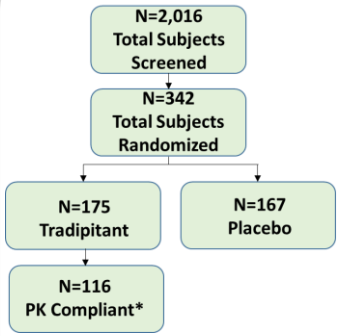
Inclusion Criteria

- 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



*PK Compliance Population includes ITT patients with tradipitant levels ≥ 140ng/ml

Results

Table 1. Study Demographics – Pooled

All Randomized Subjects	Tradipitant (N=175)	Placebo (N=167)	Total (N=342)
Sex, n (%)			
Female	142 (81.1)	145 (86.8)	287 (83.9)
Male	33 (18.9)	22 (13.2)	55 (16.1)
Age (years)			
Mean (SD)	47.7 (13.83)	48.0 (12.68)	47.8 (13.26)
Disease etiology, n (%)			
Idiopathic	97 (55.4)	92 (55.1)	189 (55.2)
Diabetic	78 (44.6)	75 (44.9)	153 (44.7)
Body Mass Index (kg/m²)			
Mean (SD)	30.5 (5.9)	30.1 (6.0)	30.3 (5.9)

Table 2. DD-Nausea, % Nausea Free Days and GCSI Total Score – ITT

Week	Tradipitant (N=175)	Placebo (N=167)	*P value*
Daily Diary (GCSDD) – Nausea			
Week 1	-0.61	-0.48	*0.1201*
Week 2	-0.88	-0.68	*0.0611*
Week 3	-1.01	-0.84	*0.1331*
Week 4	-1.15	-0.85	*0.0138*
Nausea Free Days (%)			
Week 1	6.6	5.6	*0.552*
Week 2	12.2	8.3	*0.118*
Week 3	15.1	1.7	*0.391*
Week 4	20.9	12.5	*0.0085*
GCSI Total Score			
Week 1	-	-	-
Week 2	-0.75	-0.56	*0.0293*
Week 3	-	-	-
Week 4	-0.99	-0.76	*0.0265*

Table 3. Responders on PGI-C and Overall Benefit Score – ITT

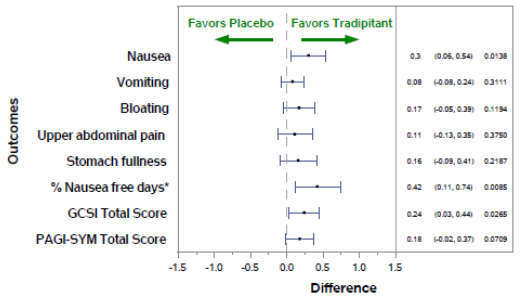
Week	Tradipitant (N=175)	Placebo (N=167)	*P value*
PGI-C Responder Rate (%)			
Week 2	72.8	58.0	*0.0047*
Week 4	79.3	69.0	*0.0365*
Overall Patient Benefit Score – Responder (%)			
Week 2	83.9	64.8	*<0.0001*
Week 4	85.3	71.1	*0.0022*

Table 4. DD-Nausea, % Nausea Free Days and GCSI Total Score – PK Compliance Population*

Week	Tradipitant (N=116)	Placebo (N=167)	*P value*
Daily Diary (GCSDD) – Nausea			
Week 1	-0.73	-0.47	*0.0105*
Week 2	-1.05	-0.68	*0.0020*
Week 3	-1.20	-0.84	*0.0042*
Week 4	-1.38	-0.84	*0.0001*
Nausea Free Days (%)			
Week 1	8.2	5.8	*0.2460*
Week 2	16.3	8.4	*0.0076*
Week 3	19.8	12.8	*0.0290*
Week 4	27.9	12.5	*<0.0001*
GCSI Total Score			
Week 1	-	-	-
Week 2	-0.90	-0.55	*0.0006*
Week 3	-	-	-
Week 4	-1.15	-0.75	*0.0006*

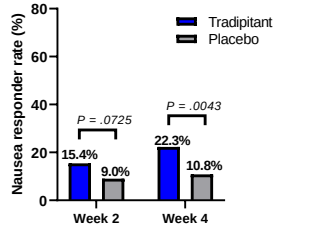
*PK Compliance Population includes ITT patients with tradipitant levels ≥ 140ng/ml

Figure 3. Forest Plot Change from Baseline in Gastroparesis Symptoms and Overall Gastroparesis Questionnaires at Week 4



*The estimated difference and its 95% CI are divided by 20.

Figure 4. Nausea Responder Rates at Week 4 in Pooled Analysis Population



*Nausea Responders include ITT patients with average nausea scores ≤ 1 at week 4

Results Summary

- Tradipitant demonstrated a clinically meaningful and statistically significant improvement in average nausea at week 4 (-1.15 for tradipitant v. -0.85 for placebo, p=0.0138) **(Table 2; Figure 3)**
- Significant improvement was seen in the percent of nausea free days (20.9% improvement for tradipitant v. 12.5% for placebo) **(Table 2)** and the percent of nausea responders at week 12 (22.3% improvement for tradipitant v. 10.8% for placebo) **(Figure 4)**
- Tradipitant showed improvement in other gastroparesis symptoms as measured by the GCSI total score (-0.99 for tradipitant v. -0.76 for placebo, p=0.0265) **(Table 2)**
- Responder rates for PGI-C were 79.3% on tradipitant versus 69% on placebo at week 4 (p value = 0.0365) **(Table 3)**
- For the Overall Patient Benefit, more patients improved on tradipitant versus placebo with 85.3% v. 71.1% at week 4 (p= 0.0022) **(Table 3)**
- In the pooled PK Compliance Population, tradipitant significantly improved average nausea at week 4 with -1.38 for tradipitant v. -0.84 for placebo (p=0.0001) **(Table 4)**

Conclusions

- Pooling the data provided an opportunity to analyze a much larger data set, increase statistical power, and confirm results and subpopulations from the two separate studies (VP-VLY-686-3301 and VP-VLY-686-2301)
- In the pooled analysis, we observed a clinically meaningful and significant effect on change of nausea severity at week 4
- Improvements were also seen across core gastroparesis symptoms and overall measures of gastroparesis

Acknowledgements

Vanda would like to acknowledge the investigators and patients who participated in these studies.

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.