



## **Velusetrag (TD-5108)**

*Top-line Results from Phase 2b Study in Gastroparesis*

August 2, 2017

# Forward Looking Statements

---

Under the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995, the company cautions investors that any forward-looking statements or projections made by the company are subject to risks and uncertainties that may cause actual results to differ materially from the forward-looking statements or projections.

Examples of forward-looking statements in this presentation include statements relating to the company's business plans and objectives, including financial and operating results, potential partnering transactions and sales targets, the company's regulatory strategies and timing and results of clinical studies, the potential benefits and mechanisms of action of the company's product and product candidates (including their potential as components of combination therapies and the timing and use of the net proceeds from the proposed offering).

The company's forward-looking statements are based on the estimates and assumptions of management as of the date of this presentation and are subject to risks and uncertainties that may cause the actual results to be materially different than those projected, such as risks related to delays or difficulties in commencing or completing clinical studies, the potential that results from clinical or non-clinical studies indicate product candidates are unsafe or ineffective (including when our product candidates are studied in combination with other compounds), delays or failure to achieve and maintain regulatory approvals for product candidates, risks of collaborating with third parties to discover, develop and commercialize products, risks associated with establishing and maintaining sales, marketing and distribution capabilities, and market conditions that may affect whether the offering will be made or consummated on the proposed terms, if at all. Other risks affecting the company are described under the heading "Risk Factors" and elsewhere in the company's Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 9, 2017, and other periodic reports filed with the SEC.

# Gastroparesis Presents a Meaningful Opportunity to Improve Lives of Patients

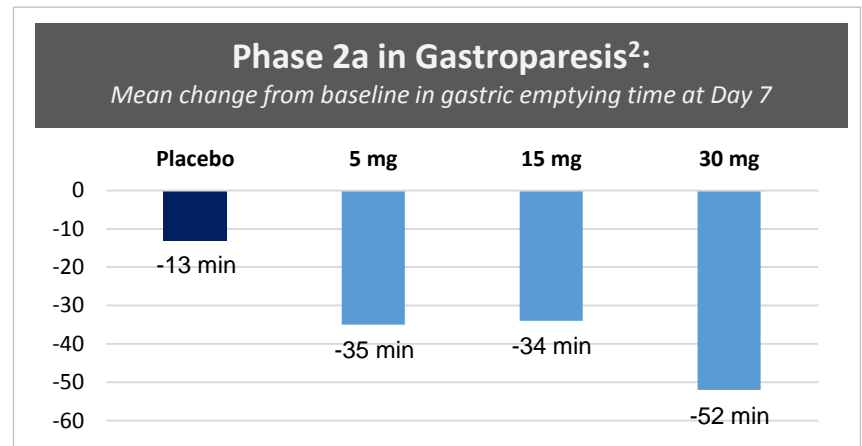
- Gastroparesis is a severe disease with debilitating symptoms
  - Characterized by delayed gastric emptying
  - Symptoms include nausea, vomiting, postprandial fullness, early satiety, and upper abdominal pain
- High prevalence<sup>1</sup>
  - Estimated 6M patients in US
  - Split between diabetic, idiopathic, and other
- One approved therapy in 35 years
  - Significant safety concerns limit use



A disease in significant need of therapeutic innovation

# Velusetrag Well Positioned to Address the Unmet Patient Need in Gastroparesis

- Highly selective 5-HT<sub>4</sub> receptor agonist with high intrinsic activity
  - Internally discovered
- Long term toxicity and carcinogenicity studies complete
- Partnered ex-US with Alfasigma<sup>1</sup>
- Fast Track designation in gastroparesis granted by FDA in late 2016
- Multiple positive Phase 2 studies complete
  - CIC and gastric emptying
  - Well-tolerated in > 600 subjects exposed



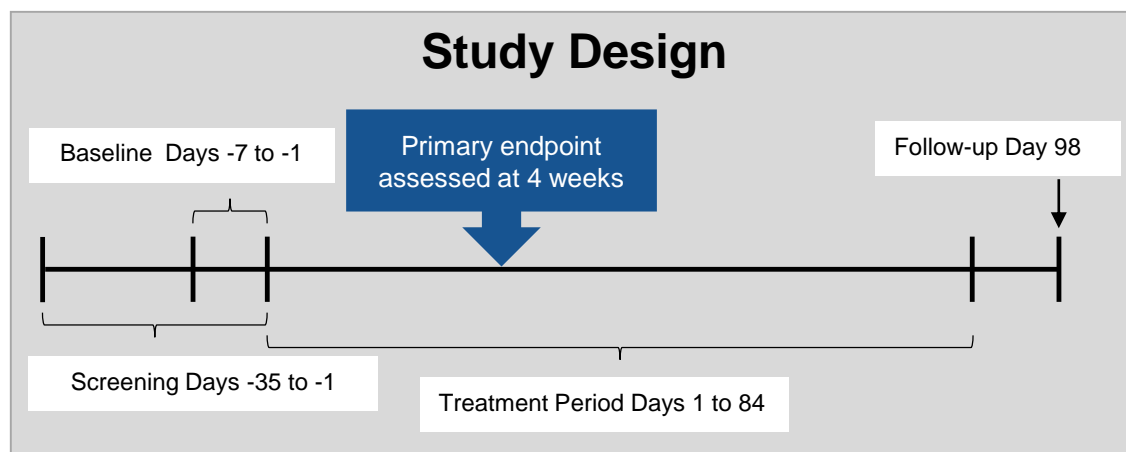
Phase 2b study serves as first clinical evaluation of effect of velusetrag on symptoms of gastroparesis

<sup>1</sup> Velusetrag is being developed by Theravance Biopharma in collaboration with Alfasigma (AS). AS holds an exclusive option to certain ex-U.S. markets. Theravance Biopharma retains all U.S. rights.  
<sup>2</sup> Similar results on gastric emptying observed in both diabetic and idiopathic gastroparesis patients.  
CIC = chronic idiopathic constipation

# Velusetrag Study Evaluated Two Distinct Populations

*Enrolled both diabetic and idiopathic gastroparesis patients*

- **Design:** Randomized, double-blind, and placebo-controlled Phase 2b study
- **Sample size:** 232 gastroparesis patients (119 diabetic, 113 idiopathic)
- **Four dose groups:** Placebo and 3 doses of velusetrag (5, 15 and 30 mg)
- **Duration of Treatment:** 12 weeks (primary endpoint assessed at 4 weeks, followed by an additional 8 weeks to assess ongoing effect and withdrawal rates)
- **Primary Endpoint:** GCSI after 4 weeks of treatment
  - *Pre-specified analysis of each dose against placebo to report nominal p-values*
  - *Multiplicity adjustment of p-values to account for 3 comparisons to placebo*



## Secondary Endpoints

- Psychometric properties of new PRO (GRS)
- Gastric emptying
- Effect on nausea
- Pharmacokinetics
- Safety and tolerability

# Velusetrag Phase 2b Included Two Separate Instruments to Capture Symptom Scores

---

## GCSI

- Gastroparesis Cardinal Symptom Index
- Current standard PRO tool in gastroparesis, developed prior to 2015 FDA Guidance<sup>1</sup>
- Evaluates 3 symptom domains
  1. Nausea/vomiting
  2. Fullness/early satiety
  3. Bloating
- Does not include pain, although the FDA now considers pain a cardinal symptom<sup>1</sup>
- Measures severity (0-5 scale)

## GRS

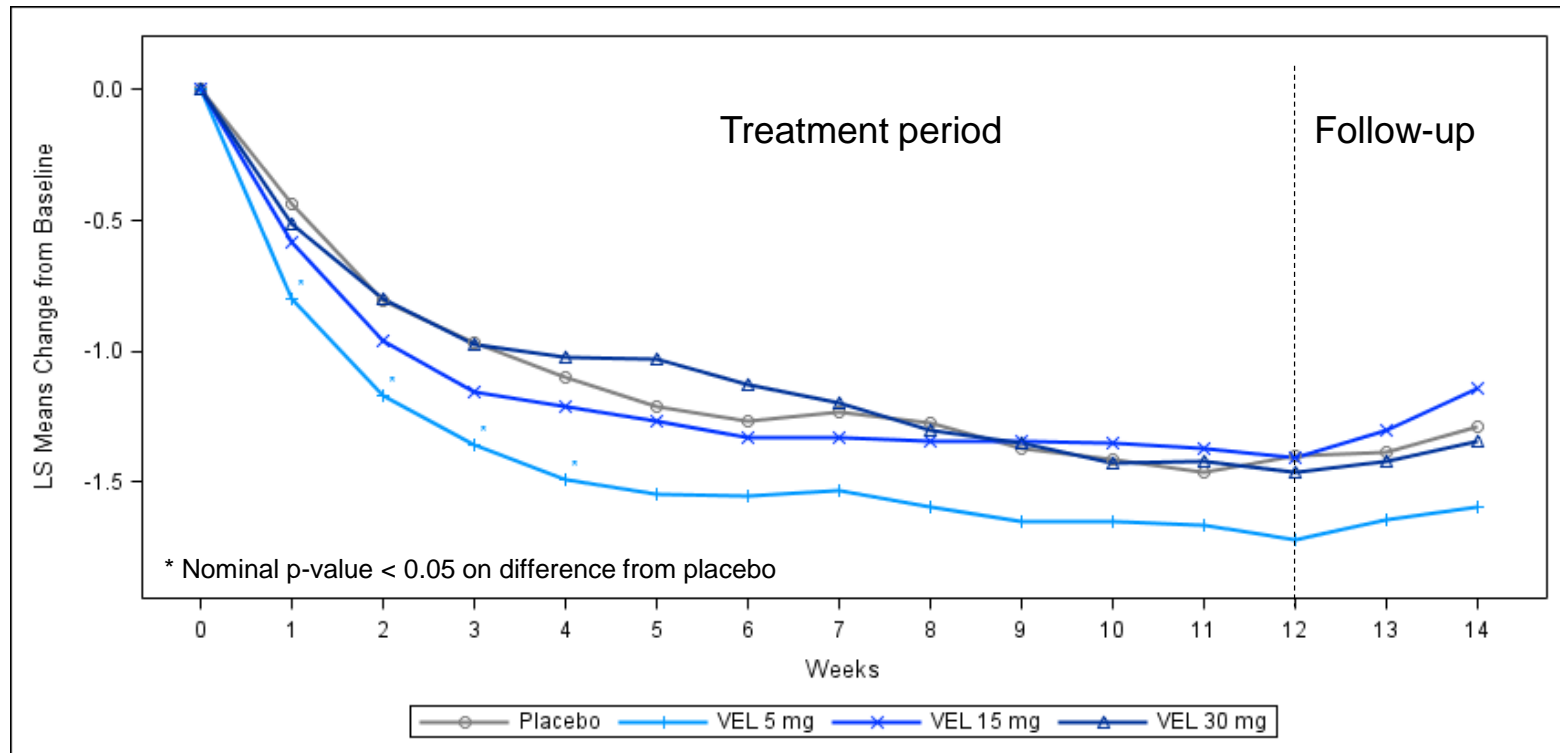
- Gastroparesis Rating Scale
- Novel proprietary PRO tool developed through academic collaboration, in alignment with current FDA guidance<sup>1</sup>
- Evaluates 7 symptom domains
  1. Nausea
  2. Vomiting
  3. Fullness and early satiety
  4. Bloating
  5. GI burning
  6. Upper abdominal pain
  7. Bowel movement
- Measures severity, frequency, and length of symptoms

<sup>1</sup>Gastroparesis: Clinical Evaluation of Drugs for Treatment Guidance for Industry Draft Guidance July 2015

6 <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm455645.pdf>

<sup>2</sup>Neither PRO tool has been validated by the FDA in gastroparesis. Symptom domains or associated scoring could change in conjunction with validation.

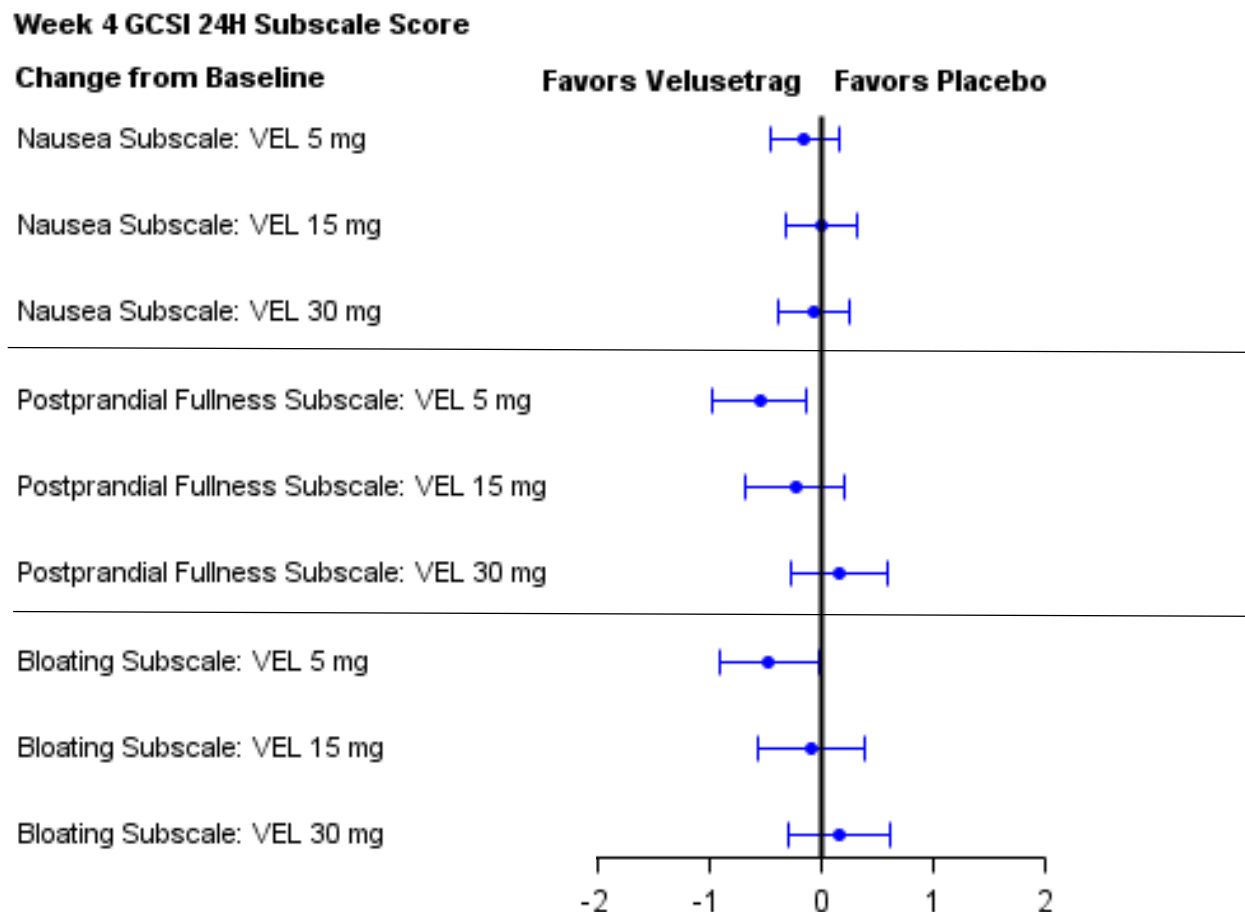
# Velusetrag 5 mg Showed Greatest Improvement in GCSI Total Score (Mean Change from Baseline)



- 5 mg dose statistically significant (nominal  $p < 0.05$ ) at weeks 1 – 4
- 15 and 30 mg doses not statistically significant
- Lack of dose response resulted in lack of statistical significance across 3 doses when adjusted for multiplicity

Statistical significance at 5 mg provides confidence in robust treatment effect

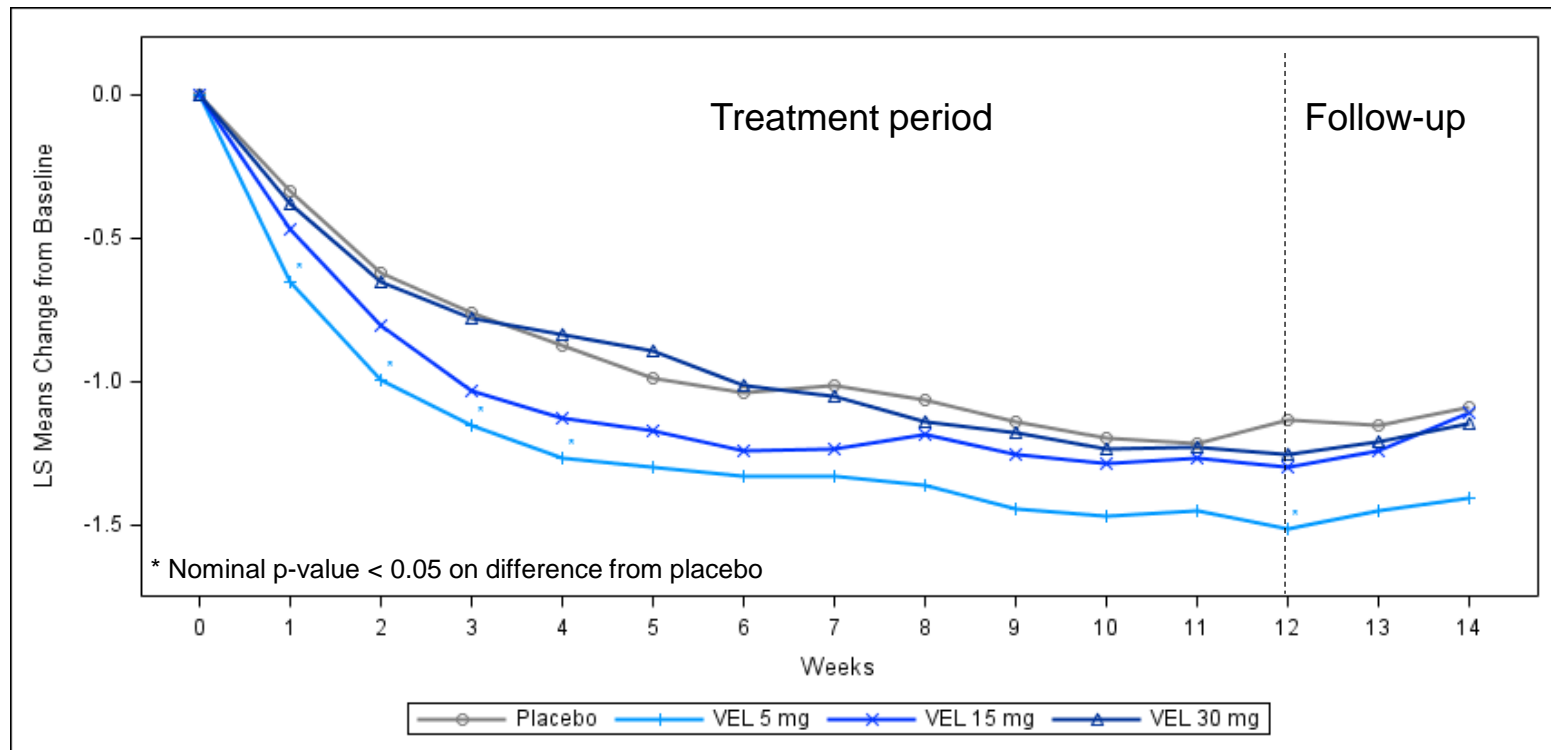
# Velusetrag Demonstrated Inverse Dose Response on GCSI Subscale Scores



5 mg dose consistent across all three GCSI subscales



# Velusetrag 5 mg Showed Greatest Improvement in GRS Total Score (Mean Change from Baseline)



- 5 mg dose statistically significant (nominal  $p < 0.05$ ) at weeks 1 - 4 and at Week 12
- Inverse dose response consistent with GCSI (15 and 30 mg not significant)

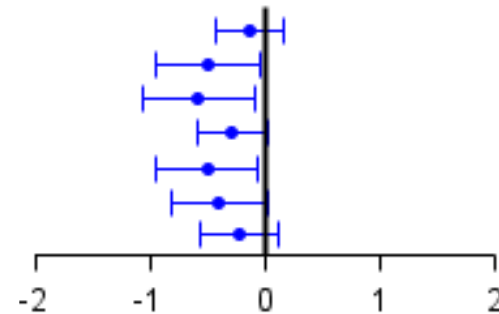
# Velusetrag 5 mg: Consistent Improvement Across All Individual GRS Subscale Scores

## Week 4 GRS Subscale Score

### Change from Baseline

Nausea Subscale: VEL 5 mg  
Bloating Subscale: VEL 5 mg  
Fullness Subscale: VEL 5 mg  
Vomiting Subscale: VEL 5 mg  
Abdominal Pain Subscale: VEL 5 mg  
Burning Subscale: VEL 5 mg  
Bowel Movements Subscale: VEL 5 mg

Favors Velusetrag    Favors Placebo

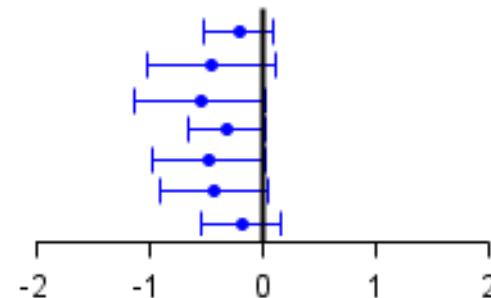


## Week 12 GRS Subscale Score

### Change from Baseline

Nausea Subscale: VEL 5 mg  
Bloating Subscale: VEL 5 mg  
Fullness Subscale: VEL 5 mg  
Vomiting Subscale: VEL 5 mg  
Abdominal Pain Subscale: VEL 5 mg  
Burning Subscale: VEL 5 mg  
Bowel Movements Subscale: VEL 5 mg

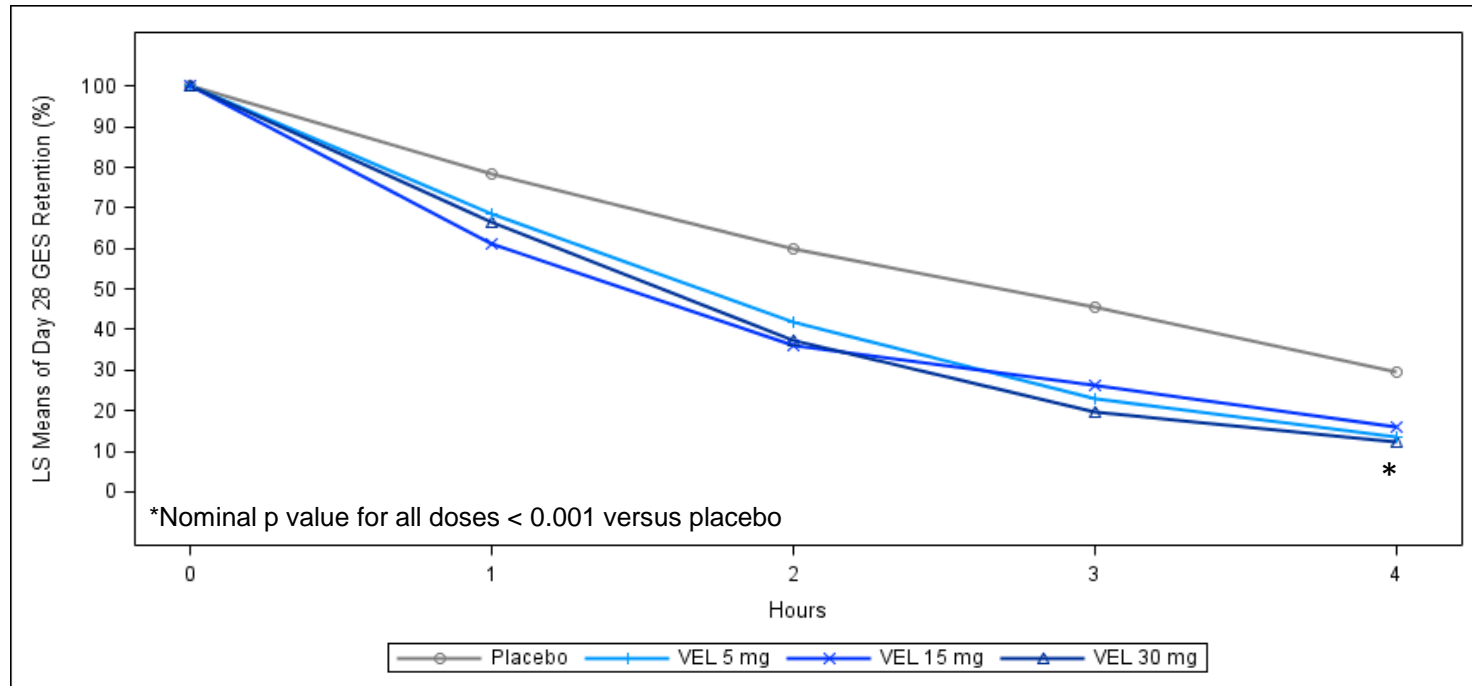
Favors Velusetrag    Favors Placebo



Enduring effect of 5 mg with symptom improvement at 4 and 12 weeks

# Velusetrag Normalized Gastric Emptying in a Dose Dependent Manner

LS Means Day 28 GES % Retention by Hour



	Placebo (N=23)	VEL 5 mg (N=23)	VEL 15 mg (N=20)	VEL 30 mg (N=21)
Patients with Normal Gastric Emptying at Day 28, n (%)	0 (0%)	10 (44%)	13 (65%)	15 (71%)

All doses significantly improve gastric emptying at 4 hours (nominal p < 0.001)

# Velusetrag 5 mg Generally Well Tolerated with Rates of AEs Comparable to Placebo

Adverse Events Reported at Frequency >5%	Placebo (N=59)	VEL 5 mg (N=59)	VEL 15 mg (N=56)	VEL 30 mg (N=58)
<b>Subjects Reporting at Least One Adverse Event</b>	<b>38 (64.4%)</b>	<b>35 (59.3%)</b>	<b>38 (67.9%)</b>	<b>29 (50.0%)</b>
Diarrhea	4 (6.8%)	7 (11.9%)	17 (30.4%)	11 (19.0%)
Nausea	2 (3.4%)	4 (6.8%)	4 (7.1%)	8 (13.8%)
Headache	8 (13.6%)		5 (8.9%)	2 (3.4%)
Abdominal pain	3 (5.1%)	6 (10.2%)	1 (1.8%)	1 (1.7%)
Urinary tract infection	3 (5.1%)	2 (3.4%)	2 (3.6%)	4 (6.9%)
Upper respiratory tract infection	5 (8.5%)	3 (5.1%)		
Abdominal pain upper	2 (3.4%)	3 (5.1%)		1 (1.7%)
Chest pain	3 (5.1%)	1 (1.7%)	1 (1.8%)	1 (1.7%)
Vomiting			2 (3.6%)	4 (6.9%)
Bronchitis		1 (1.7%)	3 (5.4%)	1 (1.7%)

➤ Higher rates of diarrhea and nausea/vomiting at 15 and 30 mg doses

- Side effects at higher doses may have blunted symptom benefits

GI side effects at higher doses could account for inverse dose response on symptom scores

# Velusetrag Phase 2b Study Summary Results

- 5 mg demonstrated statistically significant improvements in gastroparesis symptoms compared to placebo
  - Both PROs: GCSI at 4 weeks and GRS at 4 and 12 weeks<sup>1</sup>
  - Both patient sub-types: idiopathic and diabetic gastroparesis
  - Consistent effects in individual symptom domains compared to placebo
- Inverse dose response observed
  - As dose increased, symptom effect decreased<sup>2</sup>
- Meaningful improvements in gastric emptying at all doses
- Generally well tolerated: Rates of AEs and SAEs for 5mg comparable to placebo

**Next Steps: Prepare to meet with regulators to discuss validation of the GRS PRO and next phase of development for velusetrag**