Symptom Severity Influences Drug Efficacy in Women with Diabetic Gastroparesis: Results of a Phase 3 Study with Metoclopramide Nasal Spray

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Abstract

Oral and parenteral formulations of metoclopramide, a dopamine D2-receptor antagonist with prokinetic and central anti-emetic actions, remain the only products approved by the Food and Drug Administration (FDA) to treat gastroparesis (GP), a female dominated (80%), often debilitating disease, whose prevalence has grown due to the increased incidence of diabetes.

Gimoti™ is a nasal spray formulation of metoclopramide that can be absorbed locally to bypass a poorly emptying stomach to assure a systemic therapeutic dose of metoclopramide is rapidly bioavailable, even during episodes of vomiting.

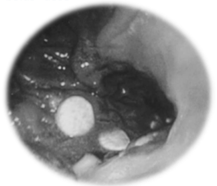
The aim of this Phase 3 trial was to evaluate the efficacy and safety of Gimoti in women with diabetes, delayed gastric emptying, and GP symptoms of varying severity.

Background

Oral and injectable formulations of metoclopramide have been used to treat diabetic GP for more than 35 years. Metoclopramide's prokinetic and antiemetic properties have been shown to be efficacious in relieving the symptoms of diabetic gastroparesis, particularly nausea, which usually precedes vomiting, and is one of the most debilitating symptoms of this disease for many patients. If oral metoclopramide cannot be reliably delivered to the small intestine, nausea may not be successfully treated and the resultant vomiting may further exacerbate the erratic or failed absorption from the gastrointestinal tract as well as impair diabetic control. The 2013 American College of Gastroenterology Clinical Guideline for Gastroparesis specifically states "*Metoclopramide is the first line of prokinetic therapy and should be administered at the lowest effective dose in a liquid formation to facilitate absorption".*

When delivered nasally, metoclopramide can be absorbed locally to bypass a dysfunctional stomach and assure a systemic therapeutic dose is rapidly bioavailable, even during an acute flare that may include nausea and vomiting. Nasal delivery also guarantees that there will be no dose dumping caused by an accumulation of metoclopramide tablets in the stomach that may eventually move into the small intestine delivering a "bolus" dose that could precipitate dose-related adverse events.

Evoke Pharma, Inc. (Evoke) has developed Gimoti (metoclopramide nasal spray) as an alternative route of administration to metoclopramide tablets. Gimoti has the potential to help diabetic GP patients avoid hospitalization during an acute flare when the tablet may be ineffective. At present, the intravenous formulation is the only option for these patients.



Simpson SE. Pharmacobezoars described and demystified. *Clinical Toxicology* 2011:49, 72-89.

Unlike oral medications, nasal delivery bypasses the gastrointestinal tract and directly enters the bloodstream

Design of Phase 3 Clinical Trial

This multicenter US study randomized female patients with symptomatic diabetic GP in a 1:1 ratio to Gimoti (10 mg) or placebo dosed four times daily; 30 minutes before meals and at bedtime for 28 days. The study consisted a 7-day Qualification Period, a 7-day Baseline Period, and a 28-day Treatment Period.

Eligible subjects were 18 to 75 years of age with type 1 or type 2 diabetes, had a documented delay in gastric emptying by scintigraphy, and met a pre-specified GP symptom score (=1.4 to =3.5 on a 5-point scale) during both the Qualification and Baseline Periods.

The primary objective of the study was evaluate the safety and effectiveness of Gimoti 10 mg compared to placebo in reducing the symptoms of diabetic gastroparesis in adult female subjects.

Methods

Seven (7) patient-reported signs and symptoms of GP were collected to assess the efficacy of Gimoti in this study: nausea, early satiety, prolonged fullness, bloating, upper abdominal pain, vomiting, and retching. The items were selected based on review of the gastroparesis literature, input from clinical experts, qualitative research conducted in the target patient population, and meetings and correspondence with FDA. Subject symptom scores and sign frequencies were collected on a daily basis using a telephone IVRS. The severity of individual symptoms and frequency of individual signs were scored from 0 (none) to 4 (very severe).

More than a year after enrollment began in this study, the first guidance on the clinical evaluation of drugs for the treatment of gastroparesis was issued (Gastroparesis: Clinical Evaluation of Drugs for Treatment, Draft Guidance, July 2015). Although many of recommendations in the Guidance were consistent with previous discussions with the Agency, and had been incorporated into the design of this Phase 3 study, there was one notable exception.

The Guidance stated; *"To optimize the ability to demonstrate a treatment effect, the trial should enroll patients with higher symptom severity (moderate to severe)."*

Results

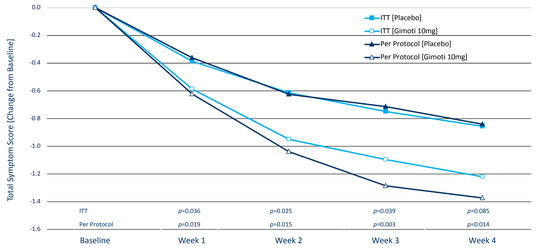
205 women (mean age 52.7, 88% type 2 diabetes; 79% postmenopausal, and 51% using insulin) were randomized and 93% completed the study.

The mean duration of diabetes was 12.9 years, the mean baseline hemoglobin A1c was 7.5% and the mean BMI was 35.1 kg/m^2 (range 15.4-63.7).

Gimoti was well-tolerated. No treatment-related trends with respect to treatment emergent adverse events (TEAEs), laboratory measurements, vital signs, new or worsened abnormal physical findings, or concomitant medications were observed.

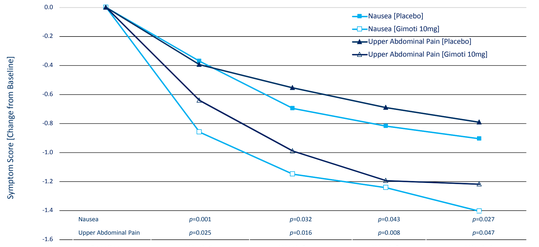
The primary endpoint, the change from Baseline to Week 4, was not statistically significant (p=0.881), however, in exploratory analyses, patients with higher (moderate to severe) baseline symptom scores in the ITT population (n=105) had a significant treatment effect (p<0.05) at Weeks 1 to 3 as well as, a significant reduction in nausea and upper abdominal pain for all four study weeks (p<0.05).

Total Symptom Scores in Analysis Populations: Change from Baseline by Week



When the subjects with moderate-to-severe symptoms at Baseline (N = 105) were separated from all treated subjects (205), treatment with Gimoti was found to result in greater improvement in GP symptoms compared to placebo.

Nausea and Upper Abdominal Pain: Change from Baseline by Week



In these female subjects with moderate-to-severe symptoms at Baseline (N=105), a significant treatment effect was observed for nausea and upper abdominal pain. These Phase 3 results for individual symptom are consistent with the Phase 2 results in female subjects.

Safety

Reports of TEAEs were similar in both groups (36% Gimoti and 35% placebo) and most were mild or moderate in severity. More CNS and nasal events occurred in subjects receiving placebo. The three SAEs in subjects receiving Gimoti (orthostatic hypotension, cellulitis, and chalazion) were assessed by the Investigators as not related to study drug.

Number of Subjects with:	Placebo (N = 103)	Gimoti 10 mg (N = 102)
Any treatment emergent adverse event (AE)	36 (35%)	37 (36%)
Severe AE	2 (2%)	4 (4%)
AE Related to Study Drug	21 (20%)	17 (17%)
Serious AE (SAE)	2 (2%)	3 (3%)
AE of Special Interest		
CNS Disorders	14 (14%)	10 (10%)
Psychiatric Disorders	3 (3%)	4 (4%)
Cardiovascular Disorders	0	4 (4%)
Nasal Events	15 (15%)	5 (5%)
AE Leading to Study Drug Withdrawal	2 (2%)	6 (6%)
AE Leading to Study Withdrawal	0	5 (5%)

Conclusions

- Although the primary efficacy outcome of this Phase 3 study of Gimoti treatment for women with diabetic gastroparesis was not statistically met for the overall ITT population (which included patients with mild symptoms), significant efficacy, compared to placebo, was observed in patients with **moderate-to-severe** symptoms.
- Gimoti was particularly effective in reducing nausea and upper abdominal pain, regarded as the most common and debilitating symptoms of gastroparesis.
- Gimoti provided statistically significant symptom relief in women with diabetic GP who had moderate to severe symptoms at Baseline consistent with FDA's draft guidance for GP which recommends enrolling GP patients with higher symptom severity to demonstrate a treatment effect.
- Gimoti 10 mg used four times per day for four weeks was well-tolerated with a safety profile similar to placebo.