CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209388Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	209388
Priority or Standard	Standard
Submit Date(s)	12/19/2019
Received Date(s)	12/19/2019
PDUFA Goal Date	06/19/2020
Division/Office	Division of Gastroenterology (DG)/Office of Immunology and Inflammation (OII)
Review Completion Date	06/18/2020
Established/Proper Name	Metoclopramide nasal spray
(Proposed) Trade Name	Gimoti
Pharmacologic Class	Dopamine-2 receptor antagonist
Applicant	Evoke Pharma
Dosage Form	Nasal spray
Applicant Proposed Dosing Regimen	The recommended Gimoti dose for the treatment of acute and recurrent diabetic gastroparesis is 15 mg 4 times daily for 2 to (b) (4) weeks, depending on symptomatic response. [Note: on June 16, 2020, the Applicant requested to revise the duration to 2 to 8 weeks]. For any single episode of gastroparesis, there should be no more than 12 cumulative weeks of metoclopramide exposure (all dosage forms and routes of administration) because of the increased risk of developing TD with longer-term use. Administer the dose 30 minutes before each meal and at bedtime. The maximum recommended daily dose is 60 mg.
Applicant Proposed Indication(s)/Population(s)	Gimoti is indicated for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Gimoti is indicated for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. Limitations of Use: Gimoti is not recommended for use in: • pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates. • moderate or severe hepatic impairment (Child-Pugh B or C), moderate or severe renal impairment (creatinine clearance less than 60 mL/minute), and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions.

Recommended Dosing Regimen	*Adults Less Than 65 Years of Age*: The recommended dosage of Gimoti for the treatment of acute and recurrent diabetic gastroparesis in adults is 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum of four times daily) for 2 to 8 weeks, depending on symptomatic response. *Adults 65 Years of Age and Older*: Elderly patients may be more sensitive to the adverse effects of metoclopramide and require a lower starting. Gimoti is not recommended in geriatric patients as initial therapy. Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to Gimoti 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum four times daily) for 2 to 8 weeks, depending on symptomatic response. Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks.

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OPQ= Office of Pharmaceutical Quality=
OPDP= Office of Prescription=Drug Promotion=
OSI= Office of Scientific Investigations=
OSE= Office of Surveillance and Epidemiology=
DEPI= Division of Epidemiology=
DMEPA= Division of Medication Error Prevention and Analysis=
DRISK= Division of Risk Management=
DPMH= Division of Pediatric and Maternal Health=
DMPP= Division of Medical Policy Programs=
ADL= Associate Director for Labeling=
CDRH= Center for=Devices and Radiological Health=

Glossary

AE	adverse event
ARIA	Active Risk Identification and Analysis
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
CDRH	Center for Devices and Radiological Health
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	Complete Response
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DEPI	Division of Epidemiology
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
GI	gastrointestinal
GP	gastroparesis
IND	Investigational New Drug
IV	intravenous
NDA	new drug application
NMS	neuroleptic malignant syndrome
OCP	Office of Clinical Pharmacology
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
TD	tardive dyskinesia

1. Executive Summary

1.1. Product Introduction

NDA 209388 for Gimoti (metoclopramide hydrochloride) nasal spray was initially submitted on June 1, 2018 and received a Complete Response (CR) action on April 1, 2019. For full details of the first review cycle, refer to the multidisciplinary review memo, dated March 29, 2019. The focus of this memo is the resubmission of NDA 209388, received on December 19, 2019, that responds to the deficiencies identified in the CR Letter. The proposed regulatory pathway for approval is Section 505(b)(2) of the Federal Food Drug and Cosmetic Act, relying upon the Agency's previous findings of safety and effectiveness for the listed drug, Reglan (metoclopramide hydrochloride) 10 mg oral tablets (NDA 17854).

Metoclopramide, a synthetic substituted benzamide and is a dopamine-2 receptor antagonist, is approved for the treatment of diabetic gastroparesis and is available as an oral tablet, oral solution, injectable, and as an orally dissolving tablet formulation. Metoclopramide is thought to be a stimulant of upper gastrointestinal (GI) motility; however, the exact mechanism of action of metoclopramide in the treatment of acute and recurrent diabetic gastroparesis has not been fully established. Metoclopramide seems to sensitize tissues to the action of acetylcholine, increases the tone and amplitude of gastric (especially antral) contractions, relaxes the pyloric sphincter and duodenal bulb, and increases peristalsis of the duodenum and jejunum, thus resulting in accelerated gastric emptying and intestinal transit.[1]

The labeling for approved metoclopramide products includes a Boxed Warning for tardive dyskinesia (TD). TD is a central nervous system (CNS) adverse event and is a syndrome of potentially irreversible and disfiguring involuntary movements of the face or tongue, and sometimes of the trunk and/or extremities. The risk of developing TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dosage of metoclopramide. The cumulative use of metoclopramide should not exceed 12 weeks due to the risk of TD. In addition, metoclopramide may also cause other extrapyramidal symptoms (EPS) such as acute dystonic reactions, parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies), and motor restlessness (akathisia).[1]

The recommended indication for Gimoti is for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis with the following Limitations of Use:

Gimoti is not recommended for use in:

- pediatric patients due to the risk of developing tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates.
- moderate or severe hepatic impairment (Child-Pugh B or C), moderate or severe renal

[1] Reglan prescribing information (source: drugs@fda; accessed 04/13/2020)

impairment (creatinine clearance less than 60 mL/minute), and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions.

The recommended Gimoti dosing is as follows:

Adults Less Than 65 Years of Age: The recommended dosage of Gimoti for the treatment of acute and recurrent diabetic gastroparesis in adults is 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum of four times daily) for 2 to 8 weeks, depending on symptomatic response.

Adults 65 Years of Age and Older: Elderly patients may be more sensitive to the adverse effects of metoclopramide and require a lower starting dosage. Gimoti is not recommended in geriatric patients as initial therapy.

Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to Gimoti 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum four times daily) for 2 to 8 weeks, depending on symptomatic response. Avoid treatment with metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The approval of Gimoti (metoclopramide) nasal spray is under the 505(b)(2) regulatory pathway, based on comparative bioavailability (BA) to Reglan (metoclopramide) 10 mg oral tablet (listed drug). The information provided in the Class 2 resubmission of NDA 209388, received on December 19, 2019, adequately addresses the concerns raised during the first review cycle, for which a CR action was taken.

To establish a bridge between Gimoti and Reglan, the Applicant conducted a BA study, METO-IN-006; at all three doses of nasal spray evaluated (15, 16 and 17 mg), Gimoti showed comparable area under the curve (AUC) to Reglan 10-mg tablet, but demonstrated on average, a 16 to 20% lower maximum plasma concentration (C_{max}), which was primarily due to aberrant pharmacokinetics (PK) profiles in 4.5% of the study subjects. During the first review cycle, the reason for the aberrant PK profiles was not entirely clear. A CR was issued due to uncertainty as to whether Gimoti was able to deliver metoclopramide in a reliable and consistent manner given that a clear explanation was lacking for the lower C_{max} observed in the BA study, and there was insufficient evidence to ensure that the quality control and essential performance characteristics of the combination product did not contribute to the observed clinical variability.

In the resubmission, the Applicant addressed the deficiencies related to the quality control and essential performance characteristics of the combination product by reevaluating the acceptance criteria for the specification using batches manufactured at the proposed commercial strength, including for spray pattern and droplet size, and adding a test and

acceptance criterion for actuation force to the finished product specification. Additionally, the Applicant submitted findings from a root cause analysis which was designed to identify the potential source(s) of the aberrant PK profiles. Review of the root cause analysis report, in conjunction satisfactory resolution of the product quality and device-related issues support that the aberrant PK profiles resulting in a lower C_{max} on average, were likely due to erroneous intranasal administration of the study drug by study staff in the comparative BA study METO-IN-006 resulting in little to no systemic exposure in some subjects across all three dose groups.

In light of identifying a plausible explanation for the aberrant PK profiles and since the quality deficiencies were addressed, it is reasonable to conclude that the results of the relative bioavailability study, METO-IN-006, provide support for relying on the findings of efficacy and safety for the listed drug (Reglan 10-mg tablet).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

NDA 209388 for Gimoti (metoclopramide hydrochloride) nasal spray was initially submitted on June 1, 2018 and received a Complete Response (CR) action on April 1, 2019. The resubmission was received on December 19, 2019 and responds to the deficiencies identified in the CR Letter. The proposed regulatory pathway for approval is Section 505(b)(2) of the Federal Food Drug and Cosmetic Act, relying upon the Agency's previous findings of safety and effectiveness for the listed drug, Reglan (metoclopramide hydrochloride) 10 mg oral tablets (NDA 17854).

To establish a bridge between Gimoti and Reglan, the Applicant conducted a relative BA study (METO-IN-006). Systemic exposure of metoclopramide was compared between single nasal administration of Gimoti at 15 mg, 16 mg, or 17 mg and single oral administration of Reglan tablet 10 mg in 98 healthy male and female subjects. For all three doses, Gimoti (15 mg, 16 mg, and 17 mg) showed comparable area under the curve (AUC) but the maximum plasma concentration (C_{max}) was 16% to 20% lower than Reglan. During the first review cycle, the review team concluded that the pharmacokinetic (PK) bridge between the Gimoti 15 mg dose and the Reglan tablet 10 mg was insufficient to justify the reliance on the findings of safety and efficacy for Reglan. Several subjects demonstrated low C_{max} (<5 ng/ml) for metoclopramide with one or more Gimoti administrations, raising concern that the product may not deliver metoclopramide in a consistent and reliable manner. The overall lower mean C_{max} was driven by individuals who appeared to receive very little drug. Additionally, there were deficiencies related to the quality control and essential performance characteristics of the combination, and the potential contribution of the quality deficiencies to the PK variability remained uncertain. Therefore, to address the deficiency, the review team recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery.

The Applicant addressed the deficiencies related to the quality control and essential performance characteristics of the combination product by reevaluating the acceptance criteria for the specification using batches manufactured at the proposed commercial strength, including for spray pattern and droplet size, and adding a test and acceptance criterion for actuation force to the finished product specification. Furthermore, the review team considered whether the root cause analysis provided in the remission supported improper administration of the study drug during METO-IN-006 as the most likely contributor to the lower C_{max}.

The Applicant claimed that insufficient training and improper behaviors of study personnel were the primary contributors of the dosing error leading to low drug exposure and provided information to support that this assertion was plausible. Twelve of 14 (86%) aberrant PK profiles were associated with 2 out of the 8 study personnel who administered Gimoti to subjects during METO-IN-006. In the absence of definitive drug product and/or device quality issues, it is likely that subjective differences among the study staff in METO-IN-006 in their comfort and ability to dose accurately, potentially differing training needs, and a large number of doses administered within a short duration, all may have

contributed to dosing errors and observed low drug concentrations in 4.5% of doses administered in METO-IN-006 (comparative bioavailability [BA] study).

As noted in the first cycle review, data from clinical trials of Gimoti in which pharmacokinetics (PK) data were collected and patients were allowed to self-administer the study drug intranasally, generally showed a lower incidence of aberrant drug levels (2-3% of doses) compared to METO-IN-006 (4.5%), suggesting fewer dosing errors when patient self-administer the drug. However, sampling timepoints in the clinical trials were not sufficient to fully capture the C_{max} because this observation is based on sparse samples compared to intensive PK sampling in the METO-IN-006 BA study. Additional information provided in a patient experience summary report supports patient comfort in self-administering an intranasal metoclopramide formulation for their gastroparesis (based on patient feedback from patients who completed the dose-ranging trial, METO-IN-002).

In light of identifying a plausible explanation for the aberrant PK profiles and since the quality and device deficiencies were addressed, it is reasonable to conclude that the results of the relative bioavailability study, METO-IN-006, provide support for relying on the findings of efficacy and safety for the listed drug (Reglan 10 mg tablet).

Finally, Gimoti 15 mg showed comparable bioavailability with Reglan Tablet 10 mg with 90% CI associated with the mean ratio for both AUC and C_{max} within 80-125% (N=94) when the data from subjects with aberrant PK profiles were excluded, which suggests that Gimoti 15 mg provides comparable bioavailability to Reglan 10 mg when dosed properly; however, the results from the original BA analysis will not be replaced with this post-hoc reanalysis that excludes the aberrant PK profiles. The median T_{max} of Gimoti is 1.25 h after dose, which is similar to that of Reglan. The elimination half-life of metoclopramide is approximately 8 hours. Given that metoclopramide is administered up to 4 times per day to relieve symptoms of gastroparesis, occasional incomplete or incorrect dose administration is not expected to have a substantial clinical implication on safety or efficacy. Any concerns related to improper nasal administration of Gimoti will be addressed in the labeling, including Instructions for Use and a Medication Guide, with instruction to ensure the proper dosing from nasal spray for self-administration. Also, to avoid potential overdosing, the labeling will include a recommendation of no additional spray per dosing even if patients perceive underdosing.

The Applicant-proposed limiting the indication to adult women with acute and recurrent diabetic gastroparesis, which was based on a post hoc subgroup analysis of the comparative BA study data which included men as well. A trend toward higher mean values of systemic exposure in females was noted for both Gimoti and Reglan. It was also noted that the overall range of systemic exposure was comparable between males and females with large inter-individual variability (50-100%). Additionally, Reglan, the listed drug, is indicated for both males and females at the same dose. The clinical pharmacology assessment focused on the analyses of relative BA without regard to sex to support the reliance on Reglan for the efficacy and safety. The data from METO-IN-006 supports the bridge between Gimoti 15 mg and Reglan regardless of sex. The effects of sex on metoclopramide PK has not been stated in Reglan label or in published literature. Therefore, Gimoti use will not be limited to women.

The safety of Gimoti was evaluated in clinical trials of patients with gastroparesis and established in clinical trials of oral metoclopramide. The adverse reactions were generally similar to those reported for oral metoclopramide. The labeling for approved metoclopramide products includes a Boxed Warning for tardive dyskinesia (TD). The risk of developing TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dose of metoclopramide. The cumulative use of metoclopramide should not exceed 12 weeks due to the risk of TD. Although the phase 2 and 3 clinical trials did not evaluate the 15 mg dose, dysgeusia was reported in 15% of patients treated during a large phase 2 trial with Gimoti 14 mg, a slightly lower dose than recommended, compared to placebo (4%). Because of the Gimoti dose (14 mg) is only slightly lower than the recommended 15 mg dose and the event may be related to the route of administration (intranasal), the Gimoti label will communicate that dysgeusia occurred during this trial at a slightly lower than recommended dose.

Additionally, there remains a theoretical concern that metoclopramide administered intranasally may result in increased neurological adverse events (AEs) relative to oral administration. To minimize the potential for serious adverse reactions associated with long-term exposure to metoclopramide, the recommended duration of Gimoti will be for 2 to 8 weeks, depending on symptomatic response. The product packaging is designed to distribute a single unit (one vial), which is sufficient for a single course of therapy. Treatment with metoclopramide (all dosage forms and routes of administration) should be avoided for longer than 12 weeks.

Per the approved label of the reference listed product (Reglan oral tablet), specific populations who have a lower capacity for drug elimination (i.e., patients with moderate to severe renal or hepatic impairment, or patients who use strong CYP2D6 inhibitors) should reduce the dose due to an increased risk of adverse reactions, including TD. In addition, geriatric patients should consider the dose reduction as geriatric patients are more likely to have decreased renal function and may be more sensitive to adverse effect compared to younger patients. Unlike Reglan, the dose delivered per spray of Gimoti cannot be adjusted and any lower strength formulation is currently unavailable. Therefore, the label will be limited to patients who do not require a dose reduction. To provide access of Gimoti to geriatric patients or patients who may have the conditions requiring dose adjustment (e.g., renal impairment), a postmarketing commitment will be issued to develop a 7.5-mg dosage strength to accommodate various situations requiring further dosage adjustments. The Applicant will also be asked to conduct a single dose pharmacokinetics study in healthy subjects to characterize dose proportionality of 7.5 mg and 15-mg dose strengths.

The risks associated with metoclopramide are adequately communicated in the labeling through a Boxed Warning and Warnings and Precautions regarding central nervous system (CNS) adverse events. To address the theoretical safety concern of the novel route of administration of Gimoti (i.e., nasal spray) and known risks of CNS adverse reactions with metoclopramide, postmarketing surveillance will be performed using the Sentinel's Active Risk Identification and Analysis (ARIA) system to evaluate the potential for increased risk of CNS adverse reactions for Gimoti relative to other marketed metoclopramide products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Gastroparesis (GP) is a disorder characterized by delayed GE of solid food in the absence of a mechanical obstruction of stomach and occurs primarily in females. The core signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety. These symptoms can be debilitating and negatively impact patients' quality of life and daily functioning.	GP remains a considerable health issue and can profoundly impact patients' quality of life.
Current Treatment Options	Reglan (metoclopramide) is the only drug currently approved for GP and is available as an oral tablet, intravenous (IV) infusion, intramuscular injection, and orally disintegrating tablet. The American College of Gastroenterology Clinical Guidelines for the treatment of GP, recommends metoclopramide as the first line pharmacologic therapy and should be administered at the lowest effective dose to decrease the risk of tardive dyskinesia (TD). Erythromycin, a motilin receptor agonist, and domperidone, another dopamine D2 receptor antagonist, are thought to accelerate GE and are also recommended by the American College of Gastroenterology. However, domperidone is associated with risk of QTc prolongation and cardiac arrhythmias. Erythromycin can be administered intravenously or orally but long-term use of the oral route is limited by tachyphylaxis. Domperidone is not approved in the United States and is available through the FDA Expanded Access program. Antiemetics, such as ondansetron, are used for symptomatic relief of nausea and vomiting. Non-pharmacologic interventions, such as dietary modifications, are often implemented (e.g., smaller meals, liquid meals, changes in nutritional composition of meals, etc.) to help control the signs and symptoms associated with delayed GE.	Reglan (metoclopramide) is currently the only approved product for the treatment of DG and is associated with safety concerns. Other therapies are used off-label and the safety and efficacy of these products has not been established for the treatment of GP. Therefore, additional treatment options are needed. Although there remains a need for additional treatment options for gastroparesis, Gimoti contains the same active ingredient as Reglan, metoclopramide, and has the same associated risks. Patients who have suboptimal efficacy with Reglan are unlikely to achieve a benefit with Gimoti. However, Gimoti offers a new route of administration as compared to the currently available therapies.
Benefit	To establish a bridge between Gimoti and Reglan, the Applicant conducted a relative BA study (METO-IN-006). Systemic exposure to metoclopramide	The quality information provided in the resubmission adequately addressed the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was compared between single nasal administration of Gimoti at 15 mg, 16 mg, or 17 mg and single oral administration of Reglan tablet 10 mg in 98 healthy male and female subjects. For all three doses, Gimoti (15 mg, 16 mg, and 17 mg) showed comparable area under the curve (AUC) but maximum plasma concentration (C_{max}) was 16% to 20% lower than Reglan. During the first review cycle, the review team concluded that the pharmacokinetic (PK) bridge between the Gimoti 15 mg dose and the Reglan tablet 10 mg was insufficient to justify the reliance on the findings of safety and efficacy for Reglan. Several subjects demonstrated low C_{max} (<5 ng/ml) for metoclopramide with one or more Gimoti administrations, raising concern that the product may not deliver metoclopramide in a consistent and reliable manner. The overall lower mean C_{max} was driven by individuals who appeared to receive very little drug. Additionally, there were deficiencies related to the quality control and essential performance characteristics of the combination, and the potential contribution of the quality deficiencies to the PK variability remained uncertain. Therefore, to address the deficiency, the review team recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery. The Applicant addressed the deficiencies related to the quality control and essential performance characteristics of the combination product by reevaluating the acceptance criteria for the specification using batches manufactured at the proposed commercial strength, including for spray pattern and droplet size, and adding a test and acceptance criterion for actuation force to the finished product specification. Furthermore, the review team considered whether the root cause analysis provided in the remission supported improper administration of the study drug during METO-IN-006 as the most likely contributor to the lower C_{max}. The Applicant claimed that insufficient training and improper behaviors of study personnel were primary contributors of the dosing error leading to low drug exposure and provided information to support that this assertion	uncertainties from the first review cycle with the quality control and essential performance characteristics of the combination product. In the absence of definitive drug product and/or device quality issues, it is likely that subjective differences among the study staff in METO-IN-006 in their comfort and ability to dose accurately, potentially differing training needs, and a large number of doses administered within a short duration, all may have contributed to dosing errors and observed low drug concentrations in 4.5% of doses administered in METO-IN-006 (comparative bioavailability [BA] study). In light of identifying a plausible explanation for the aberrant PK profiles and since the quality deficiencies were addressed, it is reasonable to conclude that the results of the relative bioavailability data from Study METO-IN-006 provide support for relying on the findings of efficacy and safety for the listed drug (Reglan 10 mg tablet). Given that metoclopramide is administered up to 4 times per day to relieve symptoms of gastroparesis, occasional incomplete or incorrect dose administration is not expected to have a substantial clinical implication on safety or efficacy. Any concerns related to improper nasal administration of Gimoti will be addressed in the labeling, including

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was plausible. Twelve of 14 (86%) aberrant PK profiles were associated with 2 out of the 8 study personnel who administered Gimoti to subjects during METO-IN-006. As noted in the first cycle review, data from clinical trials of Gimoti in which pharmacokinetics (PK) data were collected and patients were allowed to self-administer the study drug intranasally, generally showed a lower incidence of aberrant drug levels (2-3% of doses) compared to METO-IN-006 (4.5%), suggesting fewer dosing errors when patient self-administer the drug. However, sampling timepoints in the clinical trials were not sufficient to fully capture the C_{max} because this observation is based on sparse samples compared to intensive PK sampling in the METO-IN-006 BA study. Additional information provided in a patient experience summary report supports patient comfort in self-administering an intranasal metoclopramide formulation for their gastroparesis (based on patient feedback from patients who completed the dose-ranging trial, METO-IN-002). Finally, Gimoti 15 mg showed comparable bioavailability with Reglan Tablet 10 mg with 90% CI associated with the mean ratio for both AUC and C_{max} within 80-125% (N=94) when the data from subjects with aberrant PK profiles were excluded, which suggests that Gimoti 15 mg provides comparable bioavailability to Reglan 10 mg when dosed properly; however, the results from the original BA analysis will not be replaced with this post-hoc reanalysis that excludes the aberrant PK profiles. The median T_{max} of Gimoti is 1.25 h after dose, which is similar to that of Reglan. The elimination half-life of metoclopramide is approximately 8 hours. The Applicant-proposed limiting the indication to adult women with acute and recurrent diabetic gastroparesis, which was based on a post hoc subgroup analysis of the comparative BA study data which included men as well. However, Reglan, the listed drug, is indicated for both males and females at the same dose. The clinical pharmacology assessment focused	Instructions for Use and a Medication Guide, with instruction to ensure the proper dosing from nasal spray for self-administration. Also, to avoid potential overdosing, the labeling will include a recommendation of no additional spray per dosing even if patients perceive underdosing. The data from METO-IN-006 supports the bridge between Gimoti 15 mg and Reglan regardless of sex. The effects of sex on metoclopramide PK has not been stated in Reglan label or in published literature. Therefore, Gimoti use will not be limited to women.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	on the analyses of relative BA without regard to sex to support the reliance on Reglan for the efficacy and safety.	
Risk and Risk Management	Metoclopramide hydrochloride is a dopamine-2 receptor antagonist. There are safety concerns with the dopamine-2 receptor antagonist class, and include TD, other extrapyramidal symptoms (EPS), parkinsonian symptoms, motor restlessness, and potentially fatal symptom complex of neuroleptic malignant syndrome. The labeling for approved metoclopramide products includes a Boxed Warning for tardive dyskinesia (TD). The risk of developing TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dose of metoclopramide. The cumulative use of metoclopramide should not exceed 12 weeks due to the risk of TD. Per the approved label of the listed drug (Reglan oral tablet), specific populations who have a lower capacity of drug elimination (i.e., patients with moderate to severe renal or hepatic impairment, or patients who use strong CYP2D6 inhibitors) should reduce the dose due to risk of adverse reactions of metoclopramide including tardive dyskinesia. In addition, geriatric patients should consider the dose reduction as geriatric patients are more likely to have decreased renal function and may be more sensitive to adverse effect compared to younger patients. Unlike Reglan, the dose delivered per spray of Gimoti cannot be adjusted due to the nature of its nasal pump spray and any lower strength formulation is currently unavailable. Patients with diabetic gastroparesis may have conditions that warrant dose adjustment (e.g., renal or hepatic impairment, etc.). The adverse reactions were generally similar to those reported for oral metoclopramide. Dysgeusia was reported in 15% of patients treated during a large phase 2 trial with Gimoti 14 mg, a slightly lower dose than recommended, compared to placebo (4%). Because of the Gimoti dose (14 mg) is only slightly lower than the recommended 15 mg dose and the event may be related to the route of administration (intranasal), the Gimoti label	The safety of Gimoti was evaluated in clinical trials of patients with gastroparesis and established in clinical trials of oral metoclopramide. The labeling will contain the same Boxed Warning and Warnings and Precautions as Reglan. In addition, the Gimoti label will include Limitations of Use and specific language for use in patients 65 years and older. In addition to the safety information found in the listed drug (Reglan oral tablet) labeling, the Gimoti label will communicate that dysgeusia was the most commonly reported adverse reaction in the clinical trials that evaluated a lower than recommended dose of Gimoti. To minimize the potential for serious adverse reactions associated with long-term exposure to metoclopramide, the recommended duration of Gimoti will be for 2 to 8 weeks, depending on symptomatic response. The product packaging is designed to distribute a single unit (one vial), which is sufficient for a single course of therapy. The cumulative use of metoclopramide should not exceed 12 weeks due to the risk of TD. To address the need for situations that require a dose adjustment, the label will be limited to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	will communicate that dysgeusia occurred during this trial at a slightly lower than recommended dose. Additionally, there remains a theoretical concern that metoclopramide administered intranasally may result in increased neurological adverse events (AEs) relative to oral administration.	patients who do not require a dose reduction. To provide access of Gimoti to geriatric patients or patients who may have the conditions requiring dose adjustment (e.g., renal impairment), a postmarketing commitment will be issued to develop a 7.5-mg dosage strength to accommodate various situations requiring further dosage adjustments. The Applicant will also be asked to conduct a single dose pharmacokinetics study in healthy subjects to characterize dose proportionality of 7.5 mg and 15-mg dose strengths. The risks associated with metoclopramide are adequately communicated in the labeling given that labeling includes a Boxed Warning and Warnings and Precautions regarding potential for central nervous system (CNS) adverse events. To address the theoretical safety concern of the novel route of administration of Gimoti (i.e., nasal spray) and known risks of CNS adverse reactions with metoclopramide, postmarketing surveillance will be performed using the Sentinel's Active Risk Identification and Analysis (ARIA) system to evaluate the potential for increased risk of CNS adverse reactions for Gimoti relative to other marketed metoclopramide products.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Refer to first cycle COA review. There is no new COA related information in the resubmission.
		X	Patient reported outcome (PRO)	Efficacy data collected directly from patients using patient diaries were submitted and reviewed during the initial NDA review; refer to first cycle NDA multidisciplinary review and evaluation (finalized on March 29, 2019) and first cycle COA review (finalized on March 25, 2019) for details
		□	Observer reported outcome	
		□	Clinician reported outcome	
		□	Performance outcome	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
X	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	X	Other: (Please specify):		Gastroparesis - FDA-requested Patient Listening Session (December 2, 2019); Publicly available summary can be located at https://www.fda.gov/media/135878/download
□	**Patient experience data was not submitted as part of this application.**			

2. Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

Metoclopramide, a dopamine-D2 receptor antagonist, is approved for the treatment of diabetic gastroparesis in adults. Reglan (metoclopramide hydrochloride) is available as an oral tablet, oral solution, injectable, and orally dissolving tablet formulations. Metoclopramide was initially approved on February 7, 1979 as an injectable dosage form (NDA 17862). The injectable formulation carries multiple indications, including the relief of symptoms associated with acute and recurrent diabetic gastroparesis.

The Reglan tablet formulation (NDA 17854) was first approved on December 30, 1980. It is approved for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis, and for the treatment of symptomatic, documented gastroesophageal reflux in adults who fail to respond to conventional therapy. An orally disintegrating tablet formulation was approved on September 4, 2009 but was later discontinued. However, generic versions of previously approved dosage forms of metoclopramide are currently marketed. Reglan tablets are not recommended for use in pediatric patients due to the risk of TD and other EPS symptoms as well as the risk of methemoglobinemia in neonates.

The proposed formulation Gimoti (metoclopramide) nasal spray is a novel presentation for systemic delivery of metoclopramide and is not currently marketed elsewhere in the world. Under the 505(b)(2) regulatory pathway for approval, referencing Reglan 10 mg oral tablets, the Applicant is seeking an indication in diabetic gastroparesis but not for gastroesophageal reflux.

2.2. Summary of Presubmission/Submission Regulatory Activity

The initial NDA for Gimoti (metoclopramide) nasal spray (NDA 209388) was submitted on June 1, 2018 under a 505(b)(2) regulatory pathway for approval, referencing the approved Reglan 10 mg oral tablets (NDA 17854). The initial submission received a CR action on April 1, 2019. Refer to the multidisciplinary review memo, finalized on March 29, 2019, for full details of the first review cycle. The deficiencies in the CR letter are described below.

Deficiency #1: Clinical Pharmacology

The pharmacokinetic (PK) bridge between the Gimoti 15-mg dose and the Reglan tablet 10 mg is insufficient to justify the reliance on the findings of safety and efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan.

The review team was concerned that the product is not able to deliver metoclopramide in a reliable and consistent manner. Several subjects demonstrated low C_{max} (<5 ng/ml) for metoclopramide with one or more Gimoti administrations. This was not observed with Reglan

tablet administration. The overall lower mean C_{max} was driven by these individuals who appeared to receive very little drug. The reason for this observation is unclear.

Recommendations to Address Deficiencies

To address the clinical pharmacology deficiency, the review team recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery. The Applicant will need to provide evidence supporting the conclusions from the root cause analysis and provide mitigation strategies that will address the(se) issue(s). Depending on the identified cause(s), you may need to conduct additional in vitro and/or in vivo studies.

Deficiency #2: Product Quality/Device Quality

The proposed specification for the drug product is inadequate since insufficient evidence has been provided to ensure that the quality control and essential performance characteristics of the combination product do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The proposed acceptance criterion for droplet size distribution of the 15 mg/mL strength (i.e., the mean droplet sizes and calculated ranges) are not justified particularly given the observed variability of PK data.

Recommendations to Address Deficiencies

Upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by three batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device. The review team recommend that the three registration batches be manufactured at the proposed commercial manufacturing site, manufactured by the proposed commercial process, and tested using validated analytical methods at the proposed analytical site.

Additional comments were conveyed regarding dosage adjustment for specific populations and other quality and device-related issues. Refer to the CR action letter, dated April 1, 2019, for full details.

Subsequent to the CR action, a Type A meeting was held on July 25, 2019 to discuss the Applicant's proposed plan to address the CR deficiencies. A high-level summary of the meeting discussion and agreements are provided below. Refer to the meeting minutes, dated July 31, 2019, for details.

- Regarding the root cause analysis, the Division noted that although the data suggests that dose administers' behavioral variability could have contributed to the low exposure, the data are insufficient to completely rule out other possible causes. Given these gaps at the time, the Division noted that the data do not support a retrospective, statistical analysis which excludes PK profiles from the bioequivalence analysis, but that the Applicant may submit additional BE analysis from study METO-IN-006 for formal review. The Division recommended that the Applicant consider conducting a patient use/patient handling study along with PK sampling to address the potential for incomplete drug delivery that may be caused by human error. Division noted that the resubmission should include the root cause analysis.
- The Applicant stated that data describing the patient experience with using Gimoti during the clinical trials are available based on patient interviews conducted by an independent group. The Division recommended that the Applicant include in the resubmission any available data on the patient experience with Gimoti in support of the medical need for this type of intranasal product. The Division clarified that the patient use data from the clinical trials may provide reassurance that patients can properly use the device; however, the clinical trial data could not be relied upon for efficacy, safety, or PK data to support approval because the clinical trials did not include an evaluation of the to-be-marketed dose.
- The Division noted that the patient use and the need for education/training may be further evaluated in the post-marketing setting, if warranted. Therefore, the Division recommended the Applicant submit labeling, including a proposal for an Instructions for Use, with the resubmission.
- The Division noted that the root cause analysis does not completely address the "inappropriate actuation force for full dose delivery" as a potential source of error. The Division recommended establishing an actuation force specification with an adequate justification for the specification range and performing a bench study to determine whether the 14 devices *(implicated in the low doses)* had significantly different activation force from the other devices in the study and whether all devices in the METO-IN-006 study were outside of a reasonable actuation force specification. The Applicant agreed to submit the actual actuation force values with the resubmission.
- Evoke proposed their approach for setting acceptance criteria for droplet size and spray pattern for quality control and proposed the planned duration of the stability data. Division generally agreed with the approach and considered these to be review issues. Division did not agree with the Applicant's proposal to report activation force of the (b) (4) spray pump as a post-approval commitment, noting that this is an essential performance requirement critical for the delivery of the drug product and therefore recommended adequate testing on the final finished device with a statistically relevant number of samples, and that activation force should be added to release characteristics, unless other criteria are in place to address the issue.

- FDA reiterated the recommendation to submit 3 months of stability data with 3 batches of the to-be-marketed dose 15 mg. The Applicant agreed to submit 2 batches of the 15 mg stability data and include a comprehensive justification. A third 15 mg batch is currently being manufactured and will be submitted to the NDA when stability data are available.
- Regarding dosing in specific populations, the Division noted that the appropriateness of the reduced dosing frequency cannot be solely supported by achievement of similar total daily AUC because there are neither adequate exposure-response data nor available clinical data to be able to address the clinical implications of a reduced dosing frequency on efficacy for metoclopramide in the treatment of gastroparesis. Division noted that Gimoti would likely need to be limited to patients who do not require dose adjustment if a lower strength formulation does not exist to allow for administration of a lower dose in these specific populations, and that this issue may be addressed through a post-marketing requirement(s) (PMRs)/post-marketing commitment(s) (PMCs). Division recommended that the Applicant develop a lower strength formulation (e.g., 7.5 mg) to address use in specific populations.

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Office of Scientific Investigations

Not applicable to the resubmission.

3.2. Product Quality

Refer to integrated quality review memo, May 21, 2020, for full details. An overview is provided here. The information included in the resubmission has addressed all Product Quality and Device related deficiencies from the CR Letter:

Product Quality/Device Quality

The Applicant has reevaluated the acceptance criteria for the specification using batches manufactured at the proposed commercial strength, including for spray pattern and droplet size. The applicant has also added a test and acceptance criterion for actuation force to the finished product specification (as requested by the Center for Devices and Radiological Health [CDRH]) The specification provided on May 18, 2020 is appropriately justified.

Additional Comment A (CR Letter)

During this review cycle the Applicant provided additional data to further support their selected acceptance criterion for actuation force, agreed to lower the acceptance criterion to (b) (4) kg and committed to including the test in the product specification as a post marketing commitment.

A late cycle IR response was submitted by the Applicant on May 18, 2020 which added actuation force to the finished product specification (release and stability). As such the PMC to add actuation force as indicated in the CDRH review #2 is no longer necessary.

Additional Comment B (CR Letter)

The Applicant provided acceptance criteria for the cap retention force of between (b) (4) to (b) (4) kg (b) (4). This is an appropriate range for the amount of force used to remove the cap and no post approval comment is needed.

Additional Comment C (CR Letter)

A shelf life of 24 months is supported.

- No out of specification was observed through 3 months for any commercial batch under any storage condition. The 17 mg supportive stability batches likewise appear stable. The drop seen at 12 months for spray pattern across all batches can be explained by a change in method and does not appear to be related to an undesirable stability trend.
- The Applicant originally proposed a shelf-life of (b) (4) months, however, given the uncertainty of the performance characteristics through (b) (4) months particularly given the changes in testing facility, methods and criteria, the applicant can request extensions of shelf life through annual reporting based on real-time stability data following an approved stability protocol. This was agreed to via an IR response dated April 17, 2020.

Additional Comment D (CR Letter)

The comparability protocol proposed in the original submission (and discussed in the CR) is now obsolete as the new testing facility was incorporated into the resubmission. The new testing facility was qualified through the provided comparability report and has received an adequate facility recommendation.

3.3. Clinical Microbiology

Not applicable to the resubmission.

3.4. Devices and Companion Diagnostic Issues

Refer to Section 3.2 above for discussion of how the device related deficiencies were addressed in the resubmission. With respect to the root cause analysis provided by the Applicant in the resubmission:

In seq 27 mod 5.3.1.2.Root cause analysis, page 27, the (b) (4) report found no significant differences between the implicated pumps and non-implicated pumps regarding average peak forces. The study was done using automated actuation and not with users. However, since this study was to determine mechanical differences between pumps, CDRH agrees with the Applicant's methodology. CDRH agrees it is unlikely that inappropriate actuation force could

have resulted in the dose variability issue identified with review cycle #1. The revised specification (submitted May 18, 2020) which includes actuation force as a finished product test to be used at release and throughout the stability program, provides further assurance of adequate device performance.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were included in the resubmission of the NDA. The Applicant conducted several toxicology studies with the intranasal formulation which were previously reviewed. Refer to the multi-disciplinary review from the first review cycle, dated March 29, 2019.

5. Clinical Pharmacology

5.1. Executive Summary

In this resubmission dated December 19, 2019, the Applicant submitted additional information to address the clinical pharmacology deficiencies in response to the Complete Response action. In addition, the Applicant addressed the quality and device-related concerns (Refer to Section 3).

The Complete Response action was taken on April 1, 2019 for the original submission for Gimoti 15 mg nasal spray due to an insufficient bridging to the listed drug, Reglan 10 mg. In the pivotal 4-way crossover comparative BA study in 98 healthy subjects (METO-IN-006), the proposed dose, Gimoti 15 mg showed comparable AUC but 20% lower mean C_{max} than Reglan Tablet 10 mg (N=97). More importantly, 11 out of 293 PK profiles (3.75%) of Gimoti 15 to 17 mg showed no to little drug exposure whereas no such cases were found after oral administration of Reglan, which appeared to primarily contribute to 20% lower mean C_{max} of Gimoti compared to Reglan. Given the concerns for the incomplete and inconsistent absorption from the nasal spray, the bridging based on comparable BA between Gimoti nasal spray and Reglan oral tablet was not established to ensure the comparable efficacy to Reglan.

This clinical pharmacology assessment focuses on the newly submitted information including the root cause analysis report and re-analysis of the pivotal comparative BA study, METO-IN-006. For the detailed clinical pharmacology review of the data in the original submission including individual study review, please refer to Clinical Pharmacology Review dated March 7, 2019 in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS; Communication ID: 4400558) with addendum dated March 21, 2019 (Communication ID: 4407615) and March 29, 2019 (Communication ID: 4411592).

In this resubmission, the Applicant asserted that the aberrant PK profiles with low exposure in the comparative BA study was neither due to the product quality nor the device quality but could have been due to erroneous nasal administration by study personnel to a few subjects; a root cause analysis report was provided to support this position. Therefore, the Applicant proposed to use the BE assessment that excluded the data from subjects who may have received erroneous nasal spray administration by the study personnel in support of bridging between Gimoti 15 mg and Reglan 10 mg.

The Office of Clinical Pharmacology (OCP) found that the Applicant's explanation for erroneous dosing as a reason for aberrant PK plausible, given that the product quality and device deficiencies were adequately addressed (determined by the OPQ and CDRH reviewers). However, because there is no definitive documentation of improper dosing at the time of study drug administration during the comparative BA study, we cannot accept the replacement of the original BE assessment with the new BE assessment that excludes the aberrant PK profiles. In addition, we noted that in other clinical studies of Gimoti in which PK data were collected, 2 to 3% of doses may have resulted in low exposure potentially due to improper nasal administration by patients. However, as the original clinical pharmacology review also noted, Gimoti 15 mg showed comparable bioavailability with Reglan Tablet 10 mg with 90% CI associated with the mean ratio for both AUC and C_{max} within 80 to 125% (N=94) when the data from three subjects with aberrant PK profiles were excluded, which suggests that Gimoti 15 mg provides comparable bioavailability to Reglan 10 mg when dosed properly.

Therefore, we concluded that the comparative BA data with root cause analysis provided in this resubmission sufficiently supports the establishment of a bridge between Gimoti 15 mg and Reglan 10 mg, subsequently relying on the findings of safety and efficacy for the listed drug, Reglan 10 mg, is adequately justified.

Recommendation

The OCP has reviewed the submission and concluded that there is no remaining issue that precludes the approval of the proposed product, Gimoti 15 mg, from a clinical pharmacology standpoint.

Labeling Recommendation

To mitigate the risk of improper dosing from the proposed nasal spray by patients, the review team recommends detailed instruction in the labeling to ensure the proper dosing from nasal spray for self-administration. In addition, a recommendation of no more than one spray per dosing should be included in the labeling to avoid potential overdose due to perceived underdosing by patients.

We do not recommend Gimoti 15 mg for the specific populations who need dose reduction per spray. Due to risk of adverse reactions of metoclopramide including tardive dyskinesia, Reglan label recommends that patients who have lower capacity of drug elimination (i.e., patients with

moderate to severe renal or hepatic impairment, CYP2D6 poor metabolizers, or strong CYP2D6 inhibitor users) reduce the dose between 5 mg BID to 5 mg QID, compared to 10 mg QID for general patient population and Reglan is available as 10 mg tablet and 5-mg tablet. However, unlike Reglan, Gimoti will be available as one strength, 15 mg only and the nasal spray device of Gimoti cannot adjust the dose delivered per pump.

Recommended Post-Marketing Study (PMC)

The review team recommends development of a lower strength formulation, e.g., Gimoti 7.5 mg, to provide appropriate dosage for patients who need dosage adjustments. A single dose pharmacokinetics study in healthy subjects should be conducted to characterize dose proportionality of 7.5 mg and 15-mg dose strengths. See also Section 12.

5.2. Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

Metoclopramide is a dopamine-receptor antagonist, an antiemetic, and a stimulant of upper gastrointestinal motility. Oral and injectable formulations of metoclopramide have been approved for the relief of symptoms associated with acute and recurrent diabetic gastroparesis. Metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. A major oxidative metabolite is formed primarily by CYP2D6, an enzyme subject to genetic variability. Metoclopramide and its metabolites are primarily excreted in urine. The mean elimination half-life in subjects with normal renal function was 5 to 6 hours following oral administration. Metoclopramide is not extensively bound to plasma proteins (about 30%).

Pharmacokinetics of Metoclopramide Following Nasal Administration

The Applicant has developed Gimoti as a nasal spray formulation of metoclopramide, to provide systemic delivery through nasal mucosa bypassing the GI system. Even though intranasal administration is typically expected to avoid GI and hepatic first-pass effect, some extent of intranasally administered dose is known to be absorbed in the GI.[2] The absolute bioavailability of metoclopramide nasal spray from Gimoti 10 mg is 47.4% in healthy subjects compared to metoclopramide 10 mg intravenous (IV) injection. Following single dose nasal administration of metoclopramide in healthy subjects, systemic exposure increased proportionally with dose between 10 to 80 mg. The median T_{max} of Gimoti was 1.25 h after dose, which is similar to that of Reglan. Elimination half-life of metoclopramide was about 8 hours.

In the re-analysis of the pivotal comparative BA study excluding aberrant PK profiles with low exposure (N=3 out of 97 for Gimoti 15 mg), the single nasal administration of Gimoti 15 mg

[2] Grassin-Delyle et al, Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. Pharmacol Ther. 2012 Jun;134(3):366-79.

showed comparable bioavailability to oral administration of Reglan 10 mg in terms of C_{max} and AUC. Of note, in the original analysis including the aberrant PK profiles, Gimoti 15 mg showed comparable AUC but 20% lower C_{max} than Reglan 10 mg.

PK by Sex

The Applicant found that females had 34% and 43% higher AUC and C_{max}, respectively, to metoclopramide than males following single administration of Gimoti across PK studies, i.e., METO-IN-001, METO-IN-005, and METO-IN-006. Neither Reglan label nor published literature has stated the effects of sex on metoclopramide PK. Of note, in METO-IN-006, for Reglan, females had 25% and 36% higher AUC and C_{max}, respectively, than males.

Although clinical implication by sex difference in PK is not well known, dose adjustment by sex is not expected to be necessary considering the large inter-individual variability in metoclopramide PK following Gimoti administration (i.e., CV% 50~100% for AUC within each sex group) compared to the extent of sex difference in PK (i.e., 34% for AUC between males and females) as observed across the three PK studies. In addition, the labeling for Reglan, the listed drug, does not recommend dose adjustment by sex.

Reviewer comment: *The underlying reason for the sex difference in PK remains unclear. The geometric mean AUC and C_{max} were still higher in females than in males (i.e., 24% for AUC; 30% for C_{max}) after adjustment of body weight effect as a covariate in the statistical comparison. On the other hand, the Applicant's population PK analysis of Gimoti suggested that the PK difference between males and females are attributed to difference in lean body mass while sex itself turned out to be insignificant as a covariate. Females (who tend to have lower lean body mass than males) are likely to have lower systemic clearance and volume of distribution, subsequently resulting in higher exposure compared to males. Since CYP2D6 phenotype status was not identified for the subjects, it is not known if CYP2D6 phenotype was comparably distributed between males and females. In the labeling of the listed drug, it is noted that the risk of developing tardive dyskinesia is increased among the elderly, especially elderly women. It is unknown if apparently higher systemic exposure in females contributed at least in part.*

Potential for QT Prolongation of Gimoti

In METO-IN-005, the tQT study in 48 healthy subjects, no effect on QTc prolongation was found at single nasal administration of Gimoti 20 mg and 80 mg. Refer to the IRT-QT review (dated June 23, 2016 under IND 25512 in DARRTS) for further details.

5.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosage of Gimoti is one spray (15 mg) up to 4 times per day, i.e., 30 minutes before each meal and at bedtime.

Therapeutic Individualization

We do not recommend use of Gimoti 15 mg in patients who need dose reduction per spray. The proposed Gimoti product does not allow dosing of lower than 15-mg dose per spray therefore dose adjustment of Gimoti cannot be recommended in a similar way as approved for Reglan which is available in two strengths, 5 mg and 10 mg (Table 1).

Table 1. Recommended Dose Adjustment for Gimoti Compared to Reglan

Population	Gimoti Recommended Dosage Regimen	Reglan Approved Dosage Regimen
Mild hepatic impairment (Child-Pugh A)	15 mg QID (maximum 60 mg/day)	10 mg QID (maximum 40 mg/day)
Mild renal impairment (creatinine clearance ≥ 60 to 90 mL/min)	15 mg QID (maximum 60 mg/day)	10 mg QID (maximum 40 mg/day)
Elderly patients	Not recommend as initial therapy; Patients receiving oral metoclopramide at a stable dosage of 10 mg QID can be switched to Gimoti 15 mg QID.	5 mg QID with titration to 10 mg QID based upon response and tolerability (maximum 40 mg/day)
Moderate to severe hepatic impairment (Child-Pugh B or C)	Not recommended	5 mg QID (maximum 20 mg/day)
Moderate or severe renal impairment (creatinine clearance ≤ 60 mL/min)	Not recommended	5 mg QID (maximum 20 mg/day)
CYP2D6 poor metabolizers	Not recommended	5 mg QID (maximum 20 mg/day)
Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine)	Not recommended	5 mg QID (maximum 20 mg/day)
Patients with End-Stage Renal Disease (ESRD) including those treated with hemodialysis and continuous ambulatory peritoneal dialysis	Not recommended	5 mg BID (maximum 10 mg/day)

Source: Product label of Reglan oral tablet (NDC codes: 62559-165-01, 62559-166-01)
Abbreviations: BID, twice daily; QID, four times a day.

Per the approved label of Reglan, due to risk of adverse reactions of metoclopramide including tardive dyskinesia, specific populations who have lower capacity of drug elimination (i.e., patients with moderate to severe renal or hepatic impairment, CYP2D6 poor metabolizers or strong CYP2D6 inhibitor users) should reduce the dose to 5 mg QID, and to 5 mg BID in patients with end-stage renal disease compared to 10 mg QID for general patient population. Likewise, elderly patients should start from the reduced dose with 5 mg QID and can titrate up to 10 mg QID based on response and tolerability as elderly patients are more likely to have decreased renal function and may be more sensitive to adverse effect compared to younger patients.

Outstanding Issues

Until a lower strength formulation becomes available, the use in specific populations who need dose reduction (i.e., patients with moderate to severe renal or hepatic impairment, elderly patients, CYP2D6 poor metabolizers, or strong CYP2D6 inhibitor users) should be limited

because risk of adverse reactions of metoclopramide including tardive dyskinesia is considered increased at higher drug exposure.

In order to allow use in patients who needs dose adjustment, we recommend that Applicant develop a lower dosage strength as a post-marketing commitment. A single dose pharmacokinetics trial in healthy subjects should be conducted to characterize dose proportionality of 7.5 mg and 15-mg dose strengths.

5.3. Comprehensive Clinical Pharmacology Review

5.3.1. Review of the Root Cause Analysis

According to the FDA's recommendation in the CR letter, the Applicant conducted a root cause analysis to identify the sources of the little to no drug exposure observed in METO-IN-006.

During the first review cycle, we noted that in the PK dataset of METO-IN-006, 11 out of 293 PK profiles (3.8%) showed virtually no drug absorption (plasma concentrations <5 ng/ml at all time points) after single nasal administration of Gimoti 15 to 17 mg whereas no such cases were found after oral administration of Reglan. In addition, 3 more PK profiles of Gimoti were found to have C_{max} <5 ng/mL from PK data excluded from the PK dataset due to the pre-defined data exclusion criterion, i.e., pre-dose concentration was ≥5% of the C_{max}. Among all available PK profiles of Gimoti including data originally removed from the PK dataset,[3] 14 out of 307 PK profiles (4.6%) showed aberrantly low exposure, i.e., C_{max} <5 ng/mL.

In the root cause analysis report submitted in this resubmission, the Applicant concluded that its testing and analyses have ruled out the drug product quality or device issue as the source of error. Rather, the Applicant speculated that erroneous nasal administration to the subjects by a couple of study personnel may have resulted in the aberrant PK profiles. Based on the following findings, the Applicant claimed that insufficient training and improper behaviors of study personnel were primary contributors of the dosing error leading to low drug exposure.

1) Twelve of 14 aberrant PK profiles (86%) were associated with two of the eight study personnel who performed nasal of administration of Gimoti to subjects. Of note, one of the two drug administrators was associated with one subject, Subject ID (b) (6), who showed low exposure at all three doses of Gimoti. This drug administrator did not receive the second training for nasal administration right before the study while the other personnel did.

[3] Out of 307 available PK profiles after Gimoti administration, a total 14 PK profiles were excluded from the final PK dataset based on pre-defined data exclusion criteria: N=10 was excluded due to the absence of corresponding Reglan PK data to compare (N=5,3, and 2 for Gimoti 15, 16, and 17 mg, respectively); N=4 was excluded due to pre-dose concentration was ≥5% of the C_{max} (N=2 and 2 for Gimoti 15 and 17 mg, respectively)

2) The retrospective interview with study personnel indicated that study personnel generally had been hesitant when approaching subjects to insert nasal spray tips into the subjects' nostril. Especially, the contemporaneous clinical monitor note documented that one of the two drug administers who were associated with most of the aberrant PK profiles had to correct the placement of nasal spray while Gimoti was being administered during the study.
3) Based on drug administration records, it appeared that drug administrators did not have sufficient time to make sure the placement of the nasal spray because they completed nasal administration in each subject within average of 4 minutes.

Even though there is no direct evidence to confirm the Applicant's speculation, improper nasal administration appears plausible for the potential source of the aberrant PK profiles provided that there were no remaining issues in the product quality.

On the other hand, even if the low exposure was presumably caused by erroneous nasal administration by study personnel in METO-IN-006, we cannot completely rule out the potential improper nasal administration in real world where patients self-administer Gimoti as we also found similar aberrant PK profiles in other clinical studies of Gimoti. Instructions on proper dosing will be addressed through labeling.

The review team found that METO-IN-001 and METO-IN-005, in which study personnel administered nasal spray to subjects and full PK profiles were characterized after single dose, included a few aberrant PK profiles with C_{max} <5 ng/mL at 2.6% and 3.1% incidence rate (Table 2, see also Appendix 15.1.1). Of note, these two studies were conducted in different study sites from METO-IN-006. Additionally, it was unclear if nasal administrations were all properly done in clinical studies in patients when patients self-administered Gimoti, i.e., METO-IN-002, METO-IN-003, and METO-IN-004. A few patients showed concentrations <5 ng/mL post-dose but PK sampling timepoints in the three clinical studies were <u>not</u> sufficient to capture the C_{max} while the median T_{max} for Gimoti is 1.25 hours (Table 2, see also Appendix 15.1.1).

Table 2. Incidence of Low Exposure Across Clinical Studies of Gimoti

Study Number	Subjects	Gimoti Dose	Administrator	Post-dose PK Sampling	Incidence of Low Exposure[1]
METO-IN-001	Healthy	Single dose, 10 and 20 mg	Study personnel	Full PK	2/77 (2.6%)
METO-IN-005	Healthy	Single dose, 10 and 80 mg	Study personnel	Full PK	3/96 (3.1%)
METO-IN-006	Healthy	Single dose, 15, 16, 17 mg	Study personnel	Full PK	14/307 (4.6%)
METO-IN-002	Patients	10 mg, 4 time per day	Self-administration	30 min[2]	29/178 (16.3%)
METO-IN-003	Patients	10 or 14 mg, 4 time per day	Self-administration	45 min, 90 min[3]	2/91 (2.2%)
METO-IN-004	Patients	10 mg, 4 time per day	Self-administration	45 min, 90 min[3]	0/26 (0%)

Source: Reviewer's analysis using pp.xpt files of METO-IN-001, METO-IN-005, METO-IN-006; pc.xpt files of METO-IN-002 and METO-IN-003; the bioanalysis report of METO-IN-004
Abbreviation: PK, pharmacokinetics.

[1] Reviewer's analysis. The incidence rate was obtained from dataset with PK data following nasal administration of Gimoti. For METO-IN-001, 005, and 006, C_{max} <5 ng/mL was considered as the case of low exposure. For METO-IN-003, 004, and 002, post-dose concentration <5 ng/mL was considered as the case with low exposure.

[2] In METO-IN-002: Sparse PK sampling on Day 1, pre-dose and 30 min post-dose; on Day 28, 30 min post-dose.

[3] In METO-IN-003 and METO-IN-004: Sparse PK sampling on Day 1, pre-dose, 45 min, and 90 min after the first dose, pre-dose of the second dose, 90 min after the second dose.

The incidence of low exposure across clinical studies aside from METO-IN-006 suggested that 2 to 3% of doses may result in low exposure in patients potentially due to improper nasal administration in post-marketing. See Section 7 for the review of clinical implication of potential improper dosing.

To mitigate the risk of improper dosing from the proposed nasal spray by patients, the review team recommends that the labeling include detailed instruction to ensure the proper dosing from nasal spray for self-administration. In addition, to avoid potential overdosing, the labeling should include a recommendation of no additional spray per dosing even if patients perceive underdosing. See Section 7 for the review of the instruction of use and the safety.

5.3.2. Reanalysis of Pharmacokinetics of METO-IN-006

Along with the root cause analysis report, the Applicant provided the addendum of METO-IN-006 report, in which PK data of METO-IN-006 was reanalyzed after excluding the aberrant 11 PK profiles (3 from 15 mg, 3 from 16 mg, 5 from 17 mg) from 9 subjects with C_{max} <5 ng/mL. For the detailed review of METO-IN-006 including its original results, please refer to Clinical Pharmacology Review, dated March 7, 2019 in DARRTS.

As expected, after excluding the aberrant PK profiles, CV% was decreased in C_{max} and AUC and the variability in T_{max} was reduced compared to the original results (Table 3). Of note, the variability for PK parameters remains higher for Gimoti across the doses than Reglan even after exclusion of aberrant PK profiles.

Table 3. Summary of Key PK Parameters for Metoclopramide in METO-IN-006 Excluding 11 PK Profiles With C_{max} <5 ng/mL in Comparison to the Original Results

			Arithmetic Mean (CV%)			Median (Min-Max)
Result Type	Formulation	N	C_{max} (ng/mL)	AUC_t (ng*h/mL)	AUC_{inf} [1] (ng*h/mL)	T_{max} (h)
Original	Reglan 10 mg	102	42.0 (37.0)	323 (36.6)	337 (39.0)	1.0 (0.5-3.5)
	Gimoti 15 mg	97	39.8 (52.0)	338 (53.6)	359 (52.7)	1.25 (0.5-10.0)
	Gimoti 16 mg	98	39.9 (55.1)	348 (58.0)	372 (57.6)	1.25 (0.25-8.0)
	Gimoti 17 mg	98	44.4 (56.4)	384 (56.1)	422 (52.3)	1.25 (0.25-16.0)
Reanalysis [2]	Reglan 10 mg	102	42.0 (37.0)	323 (36.6)	337 (39.0)	1.0 (0.5-3.5)
	Gimoti 15 mg	94	41.0 (48.4)	349 (50.1)	367 (50.4)	1.25 (0.5-3.5)
	Gimoti 16 mg	95	41.3 (51.4)	360 (54.4)	379 (55.4)	1.25 (0.25-4.0)
	Gimoti 17 mg	93	46.7 (50.5)	403 (50.6)	422 (52.3)	1.25 (0.25-4.0)

Source: METO-IN-006 Clinical Study Report Table 14.2.2 for original results; Addendum of METO-IN-006 Clinical Study Report, pp.xpt, for re-analysis results

Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_t, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; CV, coefficient of variation; T_{max}, time to maximum plasma concentration.

[1] AUC_{inf} was analyzed after excluding data that terminal slope was not estimated or extrapolated AUC% {(AUC_{inf}-AUC_t)/AUC_{inf}} was >20%. In the original analysis, AUC_{inf} was obtained from N=101, 95, 96, and 93 for Reglan, Gimoti 15, 16, and 17 mg, respectively. In the re-analysis, AUC_{inf} was obtained from N=101, 93, 94, and 93 for Reglan, Gimoti 15, 16, and 17 mg, respectively.

[2] In re-analysis, a total 11 PK profiles were excluded from PK dataset; N=3, 3, and 5 were excluded from Gimoti 15, 16, and 17 mg, respectively.

Without the aberrant PK profiles, both C_{max} and AUC of Gimoti for all three different doses were comparable to that of Reglan, within the BE criteria, i.e., 90% CI of geometric mean ratio: 80 to 125% (Table 4). Therefore, the results of METO-IN-006 adequately support the bridging of

efficacy and safety between Gimoti 15 mg and Reglan 10 mg provided that Gimoti is properly administered. For reviewer's independent re-analysis and detailed review, see Appendix 15.1.2.

Table 4. Bioequivalence Analysis Excluding 11 PK Profiles With C_{max} <5 ng/mL in Comparison to the Original BE Analysis in METO-IN-006

	Geometric Mean Ratio to Reglan (90% CI)					
	Original Result			Reanalysis Excluding the Aberrant PK Data[1]		
Parameter	Gimoti 15 mg (N=97)	Gimoti 16 mg (N=98)	Gimoti 17 mg (N=98)	Gimoti 15 mg (N=94)	Gimoti 16 mg (N=95)	Gimoti 17 mg (N=93)
C_{max}	**80.32 (69.29-93.11)**	80.37 (69.36-93.12)	84.27 (72.74-97.64)	**90.12 (81.45-99.72)**	89.64 (81.03-99.16)	99.69 (90.06-110.3)
AUC_t	**90.25 (79.48-102.5)**	91.76 (80.84-104.2)	97.01 (85.48-110.1)	**99.82 (91.30-109.1)**	100.5 (91.96-109.9)	111.9 (102.3-122.4)
AUC_{inf}[2]	**94.96 (85.44-105.5)**	96.75 (87.09-107.5)	110.1 (100.5-124.3)	**100.3 (91.85-109.5)**	102.6 (93.97-112.0)	112.3 (102.9-122.7)

Source: Addendum of METO-IN-006 Clinical Study Report Table 8 and Table 9

Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_t, area under the curve to the last quantifiable time point; BE, bioequivalence; C_{max}, maximum plasma concentration; PK, pharmacokinetics.

The results of the proposed dose, 15 mg, are bolded.

[1] In re-analysis, a total 11 PK profiles were excluded from its original PK dataset; N=3, 3, and 5 were excluded from Gimoti 15, 16, and 17 mg, respectively.

[2] AUC_{inf} was analyzed after excluding data that terminal slope was not estimated or extrapolated AUC% {(AUC_{inf} - AUC_t)/AUC_{inf}} was >20%. The geometric mean ratio (90% CI) for AUC_{inf} was obtained from N=101, 95, 96, and 93 for Reglan, Gimoti 15, 16, and 17 mg, respectively, in the original analysis; N=101, 93, 94, and 93 for Reglan, Gimoti 15, 16, and 17 mg, respectively, in the re-analysis.

5.3.3. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The Applicant relies on the FDA's finding of efficacy and safety for Reglan as the listed drug. In the pivotal comparative BA study (METO-IN-006), when Gimoti 15 mg was compared with Reglan 10 mg without data from three subjects for whom a nasal spray administration error by the study personnel was probable, the proposed Gimoti 15 mg showed comparable bioavailability with Reglan 10 mg with 90% CI associated with the mean ratio for both AUC and C_{max} within 80 to 125%.

Therefore, the comparative bioavailability data along with the root cause analysis, provide sufficient information to establish a bridge between Gimoti 15 mg and Reglan 10 mg, and subsequently reliance on the findings of efficacy and safety for Reglan is reasonable.

Data from METO-IN-006 and other studies in which PK was collected suggested that 2 to 3% of doses may result in low exposure potentially due to improper nasal administration by subjects. However, the clinical benefit of Gimoti to patients with diabetic gastroparesis outweighs potential clinical implication by the improper nasal administration with 2 to 3% incidence. Refer to Section 7 for detailed review of the patient's experience and the potential clinical implication.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dose of Gimoti 15 mg is appropriate based on the comparable bioavailability to Reglan 10 mg as discussed above. The proposed dosing frequency, up to 4 times per day, i.e., 30 minutes before each meal and at bedtime, is consistent with the approved dosing frequency of Reglan.

The Applicant claimed that Gimoti 15-mg dose for female patients can be supported by a post hoc subgroup analysis of the comparative BA data in METO-IN-006 while Reglan, the listed drug is indicated for both males and females at the same dose. Given the fact that the METO-IN-006 was conducted in both male and female subjects and METO-IN-006 supports the bridge between Gimoti 15 mg and Reglan regardless of sex, clinical pharmacology data supports indication for both males and females with the same dose, Gimoti 15 mg.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes, use of Gimoti 15 mg is not recommended in patients who need dose reduction for metoclopramide, i.e., patients with moderate or severe renal or hepatic impairment, patients on dialysis, and CYP2D6 poor metabolizers/strong CYP2D6 inhibitor users because a dosage strength that allows proper dose adjustment will not be available.

Also, Gimoti 15 mg is not recommended in geriatric patients as initial therapy. Geriatric patients who are receiving oral metoclopramide at a stable dosage of 10 mg QID can be switched to Gimoti 15 mg QID.

Reglan labeling recommends dose adjustment for the specific populations who have lower capacity of drug elimination (Table 1) due to risk of adverse reactions of metoclopramide including tardive dyskinesia. TD is serious movement disorder that is potentially irreversible, and the risk of TD and the likelihood that TD will become irreversible increases with duration of treatment and total cumulative dose, in other words, cumulative drug exposure.

(b) (4)
(b) (4)
(b) (4) Further development of a lower strength formulation will be warranted to allow use in patients who need dose reduction.

The Applicant proposed (b) (4)
(b) (4)

6. Sources of Clinical Data and Review Strategy

6.1. Sources of Clinical Information

On December 19, 2019 the Applicant resubmitted NDA 209388 to address the deficiencies listed in the CR letter. No new clinical trials were conducted in support of the resubmission. The safety and efficacy data from Gimoti clinical trials including METO-IN-002, METO-IN-003, METO-IN-004 in patients with diabetic gastroparesis, as well as information from other phase 1 trials, including the bridging bioavailability study METO-IN-006 in healthy volunteers were reviewed in detail during the original NDA review. Refer to the multidisciplinary review, dated March 29, 2019. The clinical portions of this memo will focus on the information provided in the resubmission that were intended to address the deficiencies outlined in the CR Letter. The primary clinical components of the NDA resubmission include the root cause analysis report and accompanying appendices that were submitted to address CR letter deficiency item #1.

In addition, the resubmission included updated drafts of the proposed labeling, medication guide, instructions for use for Gimoti nasal spray. A proposed risk management plan and post-marketing safety study were included in the original submission and were considered during this cycle. The NDA multidisciplinary review, individual discipline reviews/addendums, and consultant reviews from the original NDA review cycle were also referred to as necessary.

6.2. Review Strategy

The resubmission clinical review was tailored to the deficiencies listed in the CR letter. Specifically, we assessed the Applicant's response to the CR deficiency #1 to determine whether the deficiency item had been adequately addressed, and whether the conclusions were supported by information in the root cause analysis report and related appendices.

Refer to the Clinical Pharmacology sections of this document for an assessment of the Applicant's response to address CR deficiency #1, including elements of root cause analysis, and relevance of the proposed BE reanalysis. Refer to the Office of Pharmaceutical Quality review, dated May 21, 2020, and CDRH review, dated May 1, 2020, for details related to the adequacy of the quality and device-related information submitted to address the deficiencies in the CR Letter.

7. Clinical Assessments of CR Issues

7.1. Review of the Root Cause Analysis Report

The following sections focus on the review of clinical information presented within the root cause analysis report of the NDA resubmission.

Methodology

To address the CR deficiency item #1, the Applicant conducted a root cause analysis to identify the source(s) of the low drug concentrations observed in some PK profiles of study METO-IN-006. This study evaluated the comparative bioavailability of single doses of Gimoti metoclopramide nasal spray 15 mg, 16 mg and 17 mg relative to the approved Reglan 10 mg oral tablets, in a crossover manner in healthy volunteers. While the AUC parameters met the bioequivalence criteria at all doses, the C_{max} values were lower with the Gimoti nasal spray relative to Reglan oral tablets, and were not contained within the bioequivalence bounds. The lower C_{max} on average was caused by few aberrant PK profiles following Gimoti nasal spray which showed little to no drug absorption, regardless of dose administered. Specifically, there were 14 instances of low drug levels (C_{max} <5 ng/mL), representing 4.5% (14/308) of the total doses administered to study subjects, across the three doses (5 profiles at the proposed 15-mg dose, 4 profiles at the 16-mg dose, and 6 profiles at the 17-mg dose of Gimoti nasal spray).

In their root cause analysis, the Applicant attempted to systematically identify potential sources of error that could contribute to the observed low drug concentrations. Sources of error were under the broad categories of the formulation and device constituents of the drug product, the clinical trial material, administrators and users of the drug product, as well as acquisition and analysis of the PK samples. Each source of error was then investigated further by compiling and evaluating lines of evidence that supported and/or refuted the contribution of that source to the observed low drug levels. A likelihood assessment was then made for each source of error to delineate the root cause of the aberrant results found in study METO-IN-006.

The clinical sources of potential error and evidence supporting and refuting their contribution to the aberrant PK profiles are discussed below. For information on the sources of potential error related to the drug product and device constituents, please refer to the Quality review of this resubmission.

7.1.1. Patient Experience Summary Report

At the conclusion of the phase 2b trial METO-IN-002, 98 patients with diabetic gastroparesis who had completed randomized study treatment, opted to participate in a computer assisted telephone interview regarding their intranasal drug product use experience. These patients received either Gimoti (10 mg or 14-mg doses), or placebo intranasal spray, four times daily for 4 weeks during the clinical trial. The interview questions and the corresponding patient responses are summarized:

Question 1: “Prior to participating in the clinical study, have you ever taken a medication – either prescription or over-the-counter – in the form of a nasal spray for any condition (i.e., nasal decongestants, allergy medications, etc.)?”

Results: 59% of patients had previously used nasal spray products and 41% had no prior experience. The Applicant notes that this finding may be due to the presence of comorbidities and multiple medications taken by patients with diabetic gastroparesis (GP). In the trials conducted by Evoke, the average number of medications taken by participating patients was approximately 10.

Question 2: “Overall, please rate the ease of use of using the nasal spray form of metoclopramide?”

Results: The ease of use of the nasal spray formulation was reported as shown:

- Among all patients surveyed (n=98): Extremely easy (65%), somewhat easy (31%), somewhat difficult (~3%), neither easy nor difficult (~1%)
- Among patients with prior experience using nasal sprays (n=58): Extremely easy (62%), somewhat easy (34%), somewhat difficult (4%)
- Among patients with no prior experience using nasal sprays (n=40): Extremely easy (70%), somewhat easy (25%), somewhat difficult (~3%), neither easy nor difficult (~2%)

Question 3: "If you were to take metoclopramide in the future, which type of administration(s) would you be open to using?" Options included nasal spray, tablet, liquid, and injection.

Results: The order of preference for metoclopramide dosage forms was as shown:

- Among all patients (n=98), the order of preference from most to least preferred was: nasal spray (74%), tablet (61%), liquid (21%),injection (13%)
- Among patients with prior experience using nasal sprays (n=58), the order of preference from most to least preferred was: nasal spray (71%), tablet (60%), liquid (19%), injection (10%)
- Among patients with no prior experience using nasal sprays (n=40), the order of preference from most to least preferred was: nasal spray (80%), tablet (63%), liquid (25%), injection (18%)

Question 4: "If your physician prescribed a nasal spray metoclopramide to treat your diabetic gastroparesis symptoms, would you use this medication?"

Results: 92% of the total surveyed (n=98), 90% of those with prior experience with nasal medications (n=58) and 95% of those with no prior experience (n=40), reported that they would take nasal metoclopramide if prescribed by a physician.

Assessment of the Patient Experience Data

Of the four questions to the patients, the first three are primarily asking about the route of administration. There are no direct questions related to the perceived efficacy of the product. The response to the final question on whether the patient may consider using a nasal spray metoclopramide for their diabetic gastroparesis could potentially be influenced by whether that patient perceived a treatment benefit during the preceding 4 weeks trial period and whether they received active drug or placebo nasal spray during the trial. However, responses to that question do not suggest that it was influenced by patients' perception of benefit, as a vast majority (at least 90%) indicated that they would use metoclopramide nasal spray if prescribed by their physician.

Overall, the data from this independent interview of phase 2 trial patients suggest that irrespective of whether the patients had prior experience using nasal spray products or not, or whether they received drug or placebo during the trial, the responses were positive with regard to the 1) ease of use of the nasal spray with most patients (95%) reporting either 'extremely easy' or 'somewhat easy to use', 2) order of preference for different routes of metoclopramide dosing (with most indicating a highest preference for intranasal route (~71% to 80% of patients), and 3) willingness to use intranasal metoclopramide if prescribed (~90 to 95% of patients). Interestingly, use of oral tablets was the second preferred route of metoclopramide (61% to 63% of patients) suggesting that though the use of intranasal spray may have appealed to many, the use of oral route did not appear to be a deterrent in these interviewed patients

who had type 1 or 2 diabetes and gastroparesis with a baseline GCSI-DD score of ≥2 and ≤4. Overall, the patient experience data from study METO-IN-002 indicates the patients' have a marked level of comfort and interest in the use of the intranasal route of administration of metoclopramide.

To supplement the market research results, the Applicant included limited amount of information from two separate patient discussion forums (gastroparesis social media support groups). Note that the discussion was not limited to metoclopramide use.

The social media support group posts and the discussions presented in the resubmission were intended to illustrate the concerns among gastroparesis patients with the use of solid oral dosage forms. These discussions suggest that patients were typically on multiple daily medications. The concerns raised included whether their medications are getting absorbed in presence of slow gastric emptying, whether the drug effect is going to be delayed and/or perhaps even exaggerated (e.g., if several doses become available all at once). Patients described not achieving adequate or timely effect of their pain, thyroid, or sleep medications. Participants responding in the discussion most commonly recommended switching to liquid formulations as an alternative, or if unavailable preparing a liquid formulation by crushing a tablet or opening a capsule.

There were at least two patients who described specific actions that involved their physician due to concerns related to insufficient drug absorption, including one that was switched from their oral contraceptive pill to Mirena coil, and another patient who was switched to insulin from their oral diabetes medication. Nausea and vomiting were the main issues in some patients in using solid oral formulations. Some reported changing the time of the day when the medicine is taken (e.g., taking the thyroid medication at a time when they are least queasy, instead of first thing in the morning when it is at the worst). At least one patient reported multiple pills in their stomach on endoscopy. Patients also perceived an apparent lack of information from their physicians on the potential for erratic or incomplete absorption of their multiple medications due to gastroparesis.

Together, the results from the interview of the patients who participated in the Gimoti phase 2b trial and patient discussion forums supports that patients with gastroparesis may, in general, benefit from alternatives to oral solid dosage forms, including but not limited to metoclopramide. Responses remained favorable for Gimoti nasal spray regardless of patients' prior experience with intranasal spray products and irrespective of whether they received placebo or active drug in the preceding 4 weeks. Overall, the patient experience data from study METO-IN-002 indicates that patients are comfortable with self-administration of the IN spray and that diabetic gastroparesis patients have a favorable interest in using the nasal route for metoclopramide dosing.

7.1.2. Directions for Use and Dose Administrator Training in the Comparative Bioavailability Study (METO-IN-006) Protocol

In METO-IN-006, the BE study, healthy subjects enrolled in the study were not allowed to self-administer Gimoti doses. Instead, trained study staff served as 'dose administrators' and administered the intranasal doses to all subjects. Based on the information provided in the root cause analysis report (Table 5 below), eight study staff each administered doses to multiple subjects. As previously noted, 4.5% of the resulting PK profiles showed low drug levels (<5 ng/mL). As shown in the table, of the 14 profiles with low drug concentrations from Gimoti, 6 each were seen with two members of the study staff (#7 and #8), regardless of the Gimoti dose. The remaining PK profiles from doses administered by these two staff members were not found to demonstrate low drug levels (87.5% to 91%).

Table 5. Summary of Doses Administered and Number of PK Profiles with Low Drug Absorption—Comparative BA Study METO-IN-006

Dose Administrator	Gimoti Doses Administered (n=308)	PK Profiles With Low Drug Levels (n)	Gimoti Dose and # of Aberrant PK Profiles (If Applicable)
1	2	0	-
2	42	0	-
3	22	0	-
4	40	0	-
5	55	1	16 mg (1)
6	62	1	15 mg (1)
7	48	6	15 mg (2), 16 mg (2), 17 mg (2)
8	6	6	15 mg (2), 16 mg (1), 17 mg (3)

Source: Adapted from Applicant's Table 2 of the 'Root Cause Analysis Report' Module 5.3.1.2., NDA 209388 resubmission December 19, 2019
Abbreviations: BA, bioavailability; PK, pharmacokinetic.

The educational materials (directions for use and training slides) provided to the study staff in study METO-IN-006 were reviewed for their adequacy. The illustrated directions for use and training slides appear adequate to ensure understanding of the steps involved in dose administration. The training slides specify that one spray in one nostril delivers the required dose of the drug in this single dose BA study. The training also appears to have included practicing the use of the nasal spray pumps.

The priming of the devices occurred at the pharmacy according to the instructions provided. The information provided in the root cause analysis report rules out pharmacy preparation as the source of error, noting that the pharmacist primed each device prior to its use in the study (at least 10 times, with performance confirmed by visual observation of the emitted spray, following the validated priming procedure) and that the priming was observed by Evoke clinical monitor who confirmed that the correct pharmacy procedures were followed.

The root cause analysis report also notes that in the bioequivalence study all administrators were trained at least once, 2 months prior to study drug administration. Of the 8 administrators, 7 were also retrained just prior to study start. One of the 2 dose administrators (#8 in the Table above) with the highest number of subjects with low Gimoti profiles post-dose (N=6) was trained 2 months before dosing began and was not re-trained. This individual also

dosed one study subject who had consistently low concentrations (C_{max} <5 ng/mL) after all three Gimoti doses received at weekly intervals.

Additional information in the root cause analysis document following interview with the clinical monitor indicated that dose administrators were hesitant in approaching study subjects for dosing, and that they moved quickly from subject to subject with an average of 4 minutes between doses, suggesting a high volume of doses for administration within a short timeframe.

Assessment of the Study Staff Training During METO-IN-006

The Applicant concluded that the 'training did not adequately address the need for all dose administrators to gain a level of comfort when approaching subjects' for dosing and that the 'training and behavior of the dose administrators were identified as primary contributors to the incidences of low drug values'. Though one of the two administrators with the most aberrant PK profiles did not receive re-training prior to the study start, the other individual did receive re-training and still had approximately 12.5% of the doses result in low drug concentrations. Despite few aberrant profiles (6 each), most of the intranasal doses (87.5% to 91%) given by these two administrators resulted in 'normal' PK profiles, and the majority of PK profiles suggest that subjects were appropriately dosed in study METO-IN-006. Thus, while it is not possible to broadly conclude that the training provided to the dose administrators in the study was inadequate, in the absence of definitive drug product and/or device quality issues, it is likely that subjective differences amongst 8 dose administrators in their comfort and ability to dose accurately, potentially differing training needs, and a large number of doses administered within a short duration, all may have contributed to dosing errors and observed low drug concentrations in 4.5% of doses administered in METO-IN-006.

7.1.3. Clinical Experience—Training for Phase 3 Clinical Trial Patients for Self-administration

Gimoti formulation has been evaluated in 6 clinical trials including the phase 1, comparative bioavailability study METO-IN-006. These include METO-IN-001 (a phase 1, bioavailability study in 39 healthy volunteers), METO-IN-005 (a phase 1, through QT study in 54 healthy volunteers), METO-IN-002 (a placebo controlled, dose-ranging clinical trial in 285 diabetic gastroparesis patients), METO-IN-003 (a phase 3, placebo controlled clinical trial in 205 female diabetic gastroparesis patients) and METO-IN-004 (a placebo controlled trial in 53 male diabetic gastroparesis patients; terminated early due to poor enrollment).

Study personnel administered the drug doses in all the phase 1 studies, while patients self-administered doses during the phase 2 and phase 3 clinical trials. In the phase 2 and 3 trials, patients received printed dosing instructions prior to drug self-administration. The first use by the patient was done under supervision in the clinic. At regular visits, the dosing instructions were reviewed with the patients, per information included in the protocol.

The following is a brief summary of study specific dose administration and related instructions:

METO-IN-002: This was a phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging efficacy and safety study in male and female diabetic gastroparesis patients; 10 mg, 14 mg or placebo intranasal sprays were administered four times daily for 4 weeks. In this trial, patients self-administered the study drug using a metered nasal spray pump that delivered 50 µl (10 mg) spray or 70 µl (14 mg) spray or 50 µl placebo spray. One spray was administered in the right or the left nostril four times a day, 30 minutes before each meal and at bedtime. Subjects were instructed on the correct use of the nasal spray, reminded not to exceed a total of 4 sprays a day, and self-administered their first and last doses of study drug at the site on Day 0 and Day 28. The protocol includes Subject Study Drug Instructions (Directions for Use) will illustrations. The instructions are similar to those given to the 'dose administrators' in the phase 1 studies, except that the instructions are directly addressed to the patient. According to the study procedures described in the protocol, during the randomization visit, subjects were instructed on the correct use of study drug and were provided with the printed dosing instructions. Subject was observed while self-administering the first dose of study drug in the clinic under 'appropriately trained study personnel supervision'. At visits on days 7, 14 and 21 the study drug dosing instructions were reviewed with the patient.

METO-IN-003: This was a phase 3, randomized, double-blind, placebo controlled, parallel group, efficacy and safety study in female diabetic gastroparesis patients using 10 mg Gimoti or placebo spray, 4 times daily for 4 weeks. In this trial, patients self-administered Gimoti or placebo as a single nasal spray four times per day for 4 weeks. During the randomization visit, subjects were instructed on the correct use of the nasal spray. The protocol includes Subject Study Drug Instructions (Directions for Use) will illustrations. Subjects were observed self-administering their first dose of study drug in the clinic. Subjects were instructed not to prime the pump prior to each dose and reminded not to exceed 4 sprays a day. On visits at days 7, 14, 21 the study drug dosing instructions were reviewed with the patient.

METO-IN-004: This was a phase 3, randomized, double-blind, placebo controlled, parallel group efficacy and safety study in male diabetic gastroparesis patients receiving 10 mg Gimoti or placebo spray, 4 times daily for 4 weeks. In this trial, patients self-administered Gimoti or placebo as a single nasal spray four times per day for 4 weeks. During the randomization visit, subjects were instructed on the correct use of the nasal spray and were observed self-administering their first dose of study drug in the clinic. Printed dosing instructions are provided at this visit. On visits at days 7, 14, 21 the study drug dosing instructions were reviewed with the patient.

Overall, in the Gimoti phase 2 and phase 3 clinical trials, the nasal spray formulation was self-administered four times per day for 28 days (112 doses per patient) by 318 patients (35,616 doses) with diabetic gastroparesis. No use errors with the potential to cause harm were reported in any of these studies by the Applicant. In the phase 3 clinical trials of Gimoti, the incidence of low drug concentrations post-dose (2 to 3%) was smaller compared to that seen in the relative BA study METO-IN-006 (4.5%). Because this observation is based on sparse samples compared to intensive PK sampling in the phase 1 study, information should be interpreted cautiously. In general, data from phase 3 trials of Gimoti is supportive of patient

comprehension of dosing instructions and ability to self-administer the proposed nasal spray. Refer to the Clinical Pharmacology discussion of the sparse PK sampling information from the clinical trials for an assessment of the potential for low drug concentrations following Gimoti self-administration.

7.1.4. Conclusions on the Root Cause Analysis Findings

The data submitted in the root cause analysis report support that that the aberrant PK profiles in a small fraction of subjects (4.5%) in study METO-IN-006 following Gimoti nasal spray were likely caused by individual dose administrator errors, given that the quality and device-related deficiencies have been addressed.

Data from clinical trials of Gimoti during which patients were allowed to self-administer the study drug intranasally, generally showed a lower incidence of aberrant drug levels compared to METO-IN-006. Patient experience summary report following the conclusion of the dose-ranging trial METO-IN-002 supports patient comfort in self-administering an intranasal metoclopramide formulation for their gastroparesis. In general, data from phase 3 trials of Gimoti is supportive of patient comprehension of dosing instructions and ability to self-administer the proposed nasal spray. Data from clinical trials in which PK was collected suggested that 2 to 3% of self-administered doses resulted in low exposure potentially due to improper nasal administration by subjects. However, given that metoclopramide is administered frequently during a 24-hour dosing period (up to 4 times per day) to relieve symptoms of gastroparesis, occasional low exposure due to incomplete or incorrect dose administration is not expected to have a substantial clinical implication to the patient.

Therefore, the relative bioavailability data supported by the findings from the root cause analysis to address the potential source of dosing error, provide sufficient information to conclude that relying on the findings of efficacy and safety for the listed drug (Reglan 10-mg tablet) is reasonable. Any concerns related to improper nasal administration of Gimoti will be addressed in the labeling and post-marketing setting.

8. Clinical Evaluation of Safety

8.1. Review of Safety

The NDA resubmission did not contain new safety information. For a detailed assessment of the safety data from the completed clinical trials, refer to the multidisciplinary review memo, dated March 29, 2019. The known safety information for metoclopramide including that communicated in the labeling for approved products, as well as relevant safety data from clinical trials of Gimoti were considered during this review cycle.

The approved metoclopramide products carry a Boxed Warning in the labeling for TD, a serious movement disorder, and include warnings and precautions for other CNS adverse events. The

risk of developing TD increases with duration of treatment and total cumulative dosage. Treatment with metoclopramide for longer than 12 weeks should be avoided because of the risk of developing TD with longer-term use. In addition to TD, metoclopramide may cause other EPS such as acute dystonic reactions, parkinsonian symptoms (bradykinesia, tremor, cogwheel rigidity, mask-like facies), and motor restlessness (akathisia consisting of feelings of anxiety, agitation, jitteriness, and insomnia, etc.). In addition, a rare but fatal symptom complex called neuroleptic malignant syndrome (NMS; consisting of hyperpyrexia, muscle rigidity, altered mental status, autonomic instability) is associated with metoclopramide use typically in the overdosage scenario or upon concomitant treatment with another drug associated with NMS. The use of metoclopramide with other drugs known to cause TD, EPS and NMS, and use in patients with Parkinson's disease, or use with antiparkinsonian drugs should be avoided. Metoclopramide use has also been associated with psychiatric adverse events such as depression.

The approval of Gimoti is based on the comparative bioavailability of a 15-mg dose of the nasal spray to that of Reglan 10 mg oral tablet. While phase 2 and 3 clinical trials (METO-IN-002, 003, and 004) of 4 weeks duration were initially conducted to support the intranasal product, these trials did not evaluate the proposed 15-mg dose of Gimoti, and therefore do not provide information on the safety of the dose intended for approval and labeling.

The data from clinical trials of Gimoti in which patients self-administered the nasal spray suggested that approximately 2 to 3% of doses across trials resulted in low drug exposures. Given that metoclopramide is administered frequently within a short duration (i.e., up to 4 times per day), occasional low exposure due to under-dosing is not expected to raise safety concerns.

There remains a theoretical possibility that metoclopramide administered via the nasal route may result in increased neurological adverse events relative to oral administration. Given that metoclopramide labeling already carries a Boxed Warning and other warnings and precautions regarding CNS adverse events, post-marketing safety assessments will be undertaken to address the above safety consideration. Specifically, post-marketing pharmacovigilance by the FDA using the Sentinel's Active Risk Identification and Analysis (ARIA) system is planned, with a focus on obtaining information on CNS AEs following Gimoti use relative to oral metoclopramide. Refer to Section 12 of this review for a description of the PMR.

8.2. Conclusions and Recommendations

Based on the review of the NDA resubmission, findings from the first cycle review of the NDA, as well as satisfactory resolution of the Clinical Pharmacology issues (CR deficiency #1) as well as drug product and device quality issues (CR deficiency #2), it is recommended that Gimoti (metoclopramide) nasal spray should be approved for the symptomatic relief of diabetic gastroparesis in adults. The proposed approval of Gimoti is via a 505(b)(2) regulatory pathway, based on its comparative bioavailability to Reglan (metoclopramide) 10-mg tablet. The proposed dose of Gimoti nasal spray is 15 mg administered four times daily for up to 4 weeks,

based on the results from a relative bioavailability study METO-IN-006, which showed that the bioavailability of metoclopramide from Gimoti nasal spray 15 mg is sufficiently comparable to that of Reglan tablet 10 mg and that reliance on the findings of efficacy and safety for the listed drug (Reglan 10-mg tablet) is reasonable.

To address the theoretical concern that the intranasal route of administration of Gimoti may be associated with an increased risk of CNS AEs, including TD, post-marketing assessments are planned to evaluate the risk relative to oral metoclopramide. These are described in Section 12 of this review.

9. Advisory Committee Meeting and Other External Consultations

An advisory Committee meeting was not held for this application.

10. Pediatrics

The agreed initial pediatric study plan, dated July 24, 2015, submitted under IND 25512 includes plans to request a full waiver based on studies being impossible or highly impracticable because the number of pediatric patients with diabetic gastroparesis is very small (section 505B(a)(4)(A)(i) of the Act).

Under the Pediatric Research Equity Act, (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Gimoti (metoclopramide nasal spray) represents a new dosage form and new route of administration for metoclopramide. However, diabetic gastroparesis is on the FDA-Automatic Waiver List of adult-related conditions that are rarely or never diagnosed in pediatric patients and, as such, studies would be impossible or highly impractical in pediatric patients. This resubmission was discussed at PeRC on June 2, 2020, and the PeRC agreed with issuing a full waiver.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Refer to the approved labeling for final language. The key changes to the label are summarized below.

Boxed Warning- Tardive Dyskinesia

- Warning was updated to reflect the necessary safety information for the safe use of Gimoti in a clinical setting. The statement [redacted] was removed [redacted]

Section 1 Indications and Usage

- The patient population in the indication statement was revised from [redacted] to 'adults' with acute and recurrent diabetic gastroparesis; the indication is for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.
  - Rationale: [redacted]
- An additional limitation of use has been added to communicate that Gimoti is not recommended for use in specific populations that would require dosage adjustment (i.e., patients with moderate or severe hepatic and renal impairment and patients concurrently using strong CYP2D6 inhibitors).
  - Rationale: Currently, Gimoti is marketed in only one dose strength that does not allow safe dose adjustment in these patient populations to reduce exposure. Thus, until such a time when lower dose strengths become available, Gimoti is not recommended in specific populations who require dose adjustment.

Section 2 Dosage and Administration

- A new section 2.1 Important Administration and Storage Instructions has been added to communicate dosing instructions specific to the nasal route of administration for Gimoti.
  - Rationale: Clinical trials of Gimoti involved either dosing by study staff (phase 1 studies) or self-administration by patients (phase 2/3 trials). In both scenarios, potential under-dosing, as indicated by low drug concentrations, was observed in a small number of subjects, potentially due to dosing errors. Thus, instructions regarding the nasal spray administration are included in this section to help ensure proper use of the product.
- Section 2.2 now titled as 'Recommended Dosage' is revised to include two separate sections for 'Adults less than 65 years of age' and 'Adults 65 years of age and older'.
  - Rationale: Other formulations of approved metoclopramide products recommend a lower starting dose in elderly patients. Due to the absence of lower dose strengths for Gimoti, this section clarifies that Gimoti is not intended as an initial therapy in

geriatric patients. However, elderly patients who are currently on stable metoclopramide 'standard' doses can be switched to Gimoti.

Section 3 Dosage Forms and Strengths

- For additional clarity, the description of the formulation was updated to reflect the amount of drug delivered in each spray of Gimoti [15 mg metoclopramide in each 70 microliter spray].

Section 5 Warnings and Precautions

- New section 5.9. has been added to communicate the potential risk of adverse reactions with Gimoti in patients with moderate or severe renal and hepatic impairment, CYP2D6 poor metabolizers, and patients taking strong CYP2D6 inhibitors.
  - Rationale: The dosage regimen cannot be adjusted with Gimoti to reduce exposure and thus use in these specific populations is not recommended.

Section 6 Adverse Reactions

- The following statement will be added: In a randomized, placebo-controlled clinical trial of 190 male and female patients of Gimoti 14 mg, a slightly lower than recommended dosage, administered nasally four times daily for 4 weeks, dysgeusia was the most commonly reported adverse reaction (15% of GIMOTI-treated patients and 4% of placebo-treated patients). Other adverse reactions were similar to those reported for oral metoclopramide.
  - Rationale: Although the clinical trials with Gimoti did not include the recommended 15 mg dose, dysgeusia was seen during a large phase 2 trial (Study METO-IN-002) that evaluated a 14 mg dose and occurred in a higher proportion of patients treated with this dose (15%) as compared to placebo (4%). This event may be related to the intranasal route of administration; therefore, information has been included in the labeling. Overall, the safety of Gimoti was similar to that of oral Reglan.

Section 7 Drug Interactions

- Intervention listed for use with strong CYP2D6 inhibitors has been updated.
  - Rationale: Gimoti is not recommended in this population as the dosage regimen cannot be adjusted to reduce exposure.

Section 8 Use in Specific Populations

- Dosing recommendations within each of the specific population subsections have been updated. Essentially, with the exception of the elderly in which dosing with Gimoti is allowed with some caveats as previously noted, use of Gimoti in other specific populations that otherwise require lower dosage is not recommended.
  - Rationale: The dosage regimen cannot be adjusted with Gimoti to reduce the exposure and therefore use in these specific patient populations is not recommended, and use as initial therapy in the elderly is not recommended.

- Information on [redacted] (b) (4) was deleted.
  - Rationale: [redacted] (b) (4) (b) (4)

Section 11 Description

- Information has been updated to accurately describe the dosage form, and the device.

Section 12 Clinical Pharmacology

- Cardiac electrophysiology information was updated to reflect data from all subjects regardless of sex.
- Pharmacokinetics information was updated to accurately communicate the absolute and relative bioavailability data for Gimoti, and PK data were consolidated.

Section 14 Clinical Studies

- Information on [redacted] (b) (4) was deleted from this section.
  - Rationale: [redacted] (b) (4) (b) (4)

11.2. Other Prescription Drug Labeling

Gimoti labeling will include an Instructions for Use and Medication Guide. In addition to the review team and consultants, the labeling for Gimoti, including the Instructions for Use and Medication Guide, were also reviewed by the Division of Medical Policy Programs, and the Office of Prescription Drug Promotion. Their comments and recommendations have been incorporated into the final labeling.

12. Risk Evaluation and Mitigation Strategies

A risk evaluation and mitigation strategy is not recommended by the review team. No REMS was included in the resubmission to the CR; however, a communication plan REMS was proposed by the Applicant in the original NDA submission. The team concluded that the risks are adequately communicated in the labeling, including through a Boxed Warning and other Warnings and Precautions. In addition, the risks of metoclopramide use are well documented and healthcare providers who use metoclopramide are generally well aware of the associated risks. Instructions for Use and a Medication Guide will also be included in the labeling to inform patients and prescribers on the safe use of the product. The Division of Risk Management (DRM) was consulted during the review of this NDA. Refer to DRM review, dated June 5, 2020, for details.

13. Postmarketing Requirements and Commitment

Refer to the Approval Letter for the final PMR/PMC language. Based on the novel route of administration of Gimoti (i.e., nasal spray) and known risks of CNS adverse reactions with metoclopramide, postmarketing surveillance will be performed to evaluate the potential for increased risk of CNS adverse reactions for Gimoti relative to other marketed metoclopramide products. The following PMR/PMCs are proposed.

Active Risk Identification and Analysis Sufficiency

The Division of Epidemiology (DEPI) evaluated the sufficiency of ARIA in the Sentinel Distributed Database to track the risks of neurologic adverse events in the gastroparesis population treated with metoclopramide. DEPI deemed ARIA as sufficient for monitoring TD, drug-induced dystonia, malignant neuroleptic syndrome, drug-induced parkinsonism, and other related serious adverse CNS reactions to metoclopramide in diabetic patients with gastroparesis. Postmarketing monitoring for TD and other related serious adverse CNS reactions will be performed by ARIA in lieu of a corresponding Section 505(o)(3) PMR for Gimoti NDA 209388. See DEPI ARIA Sufficiency Memo, dated May 14, 2020 for full details.

Postmarketing Commitment

The following PMC was communicated to the Applicant on June 3, 2020. On June 10, 2020, the Applicant agreed to the PMC and provided a reasonable rationale to support the proposed timeline.

- PMC: Conduct a single dose pharmacokinetics trial of Gimoti (metoclopramide) nasal spray in healthy subjects to characterize dose proportionality of the lower strength (e.g.,7.5 mg) and the 15 mg dose strengths. Develop a lower dosage strength (e.g., 7.5-mg) of Gimoti (metoclopramide) nasal spray to accommodate various situations requiring further dosage adjustments.

Rationale for the PMC

Per the approved label of the listed drug (Reglan oral tablet), due to risk of adverse reactions of metoclopramide including tardive dyskinesia, specific populations who have lower capacity of drug elimination (i.e., patients with moderate to severe renal or hepatic impairment, CYP2D6 poor metabolizers, or CYP2D6 inhibitor users) should reduce the dose. In addition, elderly patients should consider the dose reduction as elderly patients are more likely to have decreased renal function and may be more sensitive to adverse effect compared to younger patients.

Reglan oral tablet is available for two dosage strengths (i.e., 10 mg and 5 mg) to accommodate the dose reduction. However, Gimoti nasal spray will be available only for one strength (i.e., 15 mg) and the product does not allow dose reduction as the dose delivered per spray cannot be

adjusted. Subsequently, use in patients who need dose reduction of metoclopramide will be limited in the label. Given the patient population with diabetic gastroparesis may potentially have the conditions requiring dose adjustment (e.g., renal impairment), development of lower strength formulation(s) of Gimoti is warranted to benefit those patients.

Applicant's Rationale and timeline

The Applicant agreed to conduct a single dose pharmacokinetics trial in healthy subjects to characterize dose proportionality of a lower dose strength of metoclopramide nasal spray and the Gimoti 15 mg dose strength. The Applicant must first develop a lower dosage strength (e.g., 7 .5 mg) to accommodate the various situations requiring dosage adjustment. The COVID-19 pandemic has already negatively impacted the time needed for product development, manufacturing, and to conduct a clinical trial. After discussions with the several global and domestic contract research organizations that the Applicant will rely upon to perform each of the activities, a proposed timeline that includes the realistic timing for each step is shown below:

- Clinical study site identification, draft protocol preparation and submission: 03/2021
- Development, manufacture and release of clinical trial material: 06/2021
- Final protocol submission: 09/2021
- Study/Trial Completion: 03/2022
- Final Report Submission: 09/2022

14. Deputy Division Director for Safety (Clinical) Comments

I am in agreement with the review team's conclusions and recommendations regarding approval, professional labeling, Information for patients, Medication Guide and PMC. We will request one PMC as outlined above in order to provide dosing for patients that require a lower dose as recommended in the Reglan labeling. Further, there is no need for a REMS. To address the theoretical safety concern of the novel route of administration of Gimoti (i.e., nasal spray) and known risks of CNS adverse reactions with metoclopramide, postmarketing surveillance will be performed using the Sentinel's Active Risk Identification and Analysis (ARIA) system to evaluate the potential for increased risk of CNS adverse events. I have participated in the review of this product and the labeling and PMC negotiations.

15. Appendices

15.1. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.1.1. Aberrant PK Profiles Across Studies With PK Data

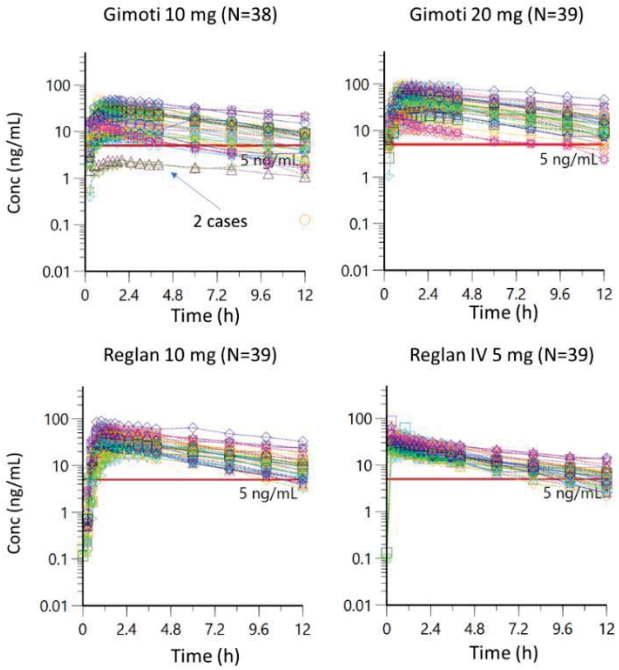
METO-IN-001: Supportive Comparative BA Study

In this 4-way crossover study, the sequence of the treatments was randomly assigned to 40 eligible subjects, and all subjects received a single dose of metoclopramide, i.e., Gimoti 10 mg, Gimoti 20 mg, oral Reglan Tablet 10 mg, and Reglan intravenous (IV) 5 mg. Blood draws for PK sampling were collected prior to dosing, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, and 36 hours post-dose.

For Gimoti 10 mg and 20 mg, PK data from 38 and 39 subjects were included the final PK dataset.

Out of a total 77 PK profiles following single nasal administration of Gimoti 10 mg or 20 mg, 2 PK profiles at Gimoti 10 mg had C_{max} <5 ng/mL, i.e., 2.117 and 2.438 ng/mL (Subject (b) (6) and (b) (6)) (Figure 1) which accounts for 2.6% of PK profiles of Gimoti. Following Reglan Tablet 10 mg and Reglan IV 5 mg, there was no such case.

Figure 1. Spaghetti Plots of Individual Time-Metoclopramide Concentration Profiles in METO-IN-001

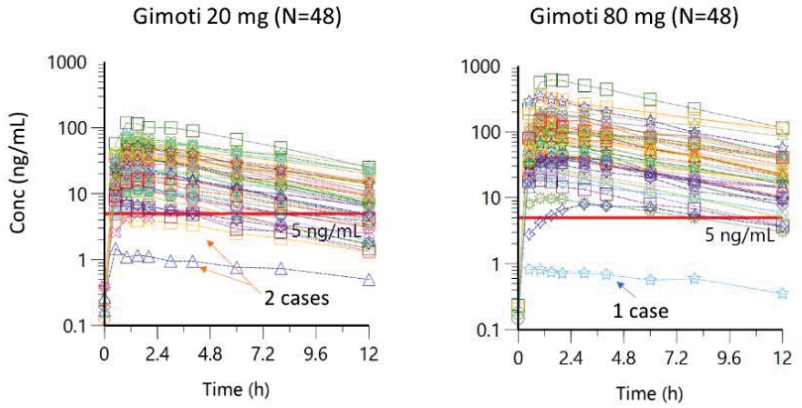


Source: Reviewer's plot using the dataset of METO-IN-001, pp.xpt
Abbreviation: IV, intravenous.

METO-IN-005: Thorough QT Study

This 4-way crossover study, the sequence of the treatments was randomly assigned to 48 eligible subjects, and all subjects received a single dose of metoclopramide, i.e., Gimoti 20 mg, Gimoti 80 mg, placebo, and moxifloxacin 400 mg. Blood draws for PK sampling were collected prior to dosing, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing. PK data from 48 subjects for each Gimoti 20 mg and 80 mg was included in the final PK dataset. Out of a total 96 PK profiles following single nasal administration of Gimoti 20 mg or 80 mg, 3 PK profiles had C_{max} <5 ng/mL, i.e., 1.47, 4.31, and 0.821 ng/mL (Subject (b) (6), and (b) (6)) (Figure 2) which accounts for 3.1% of PK profiles of Gimoti.

Figure 2. Spaghetti Plots of Individual Time-Concentration Profiles in METO-IN-005



Source: Reviewer's plot using the dataset of METO-IN-005, pp.xpt

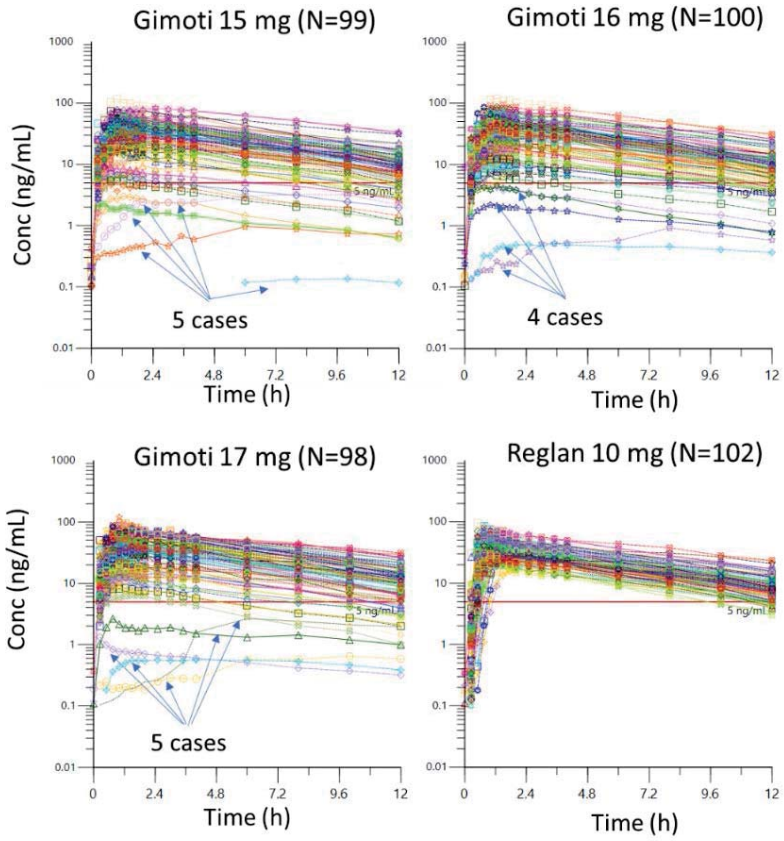
METO-IN-006: Pivotal Comparative BA Study

In this 4-way crossover study, the sequence of the treatments was randomly assigned to 108 eligible subjects, and all subjects received a single dose of metoclopramide, i.e., Gimoti 15 mg, Gimoti 16 mg, Gimoti 17 mg, and oral Reglan Tablet 10 mg. Blood draws for PK sampling were collected prior to dosing, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, and 36 hours post-dose.

For Gimoti 15, 16, and 17 mg, a total 307 PK profiles from 104, 103, and 100 subjects were available, respectively, although in the final PK dataset included PK data from 97, 98, and 98 subjects as a total 14 PK profiles were excluded based on pre-specified data exclusion criteria: N=10 was excluded due to the absence of corresponding Reglan PK data to compare (N=5,3, and 2 for Gimoti 15, 16, and 17 mg, respectively); N=4 was excluded due to pre-dose concentration was ≥5% of the C_{max} (N=2 and 2 for Gimoti 15 and 17 mg, respectively).

Out of a total 307 PK profiles following single nasal administration of Gimoti 15 mg, 16 mg, or 17 mg, 14 PK profiles had C_{max} <5 ng/mL (N=5, 4, and 5 for Gimoti 15 mg, 16 mg, or 17 mg, respectively) (Figure 3) which accounts for 4.6% of PK profiles of Gimoti. Following Reglan Tablet 10 mg, there was no such case.

Figure 3. Spaghetti Plots of Individual Time-Metoclopramide Concentration Profiles in METO-IN-006



Source: Reviewer's plot using the dataset of METO-IN-006, pp.xpt

METO-IN-002: Phase 2 Dose-Ranging Study at Gimoti 10 mg and 14 mg

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose ranging study to evaluate efficacy and safety of Gimoti 10 mg and 14 mg compared to placebo in adult subjects with diabetic gastroparesis. A total 287 male and female patients with diabetic gastroparesis were randomized to Gimoti 10 mg (N=96), Gimoti 14 mg (N=96), or placebo (N=95). Gimoti or matching-placebo was nasally administered 4 times daily, 30 minutes before meals and at bedtime, for 4 weeks.

Limited PK sampling was included in this study. Samples were collected on Day 0 pre-dose and at 30 minutes post-dose and on Day 28 at 30 minutes post-dose for metoclopramide determinations in plasma after a single dose and at steady state.

For Gimoti 10 mg and 14 mg, plasma metoclopramide concentration data from 88 and 90 patients were included the final PK dataset. Out of a total 178 patients who received Gimoti 10 mg or 14 mg and had PK data, 29 subjects (16.3%) had post-dose concentrations <5 ng/mL on Day 1 or Day 28 (Table 6). However, given Gimoti's T_{max} around 1.25 hrs after dose, a single PK sampling at 30 min after dose may not have been sufficient to adequately capture C_{max}. So, it is unclear if patients who had post-dose concentration <5 ng/mL in METO-IN-002 actually showed aberrantly lower absorption than the other patients.

Table 6. Patients With Post-dose Concentration <5 ng/mL in METO-IN-002

No.	Subject ID	Treatment	PK Sampling Day at 30 Minutes Post-dose	Concentration (ng/mL)
1	(b) (6)	Gimoti 10 mg	Day 11	3.444
2	(b) (6)	Gimoti 10 mg	Day 28	1.177
3		Gimoti 10 mg	Day 28	BQL (<0.100)
4		Gimoti 10 mg	Day 1	2.266
5		Gimoti 10 mg	Day 1	BQL (<0.100)
6		Gimoti 10 mg	Day 1	0.418
		Gimoti 10 mg	Day 28	3.187
7		Gimoti 10 mg	Day 28	0.46
8		Gimoti 10 mg	Day 28	1.019
9		Gimoti 10 mg	Day 1	BQL (<0.100)
10		Gimoti 10 mg	Day 1	3.444
		Gimoti 10 mg	Day 28	0.117
11		Gimoti 10 mg	Day 28	2.901
12		Gimoti 10 mg	Day 1	BQL (<0.100)
13		Gimoti 10 mg	Day 28	0.326
14		Gimoti 10 mg	Day 1	0.212
15		Gimoti 10 mg	Day 1	3.783
16		Gimoti 10 mg	Day 1	2.905
		Gimoti 10 mg	Day 28	3.056
17		Gimoti 10 mg	Day 1	4.574
18		Gimoti 14 mg	Day 1	4.4
19		Gimoti 14 mg	Day 1	1.654
20		Gimoti 14 mg	Day 1	BQL (<0.100)
21		Gimoti 14 mg	Day 1	3.645
22		Gimoti 14 mg	Day 1	4.646
		Gimoti 14 mg	Day 28	0.156
23		Gimoti 14 mg	Day 1	2.539
24		Gimoti 14 mg	Day 28	0.346
25		Gimoti 14 mg	Day 1	3.92
26		Gimoti 14 mg	Day 1	BQL (<0.100)
27		Gimoti 14 mg	Day 28	1.131
28		Gimoti 14 mg	Day 28	0.597
29		Gimoti 14 mg	Day 1	4.087

Source: Reviewer's analysis based on plasma concentration dataset of METO-IN-002, pc.xpt
Abbreviation: BQL, below the quantification limit.

METO-IN-003: Phase 3 Study at Gimoti 10 mg in Females

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study to evaluate efficacy and safety of Gimoti 10 mg compared to placebo in adult female patients with diabetic gastroparesis. A total 205 female patients with diabetic gastroparesis were randomized to Gimoti 10 mg (N=102) or placebo (N=103). Gimoti 10 mg or matching-placebo was nasally administered 4 times daily, 30 minutes before meals and at bedtime, for 4 weeks.

Sparse PK sampling was collected at Visit 5 (Day 7): pre-dose of the first dose, post-dose at 45 minutes (range: 30 to 60 minutes) and 90 minutes (range: 75 to 105 minutes); pre-dose of the second dose, and post-dose at 90 minutes (range: 75 to 105 minutes).

For Gimoti 10 mg, plasma metoclopramide concentration data from 91 patients were included the final PK dataset. Out of the 91 patients, 2 patients (2.2%) had post-dose concentrations <5 ng/mL on Day 7 (Table 6). However, given Gimoti's T_{max} around 1.25 hrs after dose, a single PK sampling at 30 min after dose may not have been sufficient to adequately capture C_{max}. So, it is unclear if patients who had post-dose concentration <5 ng/mL in METO-IN-002 actually showed aberrantly lower absorption than the other patients.

Table 7. Patients With Post-dose Concentration <5 ng/mL in METO-IN-003

Subject ID/Treatment	Sampling Time on Day 7	Concentration (ng/mL)
(b) (6) Gimoti 10 mg=	Pre-first dose=	BQL (<0.100)=
	45 min post first dose	**3.84**
	90 min post first dose=	33.6=
	Pre-second dose=	17.1=
	90 min post second dose	**4.2**
(b) (6) Gimoti 10 mg=	Pre-first dose=	2.7=
	45 min post first dose	**3.8**
	90 min post first dose	**4.95**
	Pre-second dose=	4.44=
	90 min post second dose=	5.16=

Source: Reviewer's analysis based on plasma concentration dataset of METO-IN-003, pc.xpt
Abbreviation: BQL, below the quantitation limit.
Post-dose concentrations <5 ng/mL are bolded.

METO-IN-004: Terminated Phase 3 Study at Gimoti 10 mg in Males

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study to evaluate efficacy and safety of Gimoti 10 mg compared to placebo in adult male patients with diabetic gastroparesis. Although 150 patients were planned, a total 53 male patients with diabetic gastroparesis were randomized to Gimoti 10 mg (N=26) or placebo (N=27) and then terminated due to the difficulty in patient enrollment. Gimoti 10 mg or matching-placebo was nasally administered 4 times daily, 30 minutes before meals and at bedtime, for 4 weeks.

Sparse PK sampling was collected at Visit 5 (Day 7): pre-dose of the first dose, post-dose at 45 minutes (range: 30 to 60 minutes) and 90 minutes (range: 75 to 105 minutes); pre-dose of the second dose, and post-dose at 90 minutes (range: 75 to 105 minutes).
Out of the 26 patients who received Gimoti 10 mg, no one showed post-dose concentrations <5 ng/mL.

15.1.2. Reanalysis of METO-IN-006

In the resubmission, the Applicant provided the addendum of METO-IN-006 report, in which PK data of METO-IN-006 was reanalyzed after excluding the aberrant PK profiles with C_{max} <5 ng/mL.

In the original analysis, a total 293 PK profiles were included, i.e., N=97, 98, and 98 for Gimoti 15, 16, and 17 mg, respectively (Table 8). For the detailed review of METO-IN-006 including its original analysis results, please refer to Clinical Pharmacology Review dated March 7, 2019 in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS).

In the re-analysis, PK data of METO-IN-006 was analyzed after excluding the aberrant 11 PK profiles (N=3, 3, and 5 from Gimoti 15 mg, 16 mg, and 17 mg, respectively) from 9 subjects with C_{max} <5 ng/mL (Table 9).

Table 8. The PK Dataset in the Original Analysis of METO-IN-006

Analysis Population Summary (Males and Females Combined)								
Population	**Gimoti 15 mg**		**Gimoti 16 mg**		**Gimoti 17 mg**		**Reglan 10 mg Tablet**	
Subjects Randomized, N	**108**		**108**		**108**		**108**	
Prespecified Exclusions	n	*Subject #*	n	*Subject #*	n	*Subject #*	n	*Subject #*
Subject Not Dosed	3	(b) (6)	5	(b) (6)	8	(b) (6)	6	(b) (6)
No Drug Concentration Data	1		0		0		0	
No Corresponding Tablet PK Data	5		3		2	(b) (6)	0	
Subjects in PK Population, N	**99**		**100**		**98**		**102**	
Prespecified Exclusion (applicable to analysis of all PK parameters)	n	*Subject #*	n	*Subject #*	n	*Subject #*	n	*Subject #*
Pre-dose Drug Conc. ≥5% of C_{max}	2	(b) (6)	2	(b) (6)	0		0	
Subjects for Analysis of AUC_{0-t} and C_{max}, N	**97**		**98**		**98**		**102**	
Prespecified Exclusions (applicable to analysis of AUC_{0-inf} only)	n	*Subject #*	n	*Subject #*	n	*Subject #*	n	*Subject #*
λ_z Not Estimated	1	(b) (6)	1	(b) (6)	2	(b) (6)	1	(b) (6)
>20% Extrapolation in AUC_{0-inf}	1		1		3		0	
Subjects for Analysis of AUC_{0-inf}, N	**95**		**96**		**93**		**101**	

Source: Addendum of METO-IN-006 Clinical Study Report, Table 8
Abbreviations: AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-t}, area under the curve to the last quantifiable time point; PK, pharmacokinetics.
Female subject #s are bolded
λ_z = elimination rate constant

Table 9. The PK Dataset in the Reanalysis of METO-IN-006

Analysis Population Summary (Males and Females Combined)								
Population	**Gimoti 15 mg**		**Gimoti 16 mg**		**Gimoti 17 mg**		**Reglan 10 mg Tablet**	
Subjects Randomized, N	**108**		**108**		**108**		**108**	
Prespecified Exclusions	n	*Subject #*	n	*Subject #*	n	*Subject #*	n	*Subject #*
Subject Not Dosed	3	(b) (6)	5	(b) (6)	8	(b) (6)	6	(b) (6)
No Drug Concentration Data	1		0		0		0	
No Corresponding Tablet PK Data	5		3		2		0	
Non-prespecified Exclusion								
All Post-dose Drug Conc. <5 ng/mL	5	(b) (6)	4	(b) (6)	5	(b) (6)	0	
Subjects in Revised PK Population, N	**94**		**96**		**93**		**102**	
Prespecified Exclusion (applicable to analysis of all PK parameters)	n	*Subject #*	n	*Subject #*	n	*Subject #*	n	*Subject #*
Pre-dose Drug Conc. ≥5% of C_{max}	0		1	(b) (6)	0		0	
Subjects for Re-analysis of AUC_{0-t} and C_{max}, N	**94**		**95**		**93**		**102**	
Prespecified Exclusions (applicable to analysis of AUC_{0-inf} only)	n	*Subject #*	n	*Subject #*	n	*Subject #*	n	*Subject #*
λ_z Not Estimated	0		1	(b) (6)	0		1	(b) (6)
>20% Extrapolation in AUC_{0-inf}	1	(b) (6)	0		0		0	
Subjects for Re-analysis of AUC_{0-inf}, N	**93**		**94**		**93**		**101**	

Source: Addendum of METO-IN-006 Clinical Study Report, Table 9
Abbreviations: AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-t}, area under the curve to the last quantifiable time point; PK, pharmacokinetics.
Female subject #s are bolded
Subjects not previously excluded from analysis are underlined
λ_z = elimination rate constant
† Subject previously excluded for all PK parameter analyses due to high pre-dose drug concentration
# Subject previously excluded for AUC_{0-inf} analysis

When the reviewer repeated the bioequivalence test using Pheonix WinNonlin (ver 8.1.0), the results (Table 10) were consistent with the Applicant's analysis indicating that bioavailability of Gimoti 15, 16, and 17 mg are similar with that of Reglan given that the 90% CIs of geometric means for area under the curve (AUC) and C_{max} fell within 80 to 125%.

During the original review, in the statistical consultation (dated February 20, 2019 in DARRTS), Dr. Meiyu Shen, the statistical reviewer, criticized that the Applicant included subjects who received at least 2 doses of study drug, one of which was the listed product even if they did not fully complete the study per protocol. Although this definition of PK population had been pre-defined in the protocol, Dr. Shen recommended using the complete cases for bioequivalence analysis because subjects with any missing cells should be either dropped out or imputed given that the statistical premise of the Latin square design is the equal carry-over effects. Therefore, bioequivalence analyses were repeated by the reviewer only including the complete cases per protocol as presented in Table 11. In these bioequivalence analyses only with the complete cases, the overall conclusion did not change from that of the original analysis and the re-analysis.

Table 10. Reviewer's Analysis for Metoclopramide Bioequivalence Analyses Excluding 11 PK Profiles with C_{max} <5 ng/mL

	Geometric Mean Ratio (%) for Gimoti/Reglan (90% CI)							
	Sponsor's Analysis				Reviewer's Analysis[1]			
Treatment	N	C_{max}	AUC_t	AUC_{inf}[2]	N	C_{max}	AUC_t	AUC_{inf}[2]
Gimoti 15 mg	94	90.12 (81.45-99.72)	99.82 (91.30-109.1)	100.3 (91.85-109.5)	94	90.12 (81.45-99.72)	99.82 (91.31-109.1)	100.3 (91.85-109.5)
Gimoti 16 mg	95	89.64 (81.03-99.16)	100.5 (91.96-109.9)	102.6 (93.97-112.0)	95	89.64 (81.04-99.15)	100.5 (91.96-109.9)	102.6 (93.97-112.0)
Gimoti 17 mg	93	99.69 (90.06-110.3)	111.9 (102.3-122.4)	112.3 (102.9-122.7)	93	99.69 (90.06-110.3)	111.9 (102.3-122.4)	112.3 (102.9-122.7)

Source: Addendum of METO-IN-006 Clinical Study Report, Table 9
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_t, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics.
[1] Reviewer's analysis based on the PK dataset that was newly submitted under SDN 28 (pp.xpt using the data only when CRIT1FL='Y' and ANL02FL='Y').
[2] AUC_{inf} was analyzed after excluding data that terminal slope was not estimated or extrapolated AUC% (AUC_{inf} - AUC_t/ AUC_{inf}) was >20% of AUC_{inf}. In original analysis of AUC_{inf}, N=95, 96, and 93 from Gimoti 15, 16, and 17 mg, respectively; In original analysis of AUC_{inf}, N=93, 94, and 93 from Gimoti 15, 16, and 17 mg, respectively.

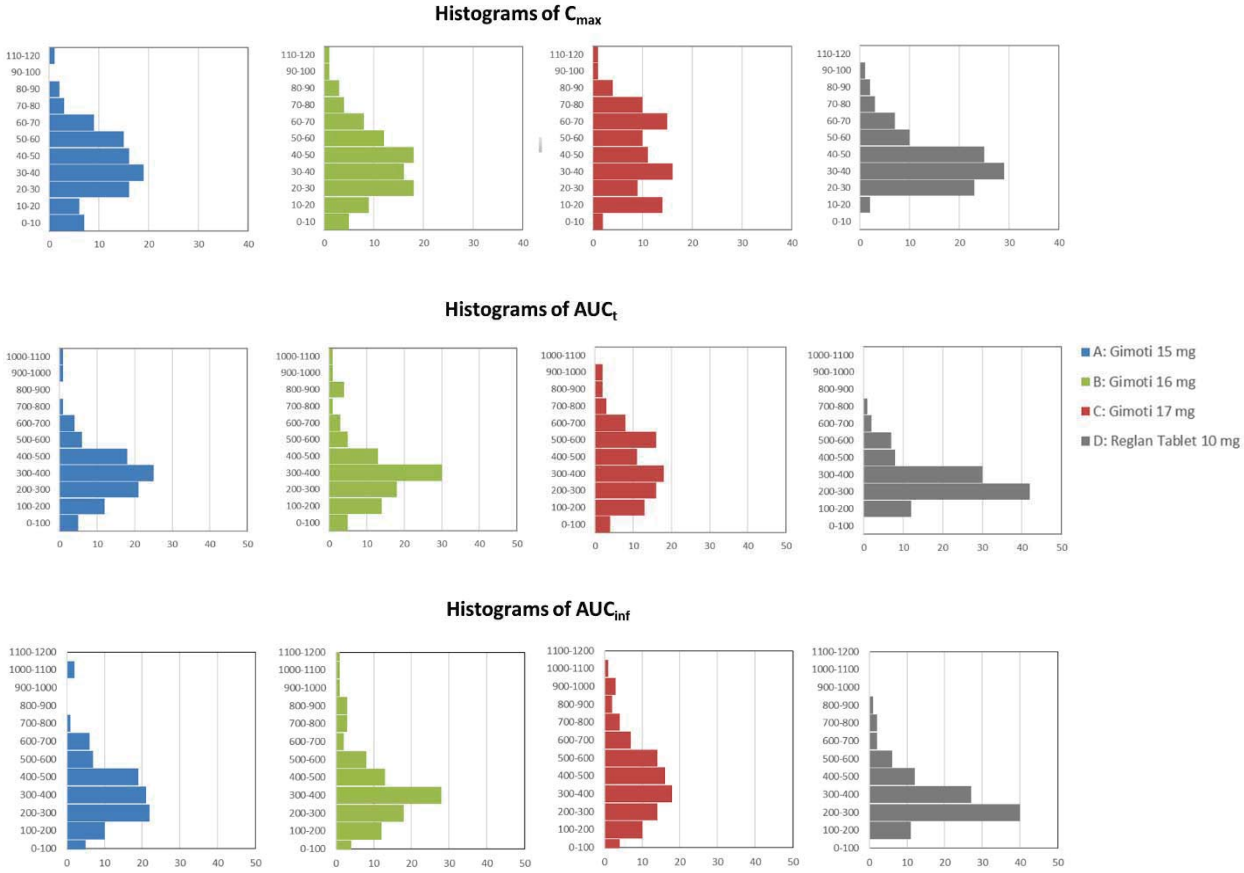
Table 11. Reviewer's Analysis for Metoclopramide Bioequivalence Analyses With Data From Subjects Who Completed All Four Periods Only, Excluding 11 PK Profiles With C_{max} <5 ng/mL in Comparison to the Original Results

	Geometric Mean Ratio (%) for Gimoti/Reglan (90% CI)							
	Original[1]				Reanalysis[2]			
Treatment	N	C_{max}	AUC_t	AUC_{inf}	N	C_{max}	AUC_t	AUC_{inf}
Gimoti 15 mg	95	77.2 (65.7-90.8)	87.4 (76.2-100.3)	93.6 (82.9-105.7)	84	96.0 (86.7-106.3)	104.1 (95.2-113.8)	104.0 (95.2-113.5)
Gimoti 16 mg	95	80.5 (68.5-94.7)	91.4 (79.6-104.8)	93.8 (83.1-105.8)	84	96.5 (87.1=106.8)	105.6 (96.6-115.5)	108.0 (98.9-118.0)
Gimoti 17 mg	95	86.5 (73.6-101.7)	99.2 (86.4-113.8)	105.2 (93.2-118.8)	84	103.3 (93.3-114.3)	114.8 (105.0-125.5)	116.5 (106.7-127.3)

Source: Statistical consultation dated February 20, 2019 in DARRTS
Abbreviations: AUC_{inf}, area under the curve to infinity; AUC_t, area under the curve to last quantifiable time point; C_{max}, maximum plasma concentration; PK, pharmacokinetics.
[1] Reviewer's analysis based on the PK dataset that was newly submitted under SDN 28 (pp.xpt using the data only when CRIT1FL='Y' and ANL02FL='Y'). Additionally, in order to only include the complete cases, N=10, 11, and 9 were further excluded from Gimoti 15, 16, and 17 mg, respectively.
[2] AUC_{inf} was analyzed after excluding data that terminal slope was not estimated or $AUC_{extrapolation}$ was >20% of AUC_{inf}. In original analysis of AUC_{inf}, N=88, 88, and 88 from Gimoti 15, 16, and 17 mg, respectively; In re-analysis of AUC_{inf} N=81, 81, and 81 from Gimoti 15, 16, and 17 mg, respectively.

In the original review, we found greater inter- and intra-subject variability in drug exposure for Gimoti as compared to that of Reglan not only individual PK profiles but also histograms of C_{max} and AUC. As expected, without the 11 aberrant PK profiles, the overall inter- and intrasubject variability in C_{max} and AUC of Gimoti still remained greater than that of Reglan (Figure 3, Figure 4).

Figure 4. Distribution of C_{max} and AUC by Treatment in METO-IN-006 Excluding 11 PK Profiles With C_{max} <5 ng/mL



Source: Reviewer's plot based on the PK dataset that was newly submitted under SDN 28 (pp.xpt using the data only when CRIT1FL='Y' and ANL02FL='Y').
Abbreviations: AUC, area under the curve; AUC_{inf}, area under the curve to infinity; AUC_t, area under the curve to the last quantifiable time point; C_{max}, maximum plasma concentration.

NDA 209338 Gimoti
Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Sojeong Yi, Ph.D.	OTS/OCP/DIIP	Sections 5 and 15.1	**Select one:** _X_ Authored ___ Approved
	Signature: Sojeong Yi -S Digitally signed by Sojeong Yi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sojeong Yi -S, 0.9.2342.19200300.100.1.1=2002075079 Date: 2020.06.17 17:33:45 -04'00'			
Clinical Pharmacology Team Leader	Insook Kim, Ph.D.	OTS/OCP/DIIP	Sections 5 and 15.1	**Select one:** __ Authored _X_ Approved
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Division Director, OCP	Chandrahas Sahajwalla, Ph.D.	OTS/OCP/DIIP	Sections 5 and 15.1	**Select one:** __ Authored _X_ Approved
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Sandhya Apparaju, Ph.D.	OII/DG	Authored Sections: 1.1, 1.2, 1.4, 2, 4, 6, 7, 8, 9, 10, 11	**Select one:** _X_ Authored __Approved
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Clinical Team Leader/CDTL	Juli Tomaino, M.D.	OII/DG	Authored: Section 1.3	**Select one:** __ Authored _X_ Approved (all sections)
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Deputy Director for Safety: Signatory	Joyce Korvick, M.D., MPH	OII/DG	Approved: All Sections	**Select one:** __ Authored _X_ Approved
	Signature:			

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/s/

MAUREEN D DEWEY
06/19/2020 01:35:27 PM

JOYCE A KORVICK
06/19/2020 02:13:37 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209388
Supporting document/s:	28
Applicant's letter date:	December 19, 2019
CDER stamp date:	December 19, 2019
Product:	Gimoti (metoclopramide) Nasal Spray
Indication:	Treatment of acute and recurrent diabetic gastroparesis
Applicant:	Evoke Pharma Inc. (Evoke)
Review Division:	Division of Gastroenterology
Reviewer:	Kenrick M. Semple, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Acting Division Director:	Jessica Lee, M.D., M.Sc
Project Manager:	Maureen Dewey, M.P.H.

Disclaimer

Except as specifically identified, all data and information discussed below are necessary for approval of NDA 209388, and are owned by Evoke Pharma Inc. or are data for which Evoke Pharma Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 209388, that Evoke Pharma Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Evoke Pharma Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 209388.

Executive Summary

Metocloporamide (Reglan) tablet is currently approved for the treatment of signs and symptoms of diabetic gastroparesis. The Applicant, Evoke, is seeking approval for an intranasal formulation (nasal spray) of metoclopramide (Gimoti) for treatment of acute and recurrent diabetic gastroparesis in adult patients. Evoke has submitted NDA 209388 for Gimoti *via* the 505(b)(2) Pathway with Reglan as the Listed Drug and relied on the Agency's previous assessment of safety of Reglan tablets for nonclinical safety. In addition, the Applicant conducted several toxicology studies with the intranasal formulation which were reviewed previously. NDA 209388 for metoclopramide nasal spray previously received a complete response on April 1, 2019 due to clinical pharmacology and product quality/device quality issues. The current Class 2/ Resubmission for NDA 209388 was received on December 19, 2019. Evoke has not submitted any additional nonclinical studies in the resubmission of the NDA.

1.1 Recommendations

1.1.1 Approvability

No nonclinical approvability issues have been identified.

1.1.2 Additional Non-Clinical Recommendations

None

1.1.3 Labeling

The proposed draft labeling of Gimoti is based on the approved labeling for Reglan tablets and is acceptable.

8.1 Pregnancy

Applicant's version:

Data
Animal data
Reproduction studies have been performed following administration of oral metoclopramide during organogenesis in pregnant rats at about 6 times the MRHD calculated on body surface area and in pregnant rabbits at about 12 times the MRHD calculated on body surface area. No evidence of adverse developmental effects due to metoclopramide was observed.

Evaluation: No changes are recommended in this section.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's version:

Carcinogenesis
A 77-week study was conducted in rats with oral metoclopramide doses up to 40 mg/kg/day (about 6 times the maximum recommended human dose on body surface area basis). Metoclopramide elevated prolactin levels, and the elevation persisted during chronic administration. An increase in mammary neoplasms was found in rodents after chronic administration of metoclopramide *[see Warnings and Precautions (5.7)].* In a rat model for assessing the tumor promotion potential, a 2-week oral treatment with metoclopramide at a dose of 260 mg/kg/day (about 35 times the MRHD based on body surface area) enhanced the tumorigenic effect of N-nitrosodiethylamine.

Mutagenesis
Metoclopramide was positive in the *in vitro* Chinese hamster lung cell/HGPRT forward mutation assay for mutagenic effects and in the *in vitro* human lymphocyte chromosome aberration assay for clastogenic effects. It was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis assay with rat and human hepatocytes, and the *in vivo* rat micronucleus assay.

Impairment of Fertility
Metoclopramide at intramuscular doses up to 20 mg/kg/day (about 3 times the maximum recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Evaluation: No changes are recommended in this section.

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/s/

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05/07/2020 10:40:45 AM

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05/07/2020 10:50:54 AM

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	209388
Priority or Standard	Standard
Submit Date(s)	06/01/2018
Received Date(s)	06/01/2018
PDUFA Goal Date	04/01/2019
Division/Office	DGIEP/ODE III
Review Completion Date	March 29, 2019
Established/Proper Name	Metoclopramide nasal spray
(Proposed) Trade Name	Gimoti
Pharmacologic Class	Dopamine-2 receptor antagonist
Applicant	Evoke Pharma
Dosage Form	Nasal spray
Applicant Proposed Dosing Regimen	The recommended Gimoti dosage for the treatment of acute and recurrent diabetic gastroparesis is one spray in one nostril four times daily for 2 to (b) (4) weeks, depending on symptomatic response. For any single episode of gastroparesis, there should be no more than 12 cumulative weeks of metoclopramide exposure (all dosage forms and routes of administration) because of the increased risk of developing TD with longer-term use. Administer the dose 30 minutes before each meal and at bedtime. The maximum recommended daily dose is 4 sprays in one nostril per day.
Applicant Proposed Indication(s)/Population(s)	Adult women with acute and recurrent diabetic gastroparesis
Applicant Proposed Indication	Gimoti is indicated for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis
Recommendation on Regulatory Action	Complete Response

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OPDP	Meeta Patel/Katie Klemm
DMPP	Kelly Jackson/Marcia Williams
505(b)(2)	Wes Ishihara/Julieann DuBeau

CDRH Center for Devices and Radiological Health
COA Clinical Outcome Assessment
DMEPA Division of Medical Error Prevention and Analysis
DMPP Division of Medical Policy Programs
DPMH Division of Pediatric and Maternal Health
DPV Division of Pharmacovigilance
OPQ Office of Pharmaceutical Quality
OPDP Office of Prescription Drug Promotion
OSI Office of Scientific Investigation
OSIS Office of Study Integrity and Surveillance
OSE Office of Surveillance and Epidemiology
DEPI Division of Epidemiology
DMEPA Division of Medication Error Prevention and Analysis
DRISK Division of Risk Management

Glossary

AE	adverse event
AUC	area under the curve
ANCOVA	analysis of covariance
BA	bioavailability
BE	bioequivalence
BID	twice a day
c/o	complaints of
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CGSS	Change in Gastroparesis Symptom Severity
CI	confidence interval
CNS	central nervous system
COA	Clinical Outcome Assessment
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRF	case report form
DG	diabetic gastroparesis
DGIEP	Division of Gastroenterology and Inborn Errors Products
DKA	diabetic ketoacidosis
DM	diabetes mellitus
ECG	electrocardiogram
EPS	extrapyramidal symptoms
GCSI-DD	Gastroparesis Cardinal Symptom Index-Daily Diary
GE	gastric emptying
GERD	gastroesophageal reflux disease
GES	gastric electrical stimulation
GP	gastroparesis
GSA	Gastroparesis Symptom Assessment
h/o	history of
hCG	human chorionic gonadotropin
HTN	hypertension
IAQ	Investigator s Assessment Questionnaire
IM	intramuscular
IN	intranasal
IND	investigational new drug
ITT	intent to treat
IV	intravenous
IVRS	interactive voice response system
LOCF	last observation carried forward
mGCSI	modified Gastroparesis Cardinal Symptom Index-Daily Diary
MMRM	mixed model for repeated measures
MRHD	maximum recommended human dose
ms	milliseconds

NCCP	non-cardiac chest pain
NDA	new drug application
NOAEL	No Adverse Effect Level
OGS	overall GP symptom
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders Symptoms
PK	pharmacokinetic
PP	per protocol
PRO	patient reported outcome
PT	preferred term
QD	once a day
QID	four times a day
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAQ	Symptom Assessment Questionnaire
SEALD	Study Endpoints and Labeling Division
SOC	system organ class
TCA	tricyclic antidepressant
TD	tardive dyskinesia
TEAE	treatment emergent adverse event
UTI	urinary tract infection

1 Executive Summary

1.1. Product Introduction

The Applicant submitted new drug application (NDA) 209388 for Gimoti (metoclopramide nasal spray) on June 1, 2018, to the Division of Gastroenterology and Inborn Errors Products (DGIEP) under the 505(b)(2) pathway based on demonstrating equivalent systemic exposure to Reglan tablets 10 mg (listed drug).

The proposed indication is for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis (DG).

Metoclopramide hydrochloride is a dopamine-2 receptor antagonist. Safety concerns associated with the dopamine-2 receptor antagonist class include tardive dyskinesia (TD), other extrapyramidal symptoms (EPS), parkinsonian symptoms, and motor restlessness, potentially fatal symptom complex of neuroleptic malignant syndrome, depression, hypertension (HTN), fluid retention, hyperprolactinemia, and possible impairment of the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle.

The Applicant proposed labeling included the following dose and administration recommendations:

- The recommended Gimoti dose for the treatment of acute and recurrent DG is 15 mg 4 times daily for 2 to (b) (4) weeks, depending on symptomatic response.
- For any single episode of gastroparesis (GP), there should be no more than 12 cumulative weeks of metoclopramide exposure (all dosage forms and routes of administration) because of the increased risk of developing TD with longer-term use.
- Administer the dose 30 minutes before each meal and at bedtime.
- The maximum recommended daily dose is 60 mg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The pharmacokinetic-bridge between the Gimoti 15 mg dose and the Reglan tablet 10 mg is not sufficient to justify the reliance on the findings of efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan. Given that at all evaluated Gimoti doses failed to demonstrate comparable bioavailability to the listed drug (Reglan 10 mg), and the lack of evidence of benefit of lower doses in clinical trials, there is no substantial evidence of effectiveness in the overall population to support approval at this time. The subgroup analyses in females do not provide substantial evidence in females given the post hoc nature of the analyses (i.e., inflated type I error), the failed clinical trial in females, and the lack of a compelling explanation for/evidence of differences between men and women in expected effects of Gimoti.

Details of these substantial issues, identified during the review of this application, are outlined below; similar issues were communicated in a Discipline Review Letter, dated February 28, 2019.

Quality

The specification for the drug product is inadequate as insufficient evidence has been provided to ensure the combination product quality control and essential performance characteristics of the device do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The variability of the proposed acceptance criterion and the significant differences between the mean droplet sizes for the 14 mg/mL, 15 mg/mL and 17 mg/mL strengths are not justified particularly given the observed variability of PK data.

Clinical

The clinical trial data do not support effectiveness of Gimoti at the proposed dose. Two randomized, placebo-controlled clinical trials (Studies METO-IN-002 and METO-IN-003) failed to show efficacy of Gimoti (these clinical trials were conducted at doses lower than the proposed dose). Furthermore, there was not a compelling explanation or sufficient evidence to support a females-only indication. The subgroup analysis in females in Study METO-IN-002 was post hoc and did not have proper type I error rate control, and the follow-up females-only study METO-IN-003 did not establish efficacy in females. In addition, the Applicant alluded to the fact that the lack of observed efficacy in males may be in part attributed to sex-related PK differences. However, the listed drug which is approved for both males and females also demonstrates sex-specific differences in PK. Therefore, lower systemic exposure in males would not be a valid reason for limiting the use of Gimoti to female patients.

Clinical Pharmacology

Gimoti failed to demonstrate comparable bioavailability (BA) to the listed drug (Reglan 10 mg) and resulted in 16% to 20% lower Cmax at the proposed 15 mg and two higher doses, 16 mg and 17 mg compared to Reglan 10 mg. However, the Applicant has not provided sufficient scientific justification to demonstrate that comparable efficacy could be achieved despite the lower C_{max} for Gimoti compared to Reglan. As such, the pharmacokinetic (PK) bridge between Gimoti and Reglan was not adequately established to justify the reliance on Reglan's efficacy to assure comparable efficacy between Gimoti and Reglan. The clinical pharmacology review noted that the high PK variability for Gimoti, including apparent inconsistent and incomplete drug delivery of Gimoti, significantly contributed to the average 16% to 20% lower C_{max} for all three different doses of Gimoti.

A Type-A meeting was held on March 21, 2019 at the request of the Applicant during which these issues were discussed. The responses and discussion did not provide additional information that changed the reviewers' assessments. For the reasons outlined above, the data provided are insufficient to support a recommendation to approve Gimoti at this time.

The specific deficiencies and recommendations to address the deficiencies, by discipline, to be communicated in the action letter are described below.

Clinical Pharmacology

The pharmacokinetic (PK) bridge between the Gimoti 15 mg dose and the Reglan tablet 10 mg is insufficient to justify the reliance on the findings of safety and efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan.

We have concerns that the product is not able to deliver metoclopramide in a reliable and consistent manner. Several subjects demonstrated low Cmax (<5 ng/ml) for metoclopramide with one or more Gimoti administrations. This was not observed with Reglan tablet administration. The overall lower mean Cmax was driven by these individuals who appeared to receive very little drug. The reason for this observation is unclear.

Recommendations to Address Deficiencies:
To address the clinical pharmacology deficiency, we recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery. The Applicant will need to provide evidence supporting their conclusions from the root cause analysis and provide mitigation strategies that will address the(se) issue(s). Depending on the identified cause(s), the Applicant may need to conduct additional in vitro and/or in vivo studies.

Quality/Device

The proposed specification for the drug product is inadequate since insufficient evidence has been provided to ensure that the quality control and essential performance characteristics of the combination product do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The proposed acceptance criterion for droplet size distribution of the 15 mg/mL strength (i.e. the mean droplet sizes and calculated ranges) are not justified particularly given the observed variability of PK data.

Recommendations to Address Deficiencies:
Upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by 3 batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device. We recommend that the three registration batches be manufactured at the proposed commercial manufacturing site, manufactured by the proposed commercial process, and tested using validated analytical methods at the proposed analytical site.

The following comments are not approvability issues but should be addressed in the complete response submission.

Quality/Device

A. We recommend that actuation force be considered an essential performance requirement and to include a test and acceptance criterion for actuation force for the to-be-marketed combination product in the product release and stability specification. The Applicant should include verification and validation data to support that specification and describe why this force is appropriate for the intended user population. Alternatively, the Applicant should provide a rationale for why they do not consider actuation force an essential performance requirement for the device constituent and how they will control the product to assure this essential performance will be consistently achieved.

B. The Applicant provided a specification for the lowest allowable cap removal force, but without the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.

C. The proposed shelf-life of (b) (4) months is not supported by the data submitted. Upon resubmission the proposed shelf life should be supported by 3 batches of the drug product using the selected commercial formulation (including strength of the product) and the proposed commercial device.

D. It is premature to agree to a reduced reporting category for an additional release and stability facility as proposed in the comparability protocol.

Clinical Pharmacology

E. (b) (4)

(b) (4) We recommend that the Applicant develop a lower dosage strength to address the dosage adjustment for patients who may need lower dose.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant submitted NDA 209388 for Gimoti on June 1, 2018, to the DGIEP under the 505(b)(2) pathway based on demonstrating equivalent systemic exposure to Reglan tablets 10 mg (listed drug).

The proposed indication is for the relief of symptoms in adult women with acute and recurrent DG. The Applicant-proposed labeling included the following dose and administration recommendations:

- The recommended Gimoti dose for the treatment of acute and recurrent DG is 15 mg 4 times daily for 2 to (b)(4) weeks, depending on symptomatic response.
- For any single episode of GP, there should be no more than 12 cumulative weeks of metoclopramide exposure (all dosage forms and routes of administration) because of the increased risk of developing TD with longer-term use.
- Administer the dose 30 minutes before each meal and at bedtime.
- The maximum recommended daily dose is 60 mg.

Metoclopramide hydrochloride is a dopamine-2 receptor antagonist. There are safety concerns with the dopamine-2 receptor antagonist class, and include TD, other EPS, parkinsonian symptoms, and motor restlessness, potentially fatal symptom complex of neuroleptic malignant syndrome, depression, hypertension, fluid retention, hyperprolactinemia, and possible impairment of the mental and/or physical abilities required for the performance of hazardous tasks such as operating machinery or driving a motor vehicle.

To establish a bridge between Gimoti and Reglan, the Applicant conducted a relative BA study (METO-IN-006). In METO-IN-006, systemic exposure to metoclopramide was compared between single nasal administration of Gimoti at 15 mg, 16 mg, or 17 mg and single oral administration of Reglan tablet 10 mg in 98 healthy male and female subjects. Gimoti for all three doses showed comparable AUC but 16% to 20% lower C_{max} than Reglan with confidence intervals failing to demonstrate comparable bioavailability to Reglan tablets. The Applicant proposed Gimoti 15-mg dose for female patients only based on a post hoc subgroup analysis of relative BA by sex claiming that Gimoti 15 mg showed the most closely matched systemic exposure to Reglan in the subgroup of female subjects. However, the female-only indication is not

adequately supported, and the bridge between Gimoti and Reglan needs to be established regardless of sex. The post hoc subgroup analysis of relative BA by sex conducted by the Applicant is not acceptable to establish a bridge between Gimoti and Reglan.

The clinical pharmacology review focused on the analyses of relative BA without regard to sex to support the reliance of the efficacy and safety of Reglan. Gimoti, at all tested doses (15 mg, 16 mg, and 17 mg), demonstrated lower metoclopramide C_{max} than Reglan, but the potential effects of the lower C_{max} on efficacy have not been adequately addressed. Therefore, the potential for suboptimal efficacy due to the lower C_{max} cannot be ruled out, and the results of METO-IN-006 do not adequately support the bridging of efficacy between Gimoti and Reglan.

In addition, substantially higher variability in systemic metoclopramide exposure after Gimoti administration was noted. Several subjects demonstrated little to no absorption of metoclopramide only when Gimoti was administered (but not with Reglan), which may indicate incomplete dosing from the Gimoti nasal spray. Review of the case report forms and the study monitor "dosing debrief summary" notes did not support the assertion that the little to no absorption observed in these subjects was a result of user-error or drainage of the drug out of the nasal passage due to head movement or sneezing after drug administration.

The Applicant proposed to limit the use of Gimoti to female patients while the listed drug, Reglan, is indicated for both male and females. To support the female-only indication, the Applicant submitted data from four trials: an open-label trial (study 25,512-302R) which collected PK information and was the only one of the four clinical efficacy and safety trials in patients to include Reglan as an active comparator; a dose-finding phase 2 trial (METO-IN-002) conducted in both females and males; and two phase 3 trials (METO-IN-003 conducted in females only and METO-IN-004 conducted in males only). The clinical trials did not evaluate the 15-mg dose that the Applicant proposed for approval and labeling. The proposed indication and dose are based on the findings of the BA study (METO-IN-006), which evaluated Gimoti 15 mg, 16 mg, and 17 mg in healthy volunteers.

Study METO-IN-002 and METO-IN-003 failed to demonstrate efficacy over placebo on the primary endpoint, and METO-IN-004 was terminated early due to enrollment challenges. In METO-IN-002, among four secondary endpoints and two dose groups, only one secondary endpoint (nausea) was nominally significant ($p<0.05$) for Gimoti 14 mg. No secondary endpoints were significant for METO-IN-003. The Applicant proposed results from post hoc subgroup analyses in female patients that achieved statistical significance; however, the Applicant's subgroup analyses did not have proper type I error rate control and hence cannot be used to establish efficacy. Furthermore, the subgroup analysis in female patients from METO-IN-002 was not replicated in METO-IN-003, the female-only phase 3 confirmatory trial, because the analyses of primary and secondary endpoints did not show evidence of efficacy. In addition, the magnitude of the estimated difference for Gimoti over placebo was small and the clinical meaningfulness of a potential effect remains uncertain. Additional analyses were performed to assess the evidence in favor of the female subgroup analyses. Efficacy results were also examined for the open-label study 25,512-302R, although this study is considered exploratory. Therefore, the data from the clinical trials cannot be utilized to support evidence of effectiveness or bridging to Reglan tablets.

The clinical trial data do not support effectiveness of Gimoti at the proposed dose. Two randomized, placebo-controlled clinical trials (Studies METO-IN-002 and METO-IN-003) failed to show efficacy of Gimoti (these clinical trials were conducted at doses lower than the proposed dose). Furthermore, there was not a compelling explanation or sufficient evidence to support a females-only indication. The subgroup analysis in females in Study METO-IN-002 was post hoc and did not have proper type I error rate control, and the follow-up females-only study, METO-IN-003, did not establish efficacy in females. In addition, the Applicant alluded to the fact that the lack of observed efficacy in males may be in part attributed to sex-related PK differences. However, the listed drug, which is approved for both males and females, also demonstrated sex-specific differences in PK. Therefore, lower systemic exposure in males would not be a valid reason for limiting the use of Gimoti to female patients.

The Applicant claimed that because Gimoti is administered intranasally and bypasses the digestive system, Gimoti has the potential to facilitate more predictable absorption than orally administered metoclopramide tablets in patients with delayed or erratic gastric emptying (GE) and/or in patients who are unable to tolerate oral medications due to severe nausea and vomiting. However, the data submitted suggest that there may be inconsistent delivery and, in some cases, incomplete dosing, from the Gimoti nasal spray. Furthermore, although the clinical trials did not evaluate the dose proposed for labeling, the clinical trials failed to demonstrate efficacy over placebo in patients with GP. Therefore, based on the data provided, we cannot conclude that the route of administration addresses the need for more predictable absorption or would provide benefit for patients who cannot tolerate oral medication.

Additionally, deficiencies were identified with the quality information submitted. The proposed specification for the drug product is inadequate since insufficient evidence has been provided to ensure that the quality control and essential performance characteristics of the combination product do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The proposed acceptance criterion for droplet size distribution of the 15 mg/mL strength (i.e. the mean droplet sizes and calculated ranges) are not justified particularly given the observed variability of PK data.

Based on the deficiencies identified during the review of this application, we conclude that there is insufficient evidence to support approval of Gimoti at this time. The recommendations to address the deficiencies are described below.

To address the clinical pharmacology deficiency, we recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery. The Applicant will need to provide evidence supporting the conclusions from the root cause analysis and provide mitigation strategies that will address the(se) issue(s). Depending on the identified cause(s), the Applicant may need to conduct additional in vitro and/or in vivo studies.

To address the quality deficiency, we recommend that upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by 3 batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device. We recommend that the three registration batches be manufactured at the proposed commercial manufacturing site, manufactured by the proposed commercial process, and tested using validated analytical methods at the proposed analytical site.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GP is a disorder characterized by delayed GE of solid food in the absence of a mechanical obstruction of stomach and occurs primarily in females. • The core signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety. • These symptoms can be debilitating and negatively impact patients' quality of life and daily functioning.	GP remains a considerable health issue and can profoundly impact patients' quality of life.
Current Treatment Options	• Reglan (metoclopramide) is the only drug currently approved for GP and is available as an oral tablet, intravenous (IV) infusion, intramuscular (IM) injection, and orally disintegrating tablet. • The American College of Gastroenterology Clinical Guidelines for the treatment of GP, recommends metoclopramide as the first line pharmacologic therapy and should be administered at the lowest effective dose to facilitate absorption to decrease the risk of TD. • Erythromycin, a motilin receptor agonist, and domperidone, another dopamine D2 receptor antagonist, are thought to accelerate GE and are also recommended by the American College of Gastroenterology. However, domperidone is associated with risk of QTc prolongation and cardiac arrhythmias. Erythromycin can be administered intravenously or orally but long-term use of the oral route is limited by tachyphylaxis. Domperidone is not approved in the United States and	Reglan (metoclopramide) is currently the only approved product for the treatment of DG and is associated with serious safety concerns. Other therapies are used off-label and the safety and efficacy of these products has not been established for the treatment of GP. Therefore, additional treatment options are needed. Although there remains a need for additional treatment options for gastroparesis, Gimoti contains the same active ingredient as Reglan, metoclopramide, and has the same associated risks. Patients who have suboptimal efficacy with Reglan are unlikely to achieve a benefit with Gimoti. Gimoti does not offer a new mechanism of action or an improved safety

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	is available through the FDA Expanded Access program. • Antiemetics, such as ondansetron, are used for symptomatic relief of nausea and vomiting. • Non-pharmacologic interventions, such as dietary modifications, are often implemented (e.g., smaller meals, liquid meals, changes in nutritional composition of meals, etc.) to help control the signs and symptoms associated with delayed GE.	profile as compared to the currently available therapies. Furthermore, patients who are unable to tolerate oral intake of medication are often vomiting and/or nauseas to a degree where they are also dehydrated and require hospitalization for intravenous hydration and medication. Patients with diabetic gastroparesis are also at risk for serious clinical sequelae of hyper- or hypoglycemia, such as diabetic ketoacidosis, if they are unable to take oral medication, food, and liquid. These patients would also require hospitalization to correct the electrolyte, fluid, and glucose levels. Patients who are unable to chronically tolerate oral intake would likely have a gastrostomy or gastro-jejunostomy tube to meet daily caloric requirements. Therefore, administration of Gimoti via an intranasal route of administration does not appear to address an unmet need in patients who are unable to swallow or tolerate oral intake of medication since those patients would likely be hospitalized for intravenous treatment and/or would have enteral feeding devices.
Benefit	• Both double-blind trials, METO-IN-002 and METO-IN-003, failed to achieve statistical significance on the primary endpoints; therefore, formal statistical hypothesis testing was stopped. Of the four secondary endpoints and two dose groups in METO-IN-002, only one secondary endpoint (nausea) was nominally significant ($p<0.05$) for metoclopramide nasal spray 14 mg, and no secondary endpoints were nominally significant for METO-	The clinical trials failed to show efficacy in female and male patients and did not evaluate the proposed dose; therefore, the clinical trial data cannot be used to inform a conclusion that Gimoti is effective at the proposed dose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	IN-003. The Applicant's subgroup analyses did not have proper type I error rate control and cannot be used to establish efficacy. Furthermore, the subgroup analysis of METO-IN-002 in females was not replicated on METO-IN-003 (females only trial). • METO-IN-004 enrolled male patients only and was stopped early due to difficulty in enrollment. None of the primary and secondary endpoints were statistically significant. • Although the efficacy results appear more promising for study 25,512-302R, the trial was open-label, the sample size was small, the efficacy results were driven by a few subjects, and there was no significant difference between treatment groups for most of the treatment period. • Gimoti (at all evaluated doses) failed to demonstrate comparable BA to the listed drug (Reglan 10 mg) in METO-IN-006, a comparative BA study. The C_{max} was 16% to 20% lower for Gimoti than Reglan. • Several subjects who were given Gimoti in METO-IN-006 showed virtually no drug absorption (plasma concentrations <5 ng/mL at all time points) while those same subjects showed consistent drug absorption when given Reglan orally. • There was no documentation in the case report forms or the study monitor "dosing debrief summary" notes to support that the little to no absorption observed in these subjects was a result of user-error or drainage of the drug out of the nasal passage due to head movement or sneezing after drug administration.	The data provided were insufficient to demonstrate that comparable efficacy could be achieved despite the difference in C_{max}. The inconsistent and incomplete drug delivery of Gimoti may have significantly contributed to the average 16% to 20% lower C_{max} for all three different doses of Gimoti. The subjects with virtually no drug absorption raise a concern for lack of or loss of efficacy. Gimoti can potentially lead to sub-optimal efficacy unless the issue of incomplete drug delivery is resolved. Based on the data provided and in the absence of a clear understanding of the root cause(s) if the variability including the issue of inconsistent and incomplete delivery, we cannot conclude that the intranasal route of administration addresses the need, as outlined by the Applicant, for more predictable absorption or would provide benefit for patients who cannot tolerate oral medication. The results of METO-IN-006 cannot support the establishment of an adequate pharmacokinetic bridge between Gimoti and Reglan. To address the clinical pharmacology deficiency, we recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		inconsistent and incomplete delivery. The Applicant will need to provide evidence supporting their conclusions from the root cause analysis and provide mitigation strategies that will address the(se) issue(s). Depending on the identified cause(s), the Applicant may need to conduct additional in vitro and/or in vivo studies.
Risk and Risk Management	• In METO-IN-006, there was higher overall inter- and intra-subject variability in drug exposure for Gimoti as compared to that of Reglan. Several subjects had substantially higher exposure (e.g., AUC_{inf}>1000 h·ng/mL) than that of the reference product. • There were no deaths in any of the clinical trials. The proportion of patients that developed serious adverse events (SAEs) was generally similar between the treatment groups. Most of the adverse events (AEs) were observed in the central nervous system (CNS) category and were considered probably and possibly related to the administration of Gimoti; a higher proportion of females discontinued the study drug compared to male patients in the Gimoti treatment groups.	The potential for substantially higher exposure (e.g., AUC_{inf}>1000 h·ng/mL) than that of the reference product raises a safety concern. Once it has been verified that the device can deliver the intended dose, then additional considerations may be needed to ensure the patient can properly use metoclopramide nasal spray.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Refer to COA review
		X	Patient reported outcome (PRO)	Efficacy data collected directly from patients using patient diaries
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
		Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

2.1.1. Gastroparesis

Gastroparesis is a disorder characterized by objectively delayed GE of solid food in the absence of a mechanical obstruction of stomach, with core signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety.[1] Often these symptoms can be debilitating and have significant negative impact on patients' quality of life and functioning, including work productivity.[2,3] Currently, GP is recognized as part of a broader spectrum of gastric neuromuscular dysfunction that includes impaired gastric accommodation. The overlap between upper gastrointestinal symptoms makes the distinction between GP and other disorders, such as functional dyspepsia, challenging.

Normal gastrointestinal motor function is a complex sequence of events that is controlled by an extrinsic nerve supply from the brain and spinal cord, the complex plexi within the wall of the stomach and intestine, and the effects of locally released transmitters, such as amines and peptides, that alter the excitability of the smooth muscle of the intestine. Abnormalities in any of these locations can lead to delayed GE. The pathophysiology of GP has not been fully elucidated but seems to involve abnormalities in the autonomic nervous system (vagus nerve), smooth muscle cells, enteric neurons, and interstitial cells of Cajal.

The etiology of GP is diverse. About one-third of the cases are associated with diabetes, and nearly half are classified as idiopathic, based on studies that did not observe any primary underlying abnormality in patients with delayed GE.[4] Connective tissue disorders, autoimmune disorders, prior gastric surgery, ischemia, and medications make up the vast majority of the remaining cases. DG, also known as gastroparesis diabeticorum, is the most recognizable form of delayed GE; DG is detected with equal frequency in type 1 and type 2 diabetic patients.[4] Symptoms that can be attributable to GP are reported by 5% to 12% of patients with diabetic mellitus.[5]

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[1] Camilleri, M, et al., 2013, Clinical guideline: management of gastroparesis, Am J Gastroenterol, 108(1):18–37.

[2] Camilleri, M, et al, 2011, Epidemiology, mechanisms, and management of diabetic gastroparesis, Clin Gastroenterol Hepatol, 9(1):5–12.

[3] Parkman, HP, et al, 2011, National Institute of Diabetes Digestive Kidney Diseases Gastroparesis Clinical Research Consortium. Similarities and differences between diabetic and idiopathic gastroparesis, Clin Gastroenterol Hepatol, 9(12):1056–64.

[4] Soykan, I, et al, 1998, Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis, Dig Dis Sci, 43(11):2398–404.

[5] Aleppo, G, et al, 2017, Reported gastroparesis in adults with type 1 diabetes (T1D) from the T1D exchange clinic registry, J Diabetes Compl, 31(12):1669–1673.

Epidemiology

The accurate figures for the prevalence, morbidity, and mortality related to the GP are not well established; the current estimates of prevalence are based on the patients seeking medical attention and are likely to be underestimates of the actual prevalence. The difficulty in estimating the true prevalence of GP is due to the relatively poor correlation of symptoms with GE,[6] the need to apply a diagnostic test in a community setting,[4] and overlap of symptoms of GP with other conditions such as functional dyspepsia.[7,8] Furthermore, it is unclear if all patients with GP seek health care. A study estimated that up to 1.8% of the general population may have GP, but only 0.2% are diagnosed.[9] Studies have shown that more than 80% of patients with GP are women and the majority are less than 45 years of age suggesting gender-specific features of GP; the authors suggest that such differences may be due to enteric innervation, hormonal action, and brain function, specifically in the areas that generate/control anxiety and emotion.[4,8] However, there are no data to confirm the biologic basis for the gender differences.

In one of the largest population-based studies, the age-adjusted incidence of GP was 2.4 per 100,000 person-years for men and 9.8 per 100,000 person-years for women, and prevalence was 9.6 per 100,000 persons for men and 38 per 100,000 persons for women.[10] A quarter of patients in the study required therapeutic interventions, and assessment included patients with probable, possible, and definite diagnosis of GP. Several published studies reported that patients with GP have increased 5-year mortality compared to those without GP.[10,11] GP has a substantial negative impact on patients' quality of life and the healthcare system.[12]

Diabetic Gastroparesis

Similarly, the exact prevalence of DG remains unknown. Nearly 6% of adults suffer from diabetes and another 5% estimated to have a subclinical form of the disease. Evidence suggests that after 10 to 20 years of clinically apparent diabetes, 30% to 60% of diabetics develop overt signs of visceral autonomic neuropathy, of which GP or gastric stasis is one form; 30% to 50%

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[6] Talley, NJ, et al, 2006, Functional dyspepsia, delayed gastric emptying, and impaired quality of life, Gut, 55(7):933–9.

[7] Stanghillini, V and J Tack, 2014, Gastroparesis: separate entity or just a part of dyspepsia? Gut, 63(12):1972–1978.

[8] Parkman, HP, et al, 2011, Clinical features of idiopathic gastroparesis vary with sex, body mass, symptom onset, delay in gastric emptying, and gastroparesis severity, Gastroenterology, 140(1): 101–115.

[9] Rey, E, et al, 2012, Prevalence of hidden gastroparesis in the community: the gastroparesis "iceberg," J Gastroenterol. Motil, 18(1): 34–42.

[10] Jung, HK, et al, 2009, The incidence, prevalence, and outcome of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006, Gastroenterology, 136(4):1225–1233.

[11] Hyett, B, et al, 2009, Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis, Gastroenterol, 137(2):445–452.

[12] Lacy, BE, et al, 2018, Gastroparesis: quality of life and health care utilization, J Clin Gastroenterol, 52(1):20–24.

of type 2 diabetic patients have delayed GE, while the prevalence of the specific symptoms of GP (nausea and vomiting) is lower by approximately 10%.[13]

DG has also been observed to be associated with significant morbidity and impaired quality of life, with anxiety and depression and effect on the self-management of diabetic control, especially with fluctuating blood glucose levels.[14,15]

The effect of GP on life expectancy is unclear. Studies conducted in referral diabetic patients showed no effect of delayed GE on mortality at 12 years[16] and after 25 years[17] of follow up. However, in a community-based study in subjects with symptoms of GP of mixed etiology, survival was lower than expected for age and sex matched subjects without GP.[10] Recent studies have shown increased hospitalization rates and emergency department consultations for GP,[18,19,20] which may also be due to the increased awareness of the GP and increased prevalence of both type 1 and type 2 diabetes mellitus (DM).[21]

DG complicates management of blood glucose for both type 1 and type 2 DM patients due to unpredictable absorption of carbohydrates. These patients frequently have alternating hypo- and hyperglycemia leading to poorly controlled diabetes, especially if treated with insulin.

Studies have shown that more than 80% of patients with GP are women and the majority are less than 45 years of age suggesting gender-specific features of GP;[4,8] the authors suggest that such differences may be due to enteric innervation, hormonal action, and brain function, specifically

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[13] Gastroparesis. Johns Hopkins Medicine. https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/esophagus_stomach/gastroparesis.pdf

[14] Teigland, T, et al, 2018, A longitudinal study on patients with diabetes and symptoms of gastroparesis-associations with impaired quality of life and increased depressive and anxiety symptoms, J Diabetes Complications, 32(1):89–94.

[15] Homko, C, et al, 2016, The impact of gastroparesis on diabetic control: Patient perception, J Diabetes complications, 30(5):826–829.

[16] Hyett, B, et al, 2009, Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis, Gastroenterology, 137(2):445–452.

[17] Chang, J, et al, 2013, Prognosis of diabetic gastroparesis--a 25-year evaluation, Diabetes Med, 30(5):e185–e185.

[18] Wang, YR, et al, 2008, Gastroparesis related hospitalizations in the United States: Trends, characteristics, and outcomes, 1995-2004, Am J Gastroenterol, 103(2):313–322.

[19] Hirsch, W, et al, 2019, Emergency department burden of gastroparesis in the United States, 2006 to 2013, J Clin Gastroenterol, 53(2):109–113.

[20] Wadhwa, V, et al, 2017, Healthcare utilization and cost associated with gastroparesis, World J Gastroenterol, 23(24):4428–4436.

[21] Nusrat, S, et al, 2013, Gastroparesis on the rise: Incidence versus awareness? Neurogastroenterol. Motil, 25(1):16–22.

in the areas that generate/control anxiety and emotion. However, there are no data to confirm the biologic basis for the gender differences.

2.1.2. Exacerbation of Gastroparesis/Diabetic Gastroparesis

Almost all patients have recurrent GP with acute exacerbation. As per the survey, conducted by the Applicant, in patients enrolled in study METO-IN-002 the occurrence rate of acute exacerbation or a flare was observed to be dependent on severity of the disease. Acute exacerbations in patients with mild, moderate, and severe GP was reported to be 27%, 40%, and 34%, respectively. The duration of acute exacerbation or flare was observed to depend on the severity of flare. Proportion of patients with flare lasting 1 to 2 days in mild, moderate, and severe disease were 85%, 70%, and 43%. In approximately half of the patients with severe category the flare lasted up to 3 to 5 days.

Hospital admissions for exacerbation of acute symptoms include inadequate glycemic control, infections (most frequently urinary tract infection (UTI)), poor adherence/ intolerance/lack of efficacy of medications, stress, and intake of large meal.[22] It is known that acute hyperglycemia slows GE in patients with diabetes and healthy controls.[23,24,25] In addition, hyperglycemia also attenuates the efficacy of prokinetic drugs.[26,27] It is important to note that uncontrolled hyperglycemia in the setting of diabetes may affect measurement of core signs and symptoms of GP and the efficacy evaluation of study drug(s) in the clinical trials.

2.2. Analysis of Current Treatment Options

In general, the aim of GP therapies is to accelerate GE and achieve symptomatic relief through dietary modifications and/or pharmacologic interventions. Drugs used for accelerating GE include prokinetic drugs such as metoclopramide, domperidone, and erythromycin. In addition, antiemetics and tricyclic antidepressants (TCAs) are often used for symptomatic relief. Venting of the gastrostomy tube or gastric decompression is recommended for patients who are refractory to therapy with prokinetic and antiemetics. Other options include pyloric botulinum toxin injection, endoscopic gastric myotomy, laparoscopic pyloroplasty, or gastrectomy. Gastric

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[22] Uppalapati, SS, et al, 2009, Factors contributing to hospitalization for gastroparesis exacerbations, Dig. Dis. Sci, 54(11):2404–2409.

[23] Fraser, R, et al, 1991, Hyperglycemia stimulates pyloric motility in normal subjects, Gut, 32(5):475–478.

[24] Barnett, JL and C Owyang, 1988, Serum glucose concentration as a modulator of interdigestive gastric motility, Gastroenterology, 94(3):739–744.

[25] Jebbink, RJA, et al, 1994, Hyperglycemia induces abnormalities of gastric myoelectrical activity in patients with type I diabetes mellitus, Gastroenterology, 107(5):1390–1397.

[26] Petrakis, IE, et al, 2002, Hyperglycemia attenuates erythromycin-induced acceleration of liquid-phase gastric emptying of hypertonic liquids in healthy subjects, Dig Dis Sci, 47(1):67–72.

[27] Petrakis IE et al, 2002, Hyperglycemia attenuates erythromycin-induced acceleration of solid-phase gastric emptying in healthy subjects, Abdom Imaging, 27(3):309–314.

electrical stimulation (GES) was approved for the treatment of chronic, intractable (drug refractory) nausea, vomiting secondary to GP of diabetic or idiopathic etiology in 2000.

Prokinetics

The American College of Gastroenterology Clinical Guidelines for the treatment of GP, recommends that metoclopramide should be used as the first line of prokinetic therapy and should be administered at the lowest effective dose to facilitate absorption to decrease the risk of TD. Additionally, patients should be instructed to discontinue therapy if side effects of involuntary movements develop. Metoclopramide is the only drug currently approved at a dose of 10 mg (to be administered four times daily for 2 to 8 weeks) in adults for treating the signs and symptoms of acute and recurrent DG. It is available as oral tablet, oral disintegrating tablet, and IV and IM injections.

Domperidone, another dopamine D2 receptor antagonist, does not cross blood brain barrier, therefore does not cause the same CNS adverse effects;[28] however, there is an associated risk of QTc prolongation and cardiac arrhythmias. Domperidone is not approved in the US; however, it is available through the Expanded Access of the FDA's Investigational Drug program.

Erythromycin, a macrolide antibiotic, is a motilin receptor agonist that leads to increased antral contraction. The IV route is generally used in hospitalized patients, although tachyphylaxis is known to occur after about 4 weeks. In addition, there are potential interactions with other drugs due to cytochrome P450 (CYP) 3A4 inhibition.

See Table 1 below for details.

Antiemetics

Antiemetics have not been studied in the management of patients with GP, and their use in GP is based on their efficacy in controlling nonspecific nausea and vomiting. Patients with persistent nausea and vomiting despite prokinetics are treated with antihistamines (e.g., diphenhydramine) and $5HT_3$ antagonists (e.g., ondansetron). Prolongation of the QT interval and central side effects have limited the use of phenothiazines (prochlorperazine). First generation 5-HT3 antagonists (e.g., ondansetron, granisetron, and dolasetron) are associated with electrocardiographic changes, and rare fatal arrhythmias have been reported in association with prolonged QT intervals.

Tricyclic Antidepressants

TCAs such as nortriptyline, used for symptomatic control, are not approved for treatment of GP. In open-label trials, low-dose nortriptyline, known to have low anticholinergic effects, was reported to decrease the symptoms of nausea, vomiting, and abdominal pain in patients with

[28] Patterson, D, et al, 1999, A double blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis, Am J Gastroenterol, 94(5):1230–1234.

diabetic and idiopathic GP.[29,30] However, the results from a randomized trial failed to demonstrate a benefit of nortriptyline compared to placebo in patients with GP.[31] It is important to note that TCAs can potentially decrease the rate of GE.

Dietary Modification

Dietary modifications include multiple small meals (four to six per day) with low fat content because fat can slow the GE.[32,33] Olausson et al. reported that a small particle size diet may reduce the symptoms based on a study in 56 patients with DG.[34]

[29] Prakash, C, PJ Lustman, et al, 1998, Tricyclic antidepressants for functional nausea and vomiting: clinical outcome in 37 patients, Dig Dis Sci, 43(9):1951–1956.

[30] Sawhney, MS, C Prakash, et al, 2007, Tricyclic antidepressants for chronic vomiting in diabetic patients, Dig Dis Sci, 52(2):418–424.

[31] Parkman, HP, et al, 2013, Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial, JAMA, 310(24):2640–2649.

[32] Bauras, EP and JS Scolapio, 2004, Gastric motility disorders: management that optimizes nutritional status, J Clin Gastroenterol, 38(7):549–557.

[33] Parrish, CR, 2005, Nutritional intervention for the patients with gastroparesis: an update, Pract Gastroenterol, 29(8):29–66.

[34] Olausson, EA, et al, 2014, A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial, Am J Gastroenterol, 109(3):375–385.

Table 1: Summary of Prokinetic Treatment Armamentarium Relevant to Proposed Indication

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Metoclopramide	Relief of symptoms in adults with acute and recurrent DG	1980	10 mg, 30 minutes before each meal and at bedtime (maximum of 40 mg per day) for 2 to 8 weeks.	Based on 2 DB, PC studies that showed improvement in nausea, vomiting, and fullness; and 2 uncontrolled studies that showed trend towards improvement of all symptoms and tolerability.	CNS: TD, Extrapyramidal Symptoms, and NMS: Depression and suicidal ideation/ suicide	The studies supportive of NDA that time did not meet the current standard of adequate and well controlled studies.
Other Treatments						
Domperidone	FDA currently allows patients 12 years of age and older with various GI conditions, including GP to be treated with domperidone through the Expanded Access to Investigational Drugs program.	Off label use	10-30 mg oral domperidone QID for 30 days initially and may be repeated. No maximum duration is outlined.	Domperidone is not approved in the U.S. It is approved in several other countries as treatment for nausea/vomiting, GERD, and upper GI motility disorders.	The drug is withdrawn if: ECGs demonstrate QTc>450 milliseconds for males, QTc>470 milliseconds for females, or there is a change in QTc≥60 milliseconds from baseline. Patient develops serious electrolyte abnormalities.	Available under expanded access IND (FDA)*
Erythromycin	Off label use	Off label use	125-250 mg 4 times daily	Tachyphylaxis occurs in 4 weeks	Nausea, diarrhea, abdominal cramps, and rash	-

* https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm368736.htm
Abbreviations: CNS central nervous system; GI gastrointestinal; NMS neuroleptic malignant syndrome; TD=Tardive Dyskinesia; QID=four times a day; DG=diabetic gastroparesis; GP gastroparesis; DB double-blind; PC=placebo-control; GERD gastroesophageal reflux disease; NDA new drug application; IND investigational new drug; ECG electrocardiogram

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Gimoti (metoclopramide intranasal (IN) spray) is not currently marketed in the United States. The active ingredient, metoclopramide, is marketed as Reglan oral tablets, orally disintegrating tablets, and IV/IM formulations, and has been marketed in the United States since 1979.

3.2. Summary of Presubmission/Submission Regulatory Activity

The earlier PK studies were conducted by the previous sponsors under the Investigational New Drug (IND) 025512. The formulation used in these studies was slightly different from the formulation used for the clinical studies conducted by the Applicant, Evoke Pharma, to support the NDA. Evoke Pharma acquired the ownership of IND 025512 from the previous sponsor Questcor Pharmaceuticals, Inc., on June 15, 2007, and reformulated the metoclopramide IN formulation in 2008.

The Division had the multiple meetings with the Applicant over a period of 10 years under the IND 025512. An overview of the pertinent regulatory history is summarized in chronological order.

1. Type B End of Phase 2 Meeting: September 30, 2008

The discussions included nonclinical, chemistry, manufacturing, control, and regulatory strategies to evaluate efficacy and safety of metoclopramide HCL nasal spray for the indication of relief of symptoms associated with acute and recurrent DG. The study endpoints and labeling development (SEALD) team, now referred to as the clinical outcome assessment (COA) staff, was consulted to provide responses to the use of the Gastroparesis Cardinal Symptom Index-Daily Diary (GCSI-DD) instrument, a patient-reported assessment of severity of GP symptoms, to measure efficacy in the clinical trials. The Division agreed to the Applicant's proposal to submit the application under 505(b)(2).

2. Clinical Outcome Assessment (Formerly SEALD) Meeting: January 15, 2009

This meeting, a follow-up to September 30, 2008, meeting, was to address proposed endpoints for the clinical development program for GP based on the patient reported outcome (PRO) dossier submitted by the Applicant to support using GCSI as the primary endpoint measure for the clinical development of metoclopramide nasal spray use in phase 2b dose-ranging study (METO-IN-002).

The Division and SEALD team pointed out several weaknesses of the PRO dossier to support using GCSI as efficacy measure. The important limitations included inadequate listings of patient reported symptoms by prevalence and bothersomeness; the origin and derivation of items; and limited cognitive research based on a small number of patients. The Applicant was informed

that pursuing a dose selection utilizing an endpoint that has not established the content validity will be at the Applicant's risk.

3. End of Phase 2 Meeting: September 27, 2011

The results of the phase 2b dose-ranging study (METO-IN-002) were discussed. The Applicant proposed a new PRO instrument, Gastroparesis Symptom Assessment (GSA), to support the primary endpoint for phase 3 studies.

Clinical:

- The Division expressed concerns whether a small mean change in individual symptoms, from baseline to Week 4, although statistically significant, is clinically meaningful.

- The Division did not agree to the Applicant's proposal to include only women in the phase 3 study and recommended that male patients should also be included in the phase 3 study to confirm the findings from phase 2b study.

- The COA team (SEALD at the time) stated that the GSA instrument looked promising and determined that GSA may be used in the clinical trials if some of the concerns were adequately addressed. These issues included unclear eligibility criteria for cognitive interviews, inability to capture severe disease based on the 0–4 symptom scale, and whether unweighted average summary score is appropriate when the instrument items and response categories are not equally spaced along the GP severity continuum. The Division recommended that the Applicant should evaluate additional response categories and use both anchor- and distribution-based methods to determine what might be a clinically important change in the instrument. Please see the meeting minutes dated September 27, 2011, for details.

4. Type C Meeting: November 7, 2011

The Division agreed with the Applicant's proposal to conduct a phase 3 trial in women only and a parallel trial in men only that will include stopping rules for futility. The Applicant proposed that prior to submission of the NDA, an interim analysis of data from the male trial will be conducted. If stopping rules for futility are met in the male-only trial, then enrollment in the trial will end. If the stopping rules for futility are not met, the trial will continue. If futility is demonstrated in the male-only trial or the trial does not demonstrate efficacy in men, the efficacy data in the agreed-upon phase 3 trial in women will be suitable for submission to support approval of an NDA.

5. Type B Pre-NDA Meeting: August 30, 2016

The purpose of the meeting was to discuss the content and format of the planned 505(b)(2) NDA submission. The Applicant was referred to the requirements needed for submission of 505(b)(2) NDA and was asked to identify the information and sections of the NDA, including the labeling, they intend to support through such reliance and how they will establish the bridge between their proposed drug product and the listed drug, Reglan tablets, and the published literature.

The Division agreed that the completed non-clinical studies and proposal to rely on FDA's finding of safety and effectiveness for Reglan tablets and on published literature is scientifically appropriate provided that the Applicant establishes an adequate bridge to Reglan tablets.

6. Type B Guidance Meeting: December 13, 2016

Clinical:

- The Division did not agree that the Applicant has demonstrated adequate efficacy for a 505(b)(2) marketing application. Several limitations and concerns were communicated to the Applicant that included the following:

Phase 3 trial (MET-IN-003):

- Phase 3 trial in women only did not achieve the prespecified endpoint. The post hoc subgroup analyses of the patients with "moderate to severe symptoms" was not a prespecified endpoint with proper type 1 error control and thus can only be considered exploratory. Therefore, proposed reliance on this subgroup analysis cannot support a marketing application and can only be considered as hypothesis generating.

Phase 2 trial (MET-IN-002):

- Results from the phase 2b study (METO-IN-002) did not achieve a statistically significant improvement in the GCSI-DD score. Only a post hoc analysis suggested better efficacy in women.

- GCSI-DD was not considered a validated, well-defined, and reliable PRO instrument to measure the primary endpoint.

Recommendations:

To optimize the ability to demonstrate a treatment effect, the Division recommended that the patients with higher symptom severity score should be enrolled with a treatment period of at least 12 weeks. The Applicant was also asked to justify the doses that will be evaluated in subsequent trials.

Safety:

The Division recommended that the Applicant should develop a safety database in which patients are exposed to the drug for the maximum recommended duration (12 weeks) for metoclopramide to establish the safety of prolonged exposure via the nasal route of administration. The Applicant presented rationale for requesting a restriction of the duration of use to 4 weeks and plans to submit a safety database for the same duration. The Applicant stated Reglan is labeled for use in DG for only 2 to 8 weeks and stated that additional safety data for 6 weeks at 10- and 14-mg doses is available from study METO-IN-002. The Division stated that GP is a chronic condition with recurrent episodic exacerbations and may thus require a safety database of longer duration. However, for the Division to comment on the adequacy of the Applicant's proposal, a plan for the intended duration of use (including repeat dosing) should be submitted for review.

Bioequivalence:

Applicant proposed a bioequivalent exposure pathway for the 505(b)(2) NDA. The Division agreed with the Applicant's proposal of conducting another bioequivalence (BE) study to establish a bridge to the existing Reglan oral tablet formulation. However, the Division reminded the Applicant that additional studies of safety or efficacy may be required pending FDA's review of the AUC and C_{max} results of the BE study. The Division recommended that the Applicant submit the protocol to the FDA for review prior to initiation of the study.

The Division did not agree to the Applicant's proposal to (b) (4) because the Applicant (b) (4) (b) (4)

7. Type A Guidance Meeting: March 28, 2017

The purpose of the meeting was to discuss the chemistry, manufacturing, and controls of Gimoti product as well as the study design and doses to be used in the planned BE study in support of the NDA.

Clinical Pharmacology:

The Division noted that the listed drug, Reglan tablet, is indicated for the relief of symptoms associated with acute and recurrent diabetic gastroparesis without any specification for sex and the proposed indication Gimoti (metoclopramide) nasal spray is for the relief of symptoms associated with acute and recurrent DG (diabetic gastroparesis in adult women only). The Division recommended that proposed relative BE study should include both male and female healthy subjects. The Applicant agreed to include a similar number of males and females in the BE study but stated that the Applicant is considering submitting an NDA seeking an indication in diabetic women only with data to support the proposed indication.

8. Type C Meeting (Written Responses): November 22, 2017

- The Applicant should address whether the differences in the formulations (e.g., inactive ingredients, physicochemical, and spray characteristics) may adversely impact BA and/or CNS uptake.
- To address the potential for direct drug delivery to the CNS by the IN route with possible exacerbation of CNS side effects, the Applicant should conduct a premarket, active-controlled, safety study of an adequate sample size for the duration of 8 weeks in the target patient population. The Applicant should incorporate a data and safety monitoring board that includes clinical experts trained in identifying EPS. The safety trial should be powered to be able to rule out a higher risk of CNS AEs including drug-induced early onset of EPS with the proposed Gimoti IN formulation relative to the listed drug. The Applicant may consider published data on the incidence of EPS with metoclopramide use in the target population for sample size calculations. A protocol should be submitted for review.
- The Division did not agree to the Applicant's proposed maximum duration of use of Gimoti to be (b) (4) weeks for any single course for the treatment of GP. The following concerns were communicated:

(b) (4)

[redacted]

9. Clarification teleconference: December 20, 2017

The Division reiterated the concern that the Applicant's proposed safety database in the target population, (i.e., females with DG) at the to-be-marketed dose (15 mg QID) may not be adequate and lower C_{max} noted with the proposed 15-mg dose of IN Gimoti (relative to Reglan tablet) warrants additional justification to rule out a lower efficacy.

10. Type B Pre-NDA Meeting: January 25, 2018

The following key issues were communicated to the Applicant:

- Although the application was considered fileable, the safety and efficacy concerns were reiterated, and the Applicant was informed that there will be significant review issues.
- The Division raised concerns regarding results of the BE study (METOIN-006) that demonstrated a lower C_{max} for IN product compared to the oral tablet. The Applicant was asked to address in the NDA whether the lower C_{max} may lead to a lower efficacy of Gimoti relative to the listed drug product. The Division acknowledged the difficulty to address this adequately, as there appears to be no data to support that C_{max} was not associated with the efficacy of metoclopramide (e.g., exposure-response data). Therefore, the acceptability of the proposed dose of 15 mg as the to-be-marketed dose of Gimoti will be considered during the application review.
- The Division expressed concern regarding (b) (4)

(b) (4)

[redacted]

- Since Gimoti is likely to have off-label long-term use in this chronic disease, the Applicant was asked to clarify a plan for defining the recommended interval between the two or more consecutive courses of treatment and submit the data used to support the dose interval. To further understand the recommended dose interval between courses of treatment and to avoid large cumulative exposures [a known risk factor for TD], the Division recommended that the Applicant investigate the prescribing practices of metoclopramide in DG (e.g., via a survey of prescribing practitioners, search of the literature, and tracking prescription data).
- The Division agreed on the proposed restriction to the target population of only adult females; however, the Applicant will need to submit adequate justification to support why the proposed drug product and dose would not be effective in males.

- The Division conveyed the limitations of the current safety database for Gimoti and potential safety implications of direct CNS delivery via the IN route for a drug already known to cause CNS AEs. The Applicant will need to provide data in the NDA concerning the characteristics of drug product and how they may impact the potential for higher CNS AEs.
- The Division did not agree to the Applicant's proposal to (b) (4) (b) (4)
- The Applicant should also include a strategy to ensure appropriate product use, which could include, but not be limited to, labeling and enhanced pharmacovigilance. Although the Division had not determined if a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of Gimoti outweigh the risks, the Applicant should ensure appropriate product use includes a REMS. The Division will determine the need for a REMS during the review of the NDA.
- The Applicant was asked to clarify if they are developing a lower strength of Gimoti for patients who require a lower dose of metoclopramide (e.g., elderly, patients with moderate/severe renal or hepatic impairment, CYP2D6 poor metabolizers/CYP2D6 inhibitor users) than the general target population.
- The Applicant discussed developing a lower strength formulation of the IN spray and identifying a dose that would provide an exposure equivalent to the 5 mg Reglan tablet and enquired what additional studies (in vitro/in vivo) and/or justification would be required to support a lower strength formulation. The Division recommended that the Applicant submit this request for Biopharmaceutical input; however, an in vivo BE assessment will likely be necessary. If the Applicant plans to submit their NDA with only the 15-mg formulation, the Division recommended a need to propose risk mitigation measures to ensure that those specific populations requiring less than 15 mg do not receive the higher dose.

During the review of this application, a type A meeting was held on March 21, 2019 to discuss the concerns communicated in the Discipline Review Letter, dated February 28, 2019, and the Applicant's responses. Refer to the Discipline Review Letter and meeting minutes from the type A meeting for details.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Inspections were conducted at three clinical investigator sites for METO-IN-003. The sites were chosen based on enrollment, inspectional history, and number of INDs in the Office of Scientific Investigation database. The Office of Scientific Investigation concluded that based on the inspections, the data are considered reliable. Two of the clinical sites have the final classification of No Action Indicated, and one clinical site has the final classification of Voluntary Action Indicated. No significant regulatory findings or data integrity issues were noted during the inspections.

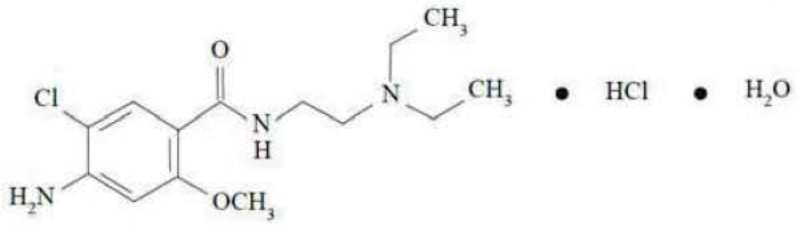
Refer to the final Clinical Inspection Summary by Dr. S. Leibenhaut, dated January 9, 2019, for full details.

In addition, the Office of Study Integrity and Surveillance reviewed the inspectional findings of the clinical site use for the relative BA study and concluded that the data from study METO-IN-006 are reliable. Refer to the Bioequivalence Establishment Inspection Report Review by the Office of Study Integrity and Surveillance, dated January 14, 2019.

4.2. Product Quality

The active pharmaceutical ingredient, metoclopramide hydrochloride, is a white to almost white crystalline powder. It is freely soluble in water. Its solubility is pH dependent. It is manufactured by (b) (4). The detailed information on structure elucidation, manufacturing and purification process, analytical methods, and stability data is provided in DMF (b) (4). A Letter of Authorization was provided by the manufacturer. The overall quality of the metoclopramide hydrochloride is controlled by its specification.

Its chemical name is 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate. The molecular formula is $C_{14}H_{22}ClN_3O_2 \cdot HCl \cdot H_2O$. Its molecular weight is 354.3. The structural formula is:



Metoclopramide nasal pump 15 mg per actuation is supplied as 10 mL metered spray pump. The (b) (4) aqueous solution contains (b) (4) mg of metoclopramide hydrochloride monohydrate ((b) (4) as well as the following inactive ingredients:

- Citric acid monohydrate and sodium citrate dihydrate (b) (4)

- Benzalkonium chloride (b) (4)
- Sorbitol (b) (4)
- Edetate disodium dihydrate (b) (4)
- Purified water (b) (4)

The Applicant states that each pump actuation delivers 15 mg of metoclopramide in 70 µL of solution as a nasal spray.

The drug product is manufactured at (b) (4)

Microbiology sections containing antimicrobial effectiveness testing, overall (b) (4) manufacturing operation, microbial limit test method and method validation, in-use stability and stability of the drug product were reviewed and deemed adequate.

The overall quality of the drug product was controlled by its specification. The pump performance attributes (e.g., droplet size distribution, spray pattern, spray content uniformity, and pump delivery) were also controlled by the drug product specification. These pump attributes are critical for consistent dose delivery by the metered pump to assure the safety and efficacy. The drug product reviewer concluded that the limited data provided for these attributes were not adequate for assuring a consistent dose delivery. This may have compromised efficacy of the drug product, particularly when excessively wide intersubject and intrasubject variability were observed in the PK data (although, it is not definitive at this time if the pump performance contributes to the observed variability in the PK data). Therefore, an approval was not recommended from the drug product perspective.

Since this proposed drug is a combination drug product, Center for Devices and Radiological Health (CDRH) was consulted for further evaluation of the performance of the metered pump. The CDRH assessed: 1) the metered pump performance; 2) biocompatibility between the patient and pump components; and 3) release specification for the device constituents; and concluded that the pump performance requirements were **not** adequately met in terms of controlling droplet size distribution; and therefore, an approval was not recommended from the CDRH perspective. Although not a CR issue actuation force was considered an essential factor and should be addressed upon resubmission.

Overall, the applicant has **not** provided sufficient chemistry, manufacturing, and control information to assure the identity, strength, purity, and quality of the drug product in terms of pump performance of this combination drug product.

The Office of Process and Facilities has made a final overall "Approval" recommendation for the facilities involved in this application.

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The labeling discussions are precluded from this review cycle.

Therefore, from the Office of Pharmaceutical Quality perspective, this NDA is **not** recommended for approval per Code of Federal Regulations (CFR) 314.125(b)(1) and CFR 314.125(b)(6), until the following deficiencies are satisfactorily resolved.

Complete Response Deficiency:

The proposed specification for the drug product is inadequate since insufficient evidence has been provided to ensure that the quality control and essential performance characteristics of the combination product do not contribute to the observed clinical variability and lack of efficacy. Specifically, the method and acceptance criterion for droplet size distribution is not deemed robust enough to guarantee consistent delivery of the drug to the patient with each actuation. The proposed acceptance criterion for droplet size distribution of the 15 mg/mL strength (i.e. the mean droplet sizes and calculated ranges) are not justified particularly given the observed variability of PK data.

Recommendation to Address the Deficiency:

Upon resubmission, all proposed tests and acceptance criteria including the droplet sizes and other essential performance characteristics for the commercial product specification should be supported by 3 batches of drug product using the selected commercial formulation (including strength of the product) and the commercial device. We recommend that the three registration batches be manufactured at the proposed commercial manufacturing site, manufactured by the proposed commercial process, and tested using validated analytical methods at the proposed analytical site.

4.3. Clinical Microbiology

N/A

4.4. Devices and Companion Diagnostic Issues

CDRH concluded that the device constituent of the combination product is not approvable for the proposed indication due to no provided actuation force specification, stability testing, or release criteria. Additionally, droplet size distribution specifications were not met in the stability testing. The following deficiencies were identified by CDRH and comments from the separate CDRH review memo are included below for reference. See final Discipline Review Letter and Complete Respo

1 [redacted] (b) (4)

(b) (4) We recommend that the Applicant submit updated stability data to demonstrate that the to-be-marketed product will meet the specifications after stability testing.

2. We recommend that actuation force be considered an essential performance requirement. A specification for this requirement was not defined in the submission, and verification and validation data were not provided for the specification. Therefore, we recommend that the Applicant provide a specification for actuation force for the to-be-marketed form of the combination product along with verification and validation data to support that specification. The Applicant should describe why this force is appropriate for the intended user population. Alternatively, provide a rationale for why the Applicant does not consider actuation force an essential performance requirement for the device constituent.
3. The stability data included droplet size distribution, spray weight, spray content uniformity, spray pattern, and weight lost. The data did not include actuation force. We recommend that the Applicant include stability data to demonstrate that the actuation force specifications are maintained over the shelf life of the product.
4. Release criteria should include all of the essential performance requirements for the combination product. The release criteria for this product includes testing of the spray content uniformity, pump delivery, droplet size distribution, and spray pattern. Actuation force was not included and is considered an essential performance requirement. We recommend that the Applicant update the release specifications to include actuation force. Alternatively, provide information showing how the Applicant will control the product to assure this performance specification is consistently achieved.
5. The Applicant provided a specification for the lowest allowable cap removal force. The Applicant has not provided a specification for the highest allowable cap removal force. This information is recommended to demonstrate that the cap will not be too difficult for the user to remove. We recommend the upper cap removal force specification be defined.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Evoke Pharma has submitted NDA 209388 via the 505(b)(2) pathway and is seeking approval of an IN formulation (nasal spray) of metoclopramide (Gimoti) for the treatment of acute and recurrent DG in adult women. For nonclinical safety, the Applicant relied on the Agency's previous assessment of the safety of metoclopramide (Reglan) oral tablets (listed drug), NDA 17854. In addition to the nonclinical studies conducted by the innovator, Evoke Pharma has conducted several IN toxicity studies of up to a 3-month duration with metoclopramide nasal spray in rabbits and/or monkeys.

IN administration of metoclopramide nasal spray at 200 and 400 mg/mL concentrations (0.1 mL/spray, 7 times/day) to male and female New Zealand rabbits for 28 days was not associated with any treatment-related adverse effects. In a 3-month IN toxicity study in New Zealand

rabbits, metoclopramide nasal spray at doses of 80, 160, and 240 mg/animal/day for 13 weeks was not associated with any treatment-related adverse effects, and the No Observed Adverse Effect Level (NOAEL) was 240 mg/animal/day. The 240 mg dose in rabbits is about 39 times the maximum recommended daily human dose of 60 mg, based on body surface area. In the IN toxicity studies in monkeys (2 weeks to 3 months duration) with metoclopramide nasal spray at dose levels up to 400 mg/animal/day, treatment-related CNS adverse effects were observed in the 3-month toxicity studies. CNS adverse effects observed included underactivity/lethargy, hunched/abnormal posture, salivation, tremors, and closed or partially closed eyes, and were observed in both males and females. In the 13-week IN toxicity study in monkeys, the NOAELs were 40 and 80 mg/animal/day for females and males respectively. The 40 mg and 80 mg doses in female and male monkeys are about 5 times and 10 times, respectively, the maximum recommended daily human dose of 60 mg, based on body surface area.

5.1.1. Referenced NDAs, BLAs, DMFs

NDA 17854, Reglan Tablets.

5.1.2. Pharmacology

No pharmacology studies were submitted in the current NDA. Metoclopramide is a synthetic substituted benzamide, a dopamine receptor antagonist, an antiemetic, and a stimulant of upper gastrointestinal (GI) motility. Metoclopramide has been shown to be efficacious in relieving the symptoms of DG, particularly nausea which usually precedes vomiting, one of the most debilitating symptoms of this disease for many patients.

5.1.3. ADME/PK

Toxicokinetics Data From Toxicokinetic Studies
3-Month Intranasal Study With Metoclopramide Nasal Spray in Rabbits With a 1-Month Recovery (Study No. 6988-102)
C_{max}: At Day 1: 306, 516 and 878 ng/ml in males and 540, 698, and 967 in females at 80, 160 and 240 mg/kg/day, respectively.
C_{max}: At Day 30: 289, 535 and 841 ng/ml in males and 544, 690, and 1126 in females at 80, 160 and 240 mg/kg/day, respectively.
C_{max}: At Day 92: 378, 421 and 814 ng/ml in males and 323, 585, and 943 in females at 80, 160 and 240 mg/kg/day, respectively.
T_{max}: At Day 1: 6.29, 6.33 and 6.27 hours in males and 6.25, 6.25, and 6.25 in females at 80, 160 and 240 mg/kg/day, respectively.
T_{max}: At Day 30: 6.29, 6.21 and 6.38 hours in males and 6.37, 6.21, and 6.38 in females at 80, 160 and 240 mg/kg/day, respectively.
Metoclopramide Toxicity Study by Intranasal Administration for Cynomolgus Monkeys for 13 Weeks (Study No. 001-994219)

T_{max}: At Day 92: 6.29, 6.25 and 6.23 ng/ml in males and 6.29, 6.21, and 6.25 in females at 80, 160 and 240 mg/kg/day, respectively.

AUC_{120}: At Day 1: 85528 (6843) ng.min/ml in males at 120 mg/day (40 mg/day) and 58130 (38834) in females at 60 mg/day (20 mg/dose) for Metaclopramide.

AUC_{120}: At Week 13: 51487 (-) ng.min/ml at 80 mg/day (20 mg/day) in males and 46039 (-) in females at 40 mg/day (10 mg/dose) for Metaclopramide.

C_{max}: At Day 1: 1060.94 (225.25) ng/ml at 120 mg/day (40 mg/dose) in males and 668.89 (534.21) ng/ml at 60 mg/day (20 mg/ml) in females for Metaclopramide.

C_{max}: At Week 13: 593.24 (-) ng/ml at 80 mg/day (40 mg/dose) in males and 440.86 (-) ng/ml at 40 mg/day (10 mg/ml) in females for Metaclopramide.

AUC_{120}: At Day 1: 42057 (24465) ng.min/ml in males at 120 mg/day (40 mg/day) and 22569 (13105) in females at 60 mg/day (20 mg/dose) for Metaclopramide menthol.

AUC_{120}: At Week 13: 29387 (5006) ng.min/ml at 80 mg/day (20 mg/day) in males and 19803 (5986) in females at 40 mg/day (10 mg/dose) for Metaclopramide menthol.

3-Month Intranasal Study With Metoclopramide Nasal Spray in Cynomolgus Monkeys With a 1-Month Recovery (Study No. 6988-101)

C_{max}: At Day 1: 495.42 (356.92) ng/ml at 120 mg/day (40 mg/dose) in males and 245.67 (134.54) ng/ml at 60 mg/day (20 mg/ml) in females for Metaclopramide menthol.

C_{max}: At Week 13: 290.16 (54.54) ng/ml at 80 mg/day (40 mg/dose) in males and 200.12 (65.51) ng/ml at 40 mg/day (10 mg/ml) in females for Metaclopramide menthol.

C_{max}: At Day 1: 258, 599 and 1429 ng/ml in males and 291, 481, and 422 in females at 40, 80 and 160 mg/kg/day, respectively.

C_{max}: At Day 29: 136, 472 and 904 ng/ml in males and 329, 467, and 907 in females at 40, 80 and 160 mg/kg/day, respectively.

C_{max}: At Day 85: 167, 486 and 908 ng/ml in males and 234, 506, and 635 in females at 40, 80 and 160 mg/kg/day, respectively.

T_{max}: At Day 1: 6.83, 6.56 and 6.64 hours in males and 6.56, 6.39, and 6.78 in females at 40, 80 and 160 mg/kg/day, respectively.

T_{max}: At Day 29: 6.78, 7.17 and 6.97 hours in males and 7.17, 7.11, and 6.61 in females at 40, 80 and 160 mg/kg/day, respectively.

T_{max}: At Day 85: 6.39, 6.61 and 6.92 ng/ml in males and 6.61, 6.39, and 6.42 in females at 40, 80 and 160 mg/kg/day, respectively.

5.2. Toxicology

5.2.1. General Toxicology

Evoke Pharma has submitted NDA 209388 for Gimoti via the 505(b)(2) pathway with metoclopramide (Reglan) tablets as the listed drug. For nonclinical safety, the Applicant relied on the Agency's previous assessment of safety of the Innovator's product (Reglan tablets). In addition, the Applicant conducted IN toxicology studies with metoclopramide nasal spray of up to a 3-month duration in rabbits and monkeys.

In a 28-day IN toxicity study in rabbits, metoclopramide nasal spray was administered seven times daily to male and female New Zealand rabbits at up to 400 mg/mL concentrations (0.1 mL/spray) for 28 days. No treatment-related findings were observed in the animals receiving IN metoclopramide for 28 days. In the 3-month IN toxicity study in New Zealand white rabbits with a 1-month recovery period, metoclopramide nasal spray was administered QID at 80, 160, and 240 mg/animal/day via IN administration for 13 weeks. No treatment-related adverse effects were observed at any dose level and the NOAEL was 240 mg/animal/day (about 39 times the maximum recommended human dose of 60 mg/day, based on body surface area).

Metoclopramide nasal spray, at up to 400 mg/day, was administered 5 times daily to Cynomolgus monkeys for 2 weeks. The drug was well tolerated, and there were no treatment-related findings. In another study, two formulations of metoclopramide (metoclopramide nasal spray and metoclopramide menthol nasal spray) at up to 120 mg/day in males and up to 60 mg/day in females were administered to Cynomolgus monkeys for 13 weeks. Underactivity/ lethargy, hunched/abnormal posture, salivation, tremors and closed or partially closed eyes were observed in animals that received both formulations. However, there was no clear difference for these adverse effects between the treatment groups or sexes. In another study, metoclopramide nasal spray was administered at 40, 80, and 160 mg/animal/day QID to Cynomolgus monkeys for 3 months followed by a 1-month recovery period. Treatment related behavioral effects, such as hypoactivity, somnolence, hyperactivity, and dissociative posturing, considered to be related to the pharmacological actions of metoclopramide, were observed at all doses. The incidence and severity of these effects were dose-related. In addition, treatment duration-related tremors were observed in males and females receiving the high dose. The CNS-related adverse effects were observed in animals receiving IN metoclopramide, and the NOAELs were 40 and 80 mg/animal/day for females and males respectively (about 5 times and 10 times, respectively, the maximum recommended human dose, based on body surface area).

5.2.2. General Toxicology; Additional Studies

N/A

5.2.3. Genetic Toxicology

No genetic toxicology studies were submitted in this 505(b)(2) NDA. Metoclopramide was positive in the in vitro Chinese hamster lung cell/hypoxanthine-guanine phosphoribosyltransferase forward mutation assay for mutagenic effects and in the in vitro human lymphocyte chromosome aberration assay for clastogenic effects. It was negative in the in

vitro Ames mutation assay, the in vitro unscheduled DNA synthesis assay with rat and human hepatocytes, and the in vivo rat micronucleus assay.

5.2.4. Carcinogenicity

No carcinogenicity studies were submitted in the current NDA. A 77-week study was conducted in rats with oral metoclopramide doses up to 40 mg/kg/day (about 6 times the maximum recommended human dose (MRHD) on body surface area basis). Metoclopramide elevated prolactin levels, and the elevation persisted during chronic administration. An increase in mammary neoplasms was found in rodents after chronic administration of metoclopramide. In a rat model for assessing the tumor promotion potential, a 2-week oral treatment with metoclopramide at a dose of 260 mg/kg/day (about 35 times the MRHD based on body surface area) enhanced the tumorigenic effect of N-nitrosodiethylamine.

5.2.5. Reproductive and Developmental Toxicology

No reproductive and developmental toxicology studies were submitted in this NDA. Metoclopramide at IM doses up to 20 mg/kg/day (about 3 times the MRHD based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

Reproduction studies have been performed following administration of oral metoclopramide during organogenesis in pregnant rats at about 6 times the MRHD calculated on body surface area and in pregnant rabbits at about 12 times the MRHD calculated on body surface area. No evidence of adverse developmental effects due to metoclopramide was observed.

5.2.6. Other Toxicology Studies

No special toxicology studies were submitted in the current NDA.

6 Clinical Pharmacology

6.1. Executive Summary

Refer to separate clinical pharmacology review, dated March 7, 2019 (with addenda, dated March 21, 2019 to correct a typographical error and March 29, 2019 to add a summary of information submitted by the Applicant in response to the Discipline Review Letter. The following summary is an excerpt from the clinical pharmacology review.

In this NDA submission, the Applicant is seeking approval of the metoclopramide nasal spray, Gimoti, for the relief of symptoms in adult women with acute and recurrent DG via 505(b)(2) pathway with Reglan oral tablet as the listed drug. The proposed dosage regimen of Gimoti is 15 mg QID, 30 minutes before each meal and at bedtime for 2 to 4 weeks. Reglan was approved for acute and recurrent DG on December 30, 1980 (NDA 17584) with a regimen of one 10 mg oral tablet QID.

Notably, the Applicant proposed to indicate use only for female patients while the listed drug, Reglan, is indicated for both male and females, claiming that benefit in male patients with acute and recurrent DG has not been demonstrated in phase 2 and phase 3 clinical studies. However, per the clinical review team, the female-only indication was not adequately justified in this submission as the clinical data is insufficient to conclude that male patients would not receive benefit at the proposed dose (See the clinical review for more details).

To establish a bridge between Gimoti and Reglan, the Applicant conducted a relative BA study (METO-IN-006) as a pivotal study. In METO-IN-006, systemic exposure to metoclopramide was compared between single nasal administration of Gimoti at 15 mg, 16 mg, or 17 mg and single oral administration of Reglan tablet 10 mg in 98 healthy male and female subjects. Gimoti for all three doses showed comparable AUC. However, mean Cmax for Gimoti was 16% to 20% lower than Reglan 10 mg and deviated from the standard no effect criteria (90% CI: 80-125%). The table below is copied from the clinical pharmacology review and summarizes the results from METO-IN-006 for the relative bioavailability of Gimoti compared to Reglan 10 mg.

Table 2: Relative Bioavailability of Gimoti to Reglan 10 mg From METO-IN-006

	Geometric mean ratio (%) for Gimoti/Reglan 10 mg (90% CI)		
	Gimoti 15 mg (N=97)	Gimoti 16 mg (N=98)	Gimoti 17 mg (N=98)
C_{max}	80.32 (69.29-93.11)	80.37 (69.36-93.12)	84.27 (72.74-97.64)
AUC_t	90.25 (79.48-102.5)	91.76 (80.84-104.1)	97.01 (85.48-110.1)
AUC_{inf}	94.96 (85.44-105.5)*	96.75 (87.09-107.5)*	111.7 (100.4-124.3)*

* N=95, N=96, and N=93 for Gimoti 15 mg, 16 mg, and 17 mg, respectively.
Source: METO-IN-006 Clinical Study Report Table 11-3.
(Source: clinical pharmacology review, dated March 7, 2019)

The Applicant proposed a Gimoti 15-mg dose for female patients based on a post hoc subgroup analysis of relative BA by sex, claiming that Gimoti 15 mg showed the most closely matched systemic exposure to Reglan in the subgroup of female subjects. However, the female only indication is not adequately supported, and the bridge between Gimoti and Reglan needs to be established regardless of sex. The post hoc subgroup analysis of relative BA by sex conducted by the Applicant is not acceptable to establish a bridge between Gimoti and Reglan.

The Office of Clinical Pharmacology review focused on the analyses of relative BA without regard to sex to support the reliance of the efficacy and safety of Reglan. Gimoti, at all tested doses (15 mg, 16 mg, and 17 mg), demonstrated lower metoclopramide C_{max} than Reglan, but the potential effects of the lower C_{max} on efficacy have not been adequately addressed. Therefore, the Office of Clinical Pharmacology has concluded that the potential for suboptimal efficacy due to the lower C_{max} cannot be ruled out and the results of METO-IN-006 do not adequately support the bridging of efficacy between Gimoti and Reglan.

Upon further sensitivity analysis, it was determined that the lower mean Cmax was driven by nine subjects who demonstrated little to no absorption (C_{max} < 5 ng/mL) of metoclopramide. Specifically, 11 PK profiles from nine subjects (6 males and 3 females) across three Gimoti doses showed extremely low systemic exposure (Cmax <5 ng/mL vs. mean Cmax ~32 ng/ml for

Gimoti 15 mg and 39.4 ng/ml for Reglan 10 mg) after Gimoti administration while those same subjects showed consistent drug absorption when given Reglan orally. These findings suggest an incomplete drug delivery either due to faulty device or improper use. Thus, the current Gimoti product can potentially lead to suboptimal efficacy unless the issue of incomplete drug delivery is resolved.

Furthermore, there was a higher overall inter- and intra-subject variability in drug exposure for Gimoti as compared to that of Reglan. This is problematic as it raises a potential safety concern for cases with substantially higher exposure.
We requested the case report forms and available documentation to better understand the reason why several these subjects demonstrated little to no absorption of Gimoti. The Applicant submitted case report forms for 17 subjects who had little to no absorption or substantially high exposure on March 19, 2019 via email to project manager, Maureen Dewey; this information was formally submitted to the NDA on March 25, 2019. The case report forms included specific questions on whether the subject moved his/her head or sneezed immediately (immediately defined as the 2 minutes following dose administration). Although several issues were documented, the information provided did not explain the PK variability observed. See the clinical pharmacology review for additional details.

Recommendation
The clinical pharmacology review concluded that the submitted data are inadequate to support the approval of the proposed product, Gimoti 15 mg, from a clinical pharmacology standpoint, and recommend a complete response.

The PK bridge between the Gimoti 15 mg dose and the Reglan tablet 10 mg is not sufficient to justify the reliance on the findings of safety and efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan.

The clinical pharmacology review recommends that the Applicant address the PK variability issue including the inconsistent delivery issues prior to approval of Gimoti as specified below.

Recommendations to Address Deficiencies:
To address the clinical pharmacology deficiency, we recommend that the Applicant investigate the root cause(s) for the variability in PK for Gimoti, including the issue of inconsistent and incomplete delivery. The Applicant will need to provide evidence supporting the conclusions from the root cause analysis and provide mitigation strategies that will address the(se) issue(s). Depending on the identified cause(s), the Applicant may need to conduct additional in vitro and/or in vivo studies.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 3 lists the clinical studies conducted by the Applicant to support the NDA.

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Table 3: Clinical Studies Conducted by the Applicant to Support the NDA

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
METO-IN-002 May 13, 2009 – Dec 15, 2010	Phase 2b, MC, R, DB, PC, PG, dose-ranging, efficacy and safety study	Gimoti 10 mg QD IN Gimoti 14 mg QD IN Placebo QD IN	mGCSI	4 weeks	95 95 95	Male and female patients with DG (M/F: 31/64) (70 females)	50 centers, US
METO-IN-003 Mar 27, 2014 – May 27, 2016	Phase 3, MC, R, DB, PC, PG, efficacy and safety study	Gimoti 10 mg QD IN Placebo QD IN	GSA	4 weeks	102 103	Female patients with DG	41 centers, US
METO-IN-004 Apr 14, 2014 – Jun 2, 2016	Phase 3, MC, R, DB, PC, PG, efficacy and safety study	Gimoti 10 mg QD IN Placebo QD IN	GSA	4 weeks	26 27	Male patients with DG	25 centers, US
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)							
25,512-302-R Dec 18, 1999 – May 14, 2000	Phase 2, R, Open label, active control, PD, PK and safety	Metoclopramide 10 mg QD IN. Metoclopramide 20 mg QD IN Reglan tab 10 mg QD Oral	TSS	6 weeks	35 36 18	Male and female patients with DG (23 females)	6 centers, US
METO-IN-001 Apr 08, 2008 – May 14, 2000	Phase 1, 4-period, 4 treatment, OL, CO, bioavailability study	Gimoti 10 mg Gimoti 20 mg Reglan tab 10 mg Reglan injection 5 mg	-	Single treatment	Same 39 healthy subjects in each treatment arm	Healthy male and female volunteers	1 center, US

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
METO-IN-005 July 28, 2014- Aug 31, 2014	Part 1 Phase 1, DB, R, PC, PG, safety and tolerability study. Part 2 Phase 1, DB, DD, R, PC, 4 period, 4 treatment cross over ECG study	Part 1 Gimoti 80 mg Placebo Single treatment Part 2 Gimoti 20 mg Gimoti 80 mg Placebo Moxifloxacin 400 mg (capsule) Placebo (capsule)	-	Part 1 Single treatment Part 2 Single treatment on Days 1, 5, 9, and 13	Part 1 6 2 Part 2 Same 48 subjects in each treatment arm	Healthy male and female volunteers	1 center, US
METO-IN-006 July 26, 2017- Sept 20, 2017	Phase 1, 4 period, 4-treatment, 4-sequence, R, cross over, comparative BA study	Gimoti 15 mg Gimoti 16 mg Gimoti 17 mg Reglan tab 10 mg	Comparative BA study	Single treatment	105 103 100 102 (Total 108)	Healthy male and female volunteers in fasted state	1 center, US

Abbreviations: QD 30 minutes before meals and at bedtime (total 4 doses); PC=placebo control; R=randomized; DB=double blind; OL=open label; DD=double dummy; CO=cross over; MC=multi center; PG=parallel group, BA=bioavailability; GSA Gastroparesis Symptom Assessment; IN=intranasal; mGCSI=modified Gastroparesis Cardinal Symptom Index; TSS=Total Symptom Score
Source: Adapted from Table 1 summary of clinical safety

7.2. Review Strategy

The protocol and SAPs of the clinical trials were reviewed. The primary efficacy analysis and subgroup analyses (b) (4) by the Applicant for studies METO-IN-002 and METO-IN-003 were replicated. Additional analyses were performed to assess the evidence in favor of the subgroup analyses. Efficacy results were also examined for the open-label study 25,512-302R, although this study is exploratory. However, the clinical trials did not evaluate the 15-mg dose that the Applicant proposed (b) (4) The proposed indication and dose are based on the findings of the BA study (METO-IN-006), which evaluated Gimoti 15 mg, 16 mg, and 17 mg in healthy volunteers.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Submitted to Support Efficacy

8.1.1. [METO-IN-002]

Trial Design

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study was conducted in the United States at approximately 60 sites and randomized 287 male and female diabetic patients with symptoms of GP aged 18 to 75.

Patients meeting the protocol-specified entry criteria were randomized 1:1:1 in a parallel-group design and self-administered IN metoclopramide 10 mg or 14 mg or placebo as a single IN spray 4 times daily, 30 minutes before meals and at bedtime for 4 weeks. Patients were instructed on the correct use of the nasal spray and self-administered their first and last doses of study drug at the site on Days 0 and 28. Patients were also reminded not to exceed a total of four sprays a day.

Patients were provided instructions on how to use the nasal spray and trained to use an interactive voice response system (IVRS) during the washout period and the treatment period for recording the following self-reported assessments for symptoms of GP:

- Severity of nine GP symptoms on the GCSI-DD
- Severity of abdominal pain and abdominal discomfort
- Number of hours of nausea
- Number of episodes of vomiting
- Overall severity of GP symptoms

Patients with a mean daily score of ≥2 to ≤4 on the GCSI-DD, during the 7-day washout period, were randomized and patients with a mean GCSI-DD total score of <2.0 or >4.0 were excluded.

The assessments and procedures performed at the following key visits during the trial are summarized.

***Screening/Baseline (Visit 1: Day -30 to -8)*:** Reviewed eligibility criteria and medical history and performed physical and laboratory examination including an electrocardiogram (ECG)**.** Patients were scheduled for the next visit 2 (washout period) for 7 days before Day 0.

***Washout Period (Visit 2: Day -7 to Day -1)*:** Provided patients with a sample diary and written instructions on the use of the IVRS. They were informed that the sample diary includes the severity of the 9-symptom GCSI-DD, severity of abdominal pain and abdominal discomfort, number of hours of nausea, number of episodes of vomiting, and overall severity of GP symptoms. The patients were instructed to call IVRS each evening at approximately the same time and on importance of completing 7 days of daily diary for determination of study eligibility. On this visit patients were trained/observed for calling in to IVRS, setting their password, and completing their first daily diary entry. Patients were scheduled for randomization (Visit 3, Day 0).

***Randomization Visit (Visit 3: Day 0±2 days)*:** During the washout period, subjects who completed at least 5 days of the daily diary were eligible for inclusion in the study and the GCSI-DD score was calculated from the available days of diary data.

At randomization, prior to administration of the study drug:

- Patients completed the following:
  - Patient Assessment of Upper Gastrointestinal Disorders Symptoms (PAGI-SYM) questionnaire
  - Short-Form 12 Health Survey
  - Sheehan Disability Scale
  - Overall GP symptom severity (OGS) scale
- The investigator completed the OGS scale.

In addition, a 12-lead ECG was performed predose and 60 minutes postdose to observe any significant abnormal finding or a QTc interval >450 milliseconds (ms) on the predose ECG (exclusion criteria). A blood sample was obtained approximately 30 minutes predose and 30 minutes postdose for determination of metoclopramide concentration. The IVRS diary instructions were reviewed, and importance of compliance and using the IVRS each evening to record symptom was reiterated.

***Follow-up Visits 4, 5, and 6 (Days 7, 14, and 21 [±1 Day])*:** The patients were followed up in clinical visit for efficacy and safety evaluation on Days 7, 14, 21 and were asked questions to elicit AEs, use of concomitant medications, checking vitals, and review of IVRS daily diary compliance. At visit Day 14, the patients completed the PAGI-SYM questionnaire and OGS scale, and the investigator completed the OGS scale.

***Final Visit (Day 28±1 Day) or Early Termination Visit*:** At the final visit on Day 28 the patients self-administered the last dose, and the assessment included a physical

examination including weight, vitals, and blood and urine sample for the central laboratory.

- Patients completed the following:
  - PAGI-SYM questionnaire
  - SF-12 Health Survey
  - Disability scale
  - OGS scale
  - Overall Treatment Effect-Subject questionnaire
- The investigator completed the OGS and Overall Treatment Effect-Investigator questionnaire.

In addition, at 30 minutes, post-last dose, a PK sample was obtained, and at 60 minutes post-last dose, an ECG was performed.

Assignment to the Treatment

Subjects who met the entry criteria after the washout period were randomized using an IVRS to metoclopramide nasal spray 10 mg, 14 mg, or placebo at the beginning of the screening process. Each subject was assigned a 5-digit number by IVRS that consisted of a 2-digit site number followed by a unique 3-digit subject number (e.g., 01103), and this number could not be re-assigned by the study site staff.

Prior and Concomitant Therapy

Patients were asked to discontinue use of all medications known to ameliorate or exacerbate symptoms associated with DG except for rescue medication (prochlorperazine 5-mg tablets) during the washout and treatment periods of the trial.

Patients taking the following medications during the washout and treatment periods were considered protocol deviation: metoclopramide, oral and parenteral formulations, domperidone, TCAs, macrolide antibiotics, prokinetic agents, cholinergic agents, agents with significant anticholinergic effects, narcotic analgesics, orally administered β-agonists, spasmolytics, dopamine agonists, monoamine oxidase inhibitors, herbal medications, fiber or bulking agents, and laxatives. Concomitant medications taken within 6 months prior to study entry and throughout the study were documented on the concomitant medication electronic case report form.

Treatment Compliance

Compliance was evaluated by weighing the study drug prior to dispensing at the randomization visit and at the final or early termination visit. In addition, patients were asked at each visit to recall any missed doses, which were then recorded as protocol deviations. Evaluation of the rescue medication used was done by pill counts and records on the IVRS diary.

Study Population

Key Inclusion Criteria

Subjects who met all the following criteria were eligible for inclusion in the study:

1. Diagnosis of type 1 or type 2 diabetes.
2. Diagnosis of DG previously documented.
3. A mean daily GCSI-DD score of ≥2 and ≤4 for the 7 days prior to the randomization visit (Day 0).
4. Male subjects and nonpregnant, nonlactating female subjects between the ages of 18 and 75 years.
5. Willing and able to give written informed consent to participate in the study.
6. Able to read and understand English.
7. Female subjects of childbearing potential, defined as not surgically sterile or at least 2 years postmenopausal, must have agreed to use one of the following forms of contraception from screening through the last dose of study drug: hormonal (oral, implant, or injection) begun >30 days prior to screening, barrier (condom, diaphragm, or cervical cap with spermicide), intrauterine device, or vasectomized partner (6 months minimum).
8. No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results (except for lipid profile, glucose and glycosylated hemoglobin (hemoglobin A1c)) during screening that, in the opinion of the prescribing information, would have jeopardized the safety of the subject or affected the validity of the study results.
9. Willingness to discontinue current treatment for DG and to avoid all medications specified by the protocol for the duration of the study.

Key Exclusion Criteria

Subjects were not eligible for the study if they met any of the following criteria:

1. Gastric bypass and gastric banding, gastric pacemakers, postsurgical causes of GP, and disorders known to be associated with abnormal gastrointestinal motility such as active gastric ulcer, active duodenal ulcer, active severe gastritis, gastric cancer, amyloidosis, neuromuscular diseases (including Parkinson's disease), collagen vascular diseases, alcoholism, uremia, malnutrition, and untreated hypothyroidism.
2. History of allergic or adverse responses including, but not limited to, acute dystonic reactions and tardive dyskinesia to metoclopramide or any comparable or similar product.
3. History of or physical findings suggestive of TD.
4. Currently using and unwilling or unable to stop any medication known to be associated with TD prior to washout (Visit 2).

5. History of allergy to any of the ingredients in the study drug formulation: metoclopramide, citric acid, sodium citrate, benzalkonium chloride, ethylenediaminetetraacetic acid, or sorbitol.
6. History of organ transplant, chronic pancreatitis, gross malabsorptive syndromes, celiac disease, or inflammatory bowel disease.
7. Malignancy (except for basal cell carcinoma of the skin) currently present, initially diagnosed, or recurring within 5 years of enrollment.
8. History of other clinically significant renal, hepatic, neurologic, hematologic, oncologic, pulmonary, psychiatric, cardiovascular, or infectious disease, or any other condition that, in the opinion of the prescribing information, would have jeopardized the safety of the subject or affected the validity of the study results.
9. Had renal dysfunction calculated as creatinine clearance (CrCl) <40 mL/min at screening (Visit 1).
10. Had hemoglobin A1c >12.5% at screening (Visit 1).
11. Inability or unwillingness to stop using the following agents for 7 days during the washout period (Day -7 to Day -1) prior to randomization (Day 0) and refrain from their use for the 4-week study period: oral and parenteral formulations of metoclopramide, domperidone, TCAs, macrolide antibiotics, prokinetic agents, cholinergic agents, agents with significant anticholinergic effects, narcotic analgesics, orally administered β-agonists, spasmolytics, dopamine agonists, monoamine oxidase inhibitors, herbal supplements, fiber or bulking products, and laxatives.
12. Use of neurotoxins (e.g., botulinum type A or B) as a treatment for GP or delayed GE within 6 months of screening (Visit 1).
13. Clinically significant abnormal finding or a QTc interval >450 ms on ECGs obtained at screening (Visit 1) OR predose or postdose at randomization (Day 0).
14. Inability or unwillingness to stop using medications associated with Torsades de Pointes or a prolonged QT interval for 30 days prior to the initial symptom assessment and refrain from their use for the 4-week study period.
15. Female subjects who were trying to conceive, were pregnant, or were lactating.
16. Positive serum human chorionic gonadotropin (hCG) pregnancy test at screening or a positive hCG urine test on Day 0 prior to administration of study drug for women of childbearing potential.
17. History of alcohol or drug abuse within the year prior to screening (Visit 1), or current known evidence of substance dependence or abuse.
18. Participation in a clinical (investigational) trial or receipt of a non-FDA-approved therapy within 30 days prior to screening (Visit 1) except for domperidone.

Study Endpoints

The GCSI-DD, a subject-reported assessment of severity of GP symptoms, instrument was used during the washout phase and the dosing phase of the study. The GCSI-DD total score was

computed as the average of the three subscale scores. The three subscales are: postprandial fullness/early satiety with four items, nausea/vomiting with three items, and bloating with two items. Each subscale score is computed as the average of the scores for the individual items in the subscale.

Primary Efficacy Endpoint: Gastroparesis Cardinal Symptom Index

- Change in the weekly mean modified GCSI-DD (mGCSI-DD) score (mean of nausea, early satiety, bloating, and upper abdominal pain) from the 7-day baseline period (Days -7 to -1) to the last 7 days (Days 21 to 28) of the treatment period between the two active treatment groups and the placebo group.

Changes from protocol to statistical analysis plan (SAP):
The primary endpoint was revised in version 1.0 of the SAP (April 4, 2011) from change from baseline to Week 4 of the treatment period for the GCSI-DD total score in the final protocol (Amendment 1 September 23, 2009) to the mGCSI-DD score based on recommendations from the FDA. In addition, supportive subgroup analyses were described.

Secondary Efficacy Endpoints:
There are four secondary efficacy endpoints based on the four individual symptoms scores that comprise the mGCSI-DD, ordered as follows:

1. Change from baseline to Week 4 of the treatment period in nausea.
2. Change from baseline to Week 4 of the treatment period in bloating.
3. Change from baseline to Week 4 of the treatment period in early satiety.
4. Change from baseline to Week 4 of the treatment period in upper abdominal pain.

Changes from protocol to SAP:

The secondary efficacy endpoints were revised from the final protocol (Amendment 1 September 23, 2009) in version 1.0 of the SAP (April 4, 2011). The proposed secondary endpoints in the protocol were as follows:

- GCSI-DD for each study week: IVRS daily diary
  - The change in mean GCSI-DD total score from the 7-day baseline to each 7-day period of the total treatment duration between the two active treatment groups and the placebo group study:
    - Days 0 and 7.
    - Days 7 and 14.
    - Days 14 to 21.
  - The change in mean total score from the 7-day baseline to the last 7 days of the treatment period between each of the two active treatment groups and placebo group for:
    - GCSI-DD subscales (nausea/vomiting, postprandial fullness, and bloating) individual symptoms.
- Abdominal pain and abdominal discomfort score: IVRS daily diary.
- Number of hours of nausea and number of episodes of vomiting: IVRS daily diary.

- Daily overall severity of GP symptoms (subject): IVRS daily diary.
- Rescue medication use: IVRS daily diary.
- PAGI-SYM Questionnaire: Randomization (Visit 3, Day 0), Visit 5 (Day 14), and final visit (Visit 7, Day 28) or early termination.
- SF-12 Health Survey: Randomization (Visit 3, Day 0) and final visit (Visit 7, Day 28) or early termination.
- Disability assessment: Randomization (Visit 3, Day 0) and final visit (Visit 7, Day 28) or early termination.
- Investigator and subject assessment of OGS severity: Randomization (Visit 3, Day 0), Visit 5 (Day 14) and final visit (Visit 7, Day 28) or early termination.
- Investigator and subject assessment of OTE: Final visit (Day 28) or early termination.

Gastroparesis Cardinal Symptom Index-Daily Diary

The GCSI-DD, a subject-reported assessment of severity of GP symptoms instrument, was used during the washout (baseline) and the treatment periods of the study to record daily symptoms. The daily diary scores were recorded using an IVRS at the same time each evening. The GCSI-DD is comprised of nine individual symptoms grouped into three subscales (i.e., nausea/vomiting, postprandial fullness/early satiety, and bloating). Each symptom is graded from 0 (none) to 5 (very severe). Subscales and symptoms included in each are shown:

- Nausea/vomiting (3 symptoms):
  - Nausea
  - Retching
  - Vomiting
- Postprandial fullness/early satiety (4 symptoms):
  - Stomach fullness
  - Not able to finish a normal sized meal
  - Feeling excessively full after meals
  - Loss of appetite
- Bloating (2 symptoms):
  - Bloating
  - Stomach visibly larger

Each subscale score is computed as the average of the scores for the individual symptoms in the subscale. If 50% or more of the individual symptom scores in a subscale are missing, then the subscale score will be set to missing. The GCSI-DD total score is computed as the average of the three subscale scores. All three subscale scores must be non-missing to calculate the total score.

Each symptom parameter was graded and recorded by the study subject at the same time each day (in the evening) to reflect the level of symptoms the subject experienced in the preceding 24 hours. Patients also recorded the use of rescue medication.

Individual symptoms were graded using the following scale:

0 None
1 Very mild symptoms
2 Mild symptoms
3 Moderate symptoms
4 Severe symptoms
5 Very severe symptoms

Expanded GCSI-DD

The expanded GCSI-DD (eGCSI-DD) is composed of the nine symptoms in the GCSI-DD plus upper abdominal pain and upper abdominal discomfort. These 11 individual symptoms are grouped into 4 subscales that include the 3 GCSI-DD subscales listed above and a 4th subscale of upper abdominal pain and discomfort (2 symptoms: upper abdominal pain (above the navel) and upper abdominal discomfort (above the navel)). Each symptom was graded on the scale described above from 0 (none) to 5 (very severe).

Modified GCSI-DD

The mGCSI-DD is composed of four individual symptoms, three from the GCSI-DD and one from the eGCSI-DD. Each symptom was graded on the scale described above from 0 (none) to 5 (very severe). The four mGCSI-DD symptoms were:

- Nausea (feeling sick to your stomach as if you were going to vomit or throw up)
- Early satiety (not able to finish a normal sized meal)
- Bloating (feeling like you need to loosen clothes)
- Upper abdominal pain (above the navel)

At least three of the four items must be non-missing in order to calculate the mGCSI-DD score. The mGCSI-DD is used for the primary endpoint.

Statistical Analysis Plan

Analysis Populations:

The primary efficacy analysis was performed on the Intent-to-Treat (ITT) population defined as all subjects who were randomized. Treatment assignment was based on the randomized treatment.

The safety population includes all subjects who were randomized and received at least one dose of study drug. Treatment assignment was based on the treatment actually received.

The per protocol (PP) population includes all ITT subjects who completed the 28-day treatment period, had no protocol violations or major protocol deviations, and had a non-missing weekly mean value for the modified GCSI-DD total score for each of the 4 weeks of the treatment period. Identification of subjects to be included in the PP population was completed prior to breaking the blind. Treatment assignment was based on the treatment actually received.

The complete case population included all ITT subjects who had a non-missing weekly mean value for the modified GCSI-DD total score for each of the 4 weeks of the treatment period.

Multiple Testing Procedure:

A hierarchical testing approach was used to control the overall alpha level at 0.05. Hypothesis tests were carried out in the following order (all endpoints are based on the change from baseline to Week 4):

1. Primary endpoint 14 mg versus placebo
2. Primary endpoint 10 mg versus placebo
3. Secondary endpoint #1 (nausea) 14 mg versus placebo
4. Secondary endpoint #1 (nausea) 10 mg versus placebo
5. Secondary endpoint #2 (bloating) 14 mg versus placebo
6. Secondary endpoint #2 (bloating) 10 mg versus placebo
7. Secondary endpoint #3 (early satiety) 14 mg versus placebo
8. Secondary endpoint #3 (early satiety) 10 mg versus placebo
9. Secondary endpoint #4 (upper abdominal pain) 14 mg versus placebo
10. Secondary endpoint #4 (upper abdominal pain) 10 mg versus placebo

The procedure stops at the first test with a p-value >0.05 in which case that test, and all subsequent tests are considered nonsignificant.

Missing Data:

For all efficacy endpoints based on daily diary data that are analyzed by week, the method of last observation carried forward (LOCF) was used to impute missing weekly values from the last available mean weekly value. A weekly value is missing if the number of days during the week with missing data is four or more. LOCF imputation approach was not carried out on the daily values.

In addition, the following sensitivity analysis were performed for primary and secondary endpoints:

- Observed case: Use only observed data without any imputation of missing values.
- Complete case: Only include subjects with non-missing values for all 4 weeks.

For the primary endpoint only, the following additional sensitivity analysis was performed:

- Multiple imputation using PROC MI and PROC MIANALYZE in SAS using a multivariate normal imputation model including the mGCSI-DD total score values at baseline and at each week during the treatment period.

Primary Efficacy Analysis:

The primary efficacy analysis was done using an analysis of covariance (ANCOVA) model with a fixed effect for treatment group (placebo, metoclopramide 10 mg, and metoclopramide 14 mg) and with the baseline mGCSI-DD total score value as a covariate. Each metoclopramide group was compared to the placebo group using a hierarchical testing procedure. Summary statistics were displayed by treatment group along with the difference in least squares means associated with each treatment comparison (and the associated 95% confidence interval (CI)). The Applicant used the LOCF approach to impute any missing Week 4 values.

Secondary Efficacy Analyses:

Each of the four secondary endpoints were analyzed using the same method as the primary efficacy analysis.

Protocol Amendments

PROTOCOL METO-IN-002 Amendment 1 (IND 25512)

The original protocol (February 10, 2009) was amended once during the study. The major changes in the amendment (September 23, 2009) are summarized below as per the section of the protocol.

- **Background and Rationale:**
  - The following text was added: If severe symptoms are present, it is recommended that metoclopramide therapy begin with the parenteral formulation.
  - Following text was italicized: *If only the earliest manifestations of diabetic GP are present, oral administration of metoclopramide may be initiated. However, if severe symptoms are present, therapy should begin with Reglan® Injection (intramuscular [IM] or intravenous [IV]). Doses of 10 mg may be administered slowly by the IV over a 1- to 2-minute period. Administration of Reglan® Injection (metoclopramide injection, USP) up to 10 days may be required before symptoms subside, at which time oral administration of metoclopramide may be instituted.*

- **Investigational Product Dosage and Administration:**
  - Added text to clarify intra nasal spray administration "one spray in either nostril".

- **Exclusion Criteria:**
  - Modified: Added gastric bypass, gastric banding, and gastric pacemakers as exclusion criteria.
  - Drugs with potential to have allergic reactions were not stated in the original protocol. The drugs were named in the amendment: metoclopramide, citric acid, sodium citrate, benzalkonium chloride, ethylenediaminetetraacetic acid, or sorbitol.
  - Exclusion criteria for A1C was increased from >10% to >12.5%.

The changes made in the protocol do not appear to affect the conduct or efficacy or safety of the trial.

Changes in the SAP

Based on guidance from an Advice/Information Request sent by the FDA on March 9, 2011, recommending a modified GCSI score, the primary endpoint, list of secondary endpoints and exploratory endpoints were added/modified as described under study endpoints. The changes in endpoints were specified in the SAP, but not in a protocol amendment because the study had completed but data were not unblinded.

Subgroup analyses of the primary efficacy endpoint were planned in the SAP. Based on the results of the by-gender analyses, additional post hoc analyses were performed by gender.

These changes were made prior to database lock and should not affect the integrity of the trial.

8.1.2. [METO-IN-003]

Trial Design

This phase 3 clinical trial was conducted only in female patients and randomized 205 patients to receive IN Gimoti 10 mg or placebo in the ratio of 1:1. Patients with a mean daily GSA score for determining study eligibility (GSA-E) between ≥1.4 to ≤3.5, during the qualification period, were randomized and patients with a mean daily GSA-E total score of <1.4 or >3.5 were excluded. The dosing regimen and instruction were similar to METO-IN-002 trial. (Patients self-administered Gimoti nasal spray 10 mg or placebo as a single IN spray in either nostril QID, 30 minutes before meals and at bedtime for 4 weeks).

The assessments and procedures performed at the following key visits during the trial are summarized.

***Screening/Baseline (Visit 1: Day -15 to -9)*:** Reviewed eligibility criteria, recorded complete medical history including medications allowed/to be discontinued, performed targeted physical, and obtained blood samples for hematology, chemistry, HbA1c, and CrCl and an ECG.

***Qualification Visit (Visit 2: Day -7 to Day -1)*:** Provided patients with a sample symptom diary (visual aid) and written instructions on the use of the IVRS.

The patients were informed that the sample symptom diary will include the five symptom questions in the GSA and 2 additional items. The GSA is a subject-reported instrument for assessment of severity of GP symptoms, and a change from the baseline to Week 4 of the treatment period in mean daily GSA total score was used as primary efficacy endpoint. The following GSA and additional signs and symptoms were collected:

1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up).
2. Feel full soon after beginning to eat.
3. Prolonged fullness (feeling of food sitting in stomach long after you finish eating a meal).
4. Bloating (seeing your belly get large and firm or feeling like you need to loosen your clothes).
5. Upper abdominal pain (above the navel).

Additional Items

6. How many times did you vomit (throwing up with food or liquid coming out) in the past 24 hours?
7. How many times did you try to vomit, but nothing came out (retching or dry heaving) in the past 24 hours?

Each symptom was graded from 0 (none) to 4 (very severe) except retching and vomiting. Severity score of vomiting and retching, were recorded based on the frequency of episodes over the preceding 24-hour period from a score from 0 (none, no episodes) to 4 (very severe, ≥5 episodes).

The patients were instructed to call IVRS each evening at approximately the same time and reminded the importance of completing the diary via the IVRS every day during the study. On this visit, patients were trained/observed for calling in to IVRS, setting their password, and completing their first daily diary entry. Patients were asked to complete their GP daily symptom diary for 7 days and mean GSA-E total score was calculated by the IVRS for determining eligibility for the randomization. Patients who did not have scintigraphy to confirm delayed GE for eligibility underwent scintigraphy during this period.

***Gastric Emptying Scintigraphy Test (Visit 3: Day -8)*:** Patients with an eligible mean daily GSA-E total score but without scintigraphy underwent scintigraphy testing to confirm delayed GE.

***Randomization Visit (Visit 4: Day 0±2 days)*:** At randomization, prior to administration of the study drug:

- Completed the following:
  - Subject: Change in Gastroparesis Symptom Severity (CGSS) question.
  - Investigator: Global Severity of Gastroparesis Symptom question.

Obtained vitals and a 12-lead ECG was performed at 1.5 hours (approximate time of C_{max}) and 2.5 hours postdose and reviewed to confirm eligibility to continue to receive study drug. Also, obtained a urine hCG test/serum hCG pregnancy test for patients of childbearing potential to confirm results are negative prior to randomization. The IVRS diary instructions were reviewed and importance of compliance and using the IVRS each evening to record symptom was reiterated and eligibility criteria confirmed.

Patients were randomized to Gimoti (metoclopramide) nasal spray 10 mg or placebo via IVR or IWR.

Follow-up Visits 5, 6 and 7 (Days 7, 14, and 21 [±1 Day]): The patients were followed up in clinical visit for efficacy and safety evaluations on Days 7, 14, 21, which included asking questions to elicit AEs, use of concomitant medications, checking vitals, and

review of IVRS daily diary instructions for symptom collection and importance of compliance.

Visit 5 (Day 7±1): The following were done:

- Collected Day 5 and Day 6 hard copy dosing diary and recorded each dose of study medication.
- Observed self-administering study drug and noted time.
- Obtained CYP 2D6 blood sample and PK blood samples: pre-first dose, and post-first dose at 45 minutes (30–60) and 90 minutes (75-105); just prior to the second dose; and 90 minutes (75-105) post-second dose.

Visit 7 (Day 21±1): Reminded patients to bring study drug to the final visit.

Final Visit (Day 28±1 Day) or Early Termination Visit:
At the final visit on Day 28 the assessment included a targeted physical examination including general appearance; head, ears, eyes, nose and throat; neurological; heart/cardiovascular; lungs; abdomen; endocrine; extremities; musculoskeletal; lymphatic; and skin, vital signs (temperature, blood pressure, heart rate, and respiratory rate), and weight. Performed urine/serum pregnancy test(s) to confirm that the results are negative. Obtained blood samples for hematology, chemistries and HbA1C and performed a 12-lead ECG.

- Completed the following:
  - Subject: Change in Gastroparesis Symptom Severity question.
  - Investigator: Global Severity of Gastroparesis Symptoms question.

Change in Gastroparesis Symptom Severity

Subjects answered the CGSS using the IVRS diary at the time points outlined. The CGSS question asked about the overall change a subject may have experienced in the severity of her symptoms since her last visit. The answer ranges from 1 (very much improved) to 7 (very much worse). Lower scores indicate less severe symptoms (symptom improvement).

Global Severity of Gastroparesis Symptoms

The Investigator used the Global Severity of Gastroparesis Symptoms to assess the severity of the subjects' GP symptoms at the time points outlined above. The answer ranges from 0 (not at all severe) to 10 (very severe). Lower scores indicate less severe symptoms (symptom improvement).

Prior and Concomitant Therapy

Concomitant medications taken within 6 months prior to study entry and throughout the study were documented on the concomitant medication electronic case report form. Patients were asked to discontinue use of all medications known to ameliorate or exacerbate symptoms associated with DG as outlined in the study inclusion and exclusion criteria.

Patients taking the following medications from the screening period until completion of study were considered protocol deviation: oral and parenteral formulations of metoclopramide, domperidone, erythromycin, clarithromycin, other prokinetic agents (e.g., bethanechol, pyridostigmine), agents with anti-emetic effects (e.g., prochlorperazine, scopolamine, meclizine, ondansetron, granisetron), nonstudy drug nasal spray products, sinus rinses, and narcotic analgesics for abdominal pain.

Treatment Compliance

The diary compliance rate was calculated as the number of diary entries from study Day 0 to study Day 27 divided by the duration of treatment. Overall diary compliance rate of >75% during the treatment period was considered acceptable and patients with <75% overall diary compliance were excluded from the PP population.

Rescreening

Patients who met the protocol entrance criteria but failed to qualify for participation in the study on mean daily GSA-E total score or results of the scintigraphy during the qualification period could be rescreened one time. If patients were rescreened for GSA/scintigraphy ≤30 days after the initial screening visit (Visit 1), study assessment could start with Visit 2, and if rescreened/retested for scintigraphy >30 days after the initial screening study (Visit 1), started with a new screening visit (Visit 1).

Key Inclusion/Exclusion Criteria

Inclusion and exclusion criteria were similar to the METO-IN-002 except the following:

Inclusion Criteria:

1. Diagnosis of DG was confirmed based on delayed GE by scintigraphy.
2. A mean daily GSA-E score of ≥1.4 and ≤3.5 during the qualification period and the baseline period prior to the randomization.
3. Only female nonpregnant female patients were enrolled.
4. Use of concomitant medications (i.e., medications not excluded by the protocol) were allowed as long as doses were stable for a minimum of 2 weeks prior to the screening visit and there were no anticipated changes in dosage or medication for the duration of the study.

Exclusion Criteria:

1. Currently using and unwilling or unable to stop any medication known to be associated with TD prior to washout (Visit 2).
2. Had hemoglobin A1c >11.5% (compared to 12.5% in METO-IN-002) at screening visit.

3. Inability or unwillingness to stop the use of medications with anti-emetic effects (e.g. prochlorperazine, scopolamine, meclizine, ondansetron, granisetron) was added. In METO-IN-002, patients were refrained from using the following medications: oral and parenteral formulations of metoclopramide, domperidone, TCAs, macrolide antibiotics, prokinetic agents, cholinergic agents, agents with significant anticholinergic effects, narcotic analgesics, orally administered β-agonists, spasmolytics, dopamine agonists, monoamine oxidase inhibitors, herbal supplements, fiber or bulking products, and laxatives.
4. Cardiac pacemaker was added to the ECG criteria of exclusion: clinically significant abnormal finding or a QTc interval >450 ms on ECGs obtained at Screening OR predose or postdose at randomization.

Study Endpoints

Primary Efficacy Endpoint: Gastroparesis Symptom Assessment

- Change in mean daily GSA total score from the baseline period to Week 4 of the treatment period.

Changes from the protocol to the SAP:

The definition of the GSA total score was altered from the final protocol (Version 2.0 December 23, 2015) to Version 1.1 of the SAP (June 18, 2016). The GSA total score used as the primary endpoint in the protocol was identical to the GSA-E score used to determine eligibility. The vomiting item was replaced by prolonged fullness for calculating the GSA total score in the SAP. The endpoints were changed based on results from concurrent psychometric studies, which investigated test-retest reliability, internal consistency, and construct validity of the GSA instrument independently of the phase 3 study (EVO 1001), but the studies used blinded phase 3 data to assess minimally important differences (EVO 1002). The Applicant justified the removal of vomiting by stating that there were few episodes of vomiting during the trials, patients often experience nausea that does not result in vomiting, and reduction of nausea reduces vomiting.

Secondary Efficacy Endpoints

Changes in each of the five individual symptom scores that comprise the GSA total score from baseline to Week 4 of the treatment period.

Changes from the protocol to the SAP:

The alteration in the definition of the GSA total score for the primary endpoint also changed the secondary endpoints.

Gastroparesis Symptom Assessment

The GSA, a subject-reported assessment of severity of GP symptoms, instrument was used as assessment of primary efficacy. The GSA is a daily diary consisting of five items related to the symptoms of GP: nausea, fullness soon after beginning to eat (early satiety), bloating, upper abdominal pain, and vomiting. Two exploratory items (prolonged fullness and retching (dry

heaving)), were added following additional qualitative and quantitative analyses. The GSA consists of the following items:

1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)
2. Early satiety (feel full soon after beginning to eat)
3. Prolonged fullness (feeling of food sitting in stomach long after you finish eating a meal)
4. Bloating (seeing your belly get large and firm or feeling like you need to loosen your clothes)
5. Upper abdominal pain (above the navel)

Each symptom parameter is graded using the following five-point (0 to 4) Likert scale:

0 None
1 Mild symptoms
2 Moderate symptoms
3 Severe symptoms
4 Very severe symptoms

The daily GSA score used for the primary endpoint is computed as the average of the five individual symptom scores. If two or more of the individual item scores are missing, the total daily GSA score for that day will be set to missing. Five or more daily GSA total scores must be available during a study for the weekly mean to be non-missing.

Two additional items were included in the daily diary:

6. How many times did you vomit in the past 24 hours (throwing up with food or liquid coming out)?
7. How many times did you try to vomit, but nothing came out (dry heave or retching) in the past 24 hours?

Vomiting and retching scores assessments were based on vomiting or retching frequency over the preceding 24-hour period. The total number of episodes of vomiting or retching were assigned a severity score programmatically:

0 None (no vomiting)
1 Mild (1–2 episodes)
2 Moderate (3 episodes)
3 Severe (4 episodes)
4 Very severe (≥5 episodes)

The GSA score used to determine study eligibility (GSA-E) differs from the GSA total score used for the primary endpoint. The GSA-E score is calculated using the answers to the questions 1, 2, 4, 5, and 6.

Statistical Analysis Plan

Analysis Populations:

The safety population included all subjects who were randomized and received at least one dose of study drug. Treatment assignments were based on the treatment actually received. Safety analyses were based on the safety population.

The primary efficacy analysis, as well as all other efficacy analyses, was performed on the ITT population, defined as all subjects who were randomized. Treatment assignments in the ITT population were based on the randomized treatment.

The completers population included all randomized subjects who completed the 28-day treatment period and had a nonmissing weekly mean daily value for the GSA total score for Week 4. Treatment assignments were based on the randomized treatment.

The PP population included all randomized subjects who completed the 28-day treatment period, had no protocol violations or major protocol deviations, had at least 75% overall diary compliance (i.e., 21 or more completed diaries) during the treatment period, and had a nonmissing weekly mean daily value for the GSA total score for Week 4. Identification of subjects included in the PP population was completed prior to breaking the blind. Treatment assignment was based on the randomized treatment. The primary efficacy variable and secondary efficacy variables will be analyzed for the PP population.

Primary Efficacy Analysis:

The primary efficacy analysis was carried out using the ITT, completers, and PP populations, with the ITT population considered as primary. Missing Week 4 values will be imputed with the baseline value for the ITT population.

The primary variable (change from the baseline period to Week 4 of the treatment period in the mean daily GSA total score) was analyzed using an ANCOVA model with a fixed effect for treatment group and with the baseline mean daily GSA total score value as a covariate. Assumptions underlying the ANCOVA model (i.e., normality of errors, equality of variances, parallelism of treatment regression lines, and linearity of regression) were evaluated using diagnostic plots. The Shapiro-Wilk test was also used to assess normality and, if not statistically significant at $p<0.01$, the ANCOVA was considered the primary analysis; otherwise the corresponding rank ANCOVA model was considered as primary.

The parallelism of treatment regression lines was evaluated in a supplemental model that includes the baseline-by-treatment interaction. If the parallelism p-value <0.20 and there was crossing of the regression lines within the observed range of the baseline covariate values; treatment comparisons at each of the posttreatment visits were also presented at the least squares means associated with the first (Q1) and third (Q3) quartiles of the baseline mean daily GSA total score.

We note that the cutoff value of $p<0.01$ for the Shapiro-Wilk test for normality is quite stringent. A cutoff of $p<0.05$ or $p<0.10$ would have been more appropriate. A lack of significance for the Shapiro-Wilk test does not mean the data are normally distributed, it only indicates that there is

no strong evidence against normality. Also, the primary efficacy analysis should not have been altered based on testing the same data used for the hypothesis test of efficacy.

Secondary Efficacy Analyses:

Secondary endpoints were analyzed using a similar approach to the primary efficacy analysis.

Multiple Testing Procedure:

A hierarchical testing approach was used to control the overall alpha level at 0.05. Hypothesis tests were carried out in the following order (all comparisons are based on the change in the mean daily score from the baseline period to Week 4):

1. GSA total score (primary)
2. Nausea score
3. Upper abdominal pain score
4. Prolonged fullness score
5. Bloating score
6. Early satiety score

The procedure stops at the first test with a p-value >0.05 in which case that test, and all subsequent tests, are considered non-significant.

Missing Data:

For all efficacy variables based on IVRS daily diary data that are analyzed by week, baseline observation carried forward was used to impute missing weekly treatment period values for the ITT populations. Missing postbaseline weekly mean daily values were not imputed for the PP population. Note that imputation was carried out on the weekly values, not on the daily values.

The following sensitivity analyses were used to explore the impact of missing data for the ITT population:

- Observed cases: Use only observed data without any imputation of missing values. Subjects who provided no assessments during Week 4 were excluded.
- Last seven assessments: For subjects who provided no assessments for the variable score/ frequency during Week 4, the average of the most recent seven assessments of the variable value from the postbaseline study period were used as the value for the "Last Week." For subjects who provided fewer than seven assessments during the postbaseline period, the average of all available postbaseline assessments were used. For subjects who provided no postbaseline assessments, the baseline variable value was used.

For the primary efficacy variable only, the following additional sensitivity analyses were performed for:

- Multiple imputation was performed using a multivariate normal imputation model that included the mean daily GSA total score values from the baseline period and at each week during the treatment period. Change from baseline to Week 4 was analyzed for each imputed dataset using an ANCOVA model with a fixed effect for treatment group and baseline GSA value as a covariate. The ANCOVA was based on raw or ranked

values for the change from baseline and the baseline consistent with the model determination made for the primary endpoint analysis in this population.

Mixed Model Repeated Measures: A supportive efficacy analysis for the ITT used a mixed model for repeated measures (MMRM) of the dependent variable, change from baseline in mean daily GSA total score, at all postbaseline assessment times. The analysis was based on observed data and included subject as a random effect, fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as baseline mean daily GSA total score as a fixed covariate. The baseline-by-treatment interaction was also included as a covariate in the primary MMRM if the parallelism p-value <0.20. Treatment comparisons were made at each of the posttreatment visits and overall across all visits. Only ITT subjects who have contributed at least one postbaseline measurement were included in the model. An unstructured covariance was used to model the within-subject errors; a Kenward-Roger correction will be used for computing the denominator degrees of freedom for the treatment comparison.

Protocol Amendments

PROTOCOL METO-IN-003 Amendment 1 (IND 25512)

The original protocol was amended once during the study. The key changes in the amendment are summarized below as per the section of the protocol.

Study Design:

- Number of subjects changed from 125 per group to 100 per group.
- Added that the gastric emptying scintigraphy test could be done during the screening period or the qualification period.
- Instructed investigators to notify IVRS that subjects are entering the baseline period.
- Blood sample would be drawn if a subject experienced an SAE related to study drug or exhibited neurologic symptoms suggestive of TD.
- Clarified that use of excluded medications during the washout period would not be considered a protocol deviation.
- Added that rescreening subjects would be permitted and the conditions under which it would be permitted.
- Added that subjects would record the frequency of vomiting in the IVRS diary.
- Clarified that in the ITT population, subjects would be analyzed based on their randomized treatment, and in the safety population, subjects would be analyzed based on their actual treatment.
- Added completers and PP populations.
- For the primary efficacy analysis, clarified that if a subject provided no assessments of the daily GSA total score during Week 4, the baseline mean daily GSA total score would be used as the Week 4 value.
- Added that the primary efficacy analysis would be done on the completers and PP populations if the numbers of subjects in those populations were substantially different from the ITT population.

- Added analyses of the change in CGSS.
- Clarified what the baseline covariate would be for secondary efficacy analyses.

Inclusion criteria:

- Stable doses of medications not excluded by the protocol could be taken if stable for a minimum of 2 weeks prior to the screening visit.

Exclusion criteria:

- Cockcroft-Gault formula would be used to calculate CrCl.
- Patients would be allowed to use a saline nasal spray as long as it was at least 1 hour before or at least 1 hour after study drug administration.
- Clarified that the use of cannabinoids was to treat nausea or vomiting.

The changes made in the protocol do not appear to affect the conduct or efficacy or safety of the trial.

Changes in the SAP

Both the primary and secondary endpoints were altered from the final protocol (Version 2.0, December 23, 2015) to Version 1.1 of the SAP (June 18, 2016). The endpoints were altered based on results obtained from concurrent psychometric studies EVO 1001 and EVO 1002.

These changes were made prior to database lock and should not affect the integrity of the trial.

Changes Made in the Planned Analyses

The following tables related to subgroup analyses for patients with a baseline GSA score >2.7 were not planned in the SAP and added later (post hoc)

The following tables were not planned in the SAP but were programmed:

1. Table P1: Mean Daily GSA Total Score for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
2. Table P2: Mean Daily GSA Total Score for Baseline (BL) Mean Total GSA >2.7 (Completers, PP and Observed Cases Populations)
3. Table P3: Mean Daily Nausea Score for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
4. Table P4: Mean Daily Nausea Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)
5. Table P5: Mean Daily Upper Abdominal Pain Score for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
6. Table P6: Mean Daily Upper Abdominal Pain Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)
7. Table P7: Mean Daily Prolonged Fullness Score for Baseline (BL) Mean Total GSA >2.7 (ITT Population)

8. Table P8: Mean Daily Prolonged Fullness Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)
9. Table P9: Mean Daily Early Satiety Score for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
10. Table P10: Mean Daily Early Satiety Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)
11. Table P11: Mean Daily Bloating Score for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
12. Table P12: Mean Daily Bloating Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)
13. Table P13: Mean Daily Vomiting for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
14. Table P14: Mean Daily Vomiting Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)
15. Table P15: Mean Daily Retching for Baseline (BL) Mean Total GSA >2.7 (ITT Population)
16. Table P16: Mean Daily Retching Score for Baseline (BL) Mean Total GSA >2.7 (Completers and PP Populations)

8.1.3. [METO-IN-004]

Trial Design

METO-IN-004 was conducted in parallel to METO-IN-003 in male patients. Both studies were similar in design including dosing regimens and efficacy endpoints.

The study was stopped early due to difficulty in enrollment. Only 53 subjects were randomized out of a planned sample size of 150.

8.1.4. [Study 25,512-302R]

Trial Design

The study 25,512-302R was conducted by the previous sponsor of the IND. Of note, the (b) (4) metoclopramide nasal spray (b) (4) formulation.

This was an open-label, multicenter, randomized, parallel design study conducted in the United States at six centers to compare the PK and safety of (b) (4) (metoclopramide) nasal spray versus orally administered Reglan® (metoclopramide tablets, USP) in patients with DG. The study enrolled 89 adult diabetic patients with DG symptoms score between 8 and 20 on each of the assessment tools (Symptom Assessment Questionnaire (SAQ) and the Investigator's Assessment Questionnaire (IAQ)). Additionally, minimum of two out of the six symptoms had to be rated moderate or higher (≥2) on each of the scales.

Inclusion and exclusion criteria for study 25,512-302R were similar to the other clinical studies conducted by the Applicant.

Study objectives included the following:

Primary:

To characterize the pharmacokinetics of single and multiple doses of 10 mg and 20 mg (b) (4) metoclopramide, nasal spray), and 10 mg oral Reglan® tablets (metoclopramide tablets, USP) when administered QID before meals and at bedtime in patients with DG.

Secondary:

- To compare the safety of the 10 mg and 20 mg metoclopramide nasal sprays to metoclopramide 10 mg oral tablets when administered QID.
- To assess the pharmacokinetic-pharmacodynamic relationships of the 10 mg and 20 mg metoclopramide nasal sprays and oral metoclopramide 10 mg when administered QID.

Patients were randomized, based on computer generated schedule and randomization blocks of five, to receive metoclopramide nasal spray 10 mg, 20 mg, or oral metoclopramide 10-mg tablets in a 2:2:1 ratio. Each patient self-administered the assigned treatment QID before meals and at bedtime for 6 weeks.

The study drug (metoclopramide) (b) (4) mg/ml solution was packaged with a (b) (4) pump which delivered 0.05 ml per spray for 10-mg dose, and (b) (4) pump which delivered 0.1 ml per spray for the 20-mg dose. The patients were instructed to "prime" the pump five times before using it the first time and then each morning before administering their first morning dose.

Procedures and Schedule:

The assessments and procedures performed at the key visits during the trial are summarized.

Screening/Baseline Period

Obtained informed consent, reviewed eligibility criteria, recorded complete medical history including conditions affecting nasopharynx, allergies, sinusitis, and nasal surgery. Performed targeted physical including nasopharyngeal assessment, obtained blood samples for hematology, chemistry, HbA1c, and CrCl. All the medications included in the exclusion criteria were discontinued at least 7 days prior to the initial symptom assessment.

Enrollment Visit

Patients were admitted to the clinical research facility on study Day 1, the day of the first dose of study medication. Patients completed SAQ and IAQ and had physical examination and assessment of vital signs. Instruction were given for the proper technique for IN administration of metoclopramide and provided drug for 2 weeks.

Patients had blood drawn within 30 minutes prior to the administration of study medication. After the administration of the first dose of study medication, patients on nasal metoclopramide

ingested a meal. Patients receiving oral metoclopramide had 100 mL of water with their study drug and ingested a meal 30 minutes postdose. Patients received lunch (4 hours postdose), and dinner (9 hours postdose). Blood was obtained at the following time points for the determination of metoclopramide concentrations: 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 10, 12, and 14 hours postdose. No other doses of study medication were administered on study Day 1. Patients were sent home after the 14 hours blood sample and allowed their normal routine. Patients returned to the clinic on study Day 2 for the 24-hour blood draw followed by administration of their second dose. Patients were discharged with instructions to use the medication QID before meals and at bedtime.

During the study period patients were followed up as below:

- Safety and symptom assessments were completed by telephone interview on Day 7.
- Clinic visit (Day 14): Patients had a standard clinical and laboratory assessment, a single blood sample for determination of metoclopramide concentrations, and completed the symptom assessments. Telephone assessments were completed on Days 21, 28, and 35.
- Final study visit (Day 42): Patients were admitted to the clinical unit and had blood sampling within 30 minutes prior to their last dose of study medication and at 0.17, 0.33, 0.5, 0. 75, 1, 1.5, 2, 3, 4, 8, 10, 12, and 14 hours postdose for the determination of metoclopramide plasma concentrations and discharged home.
- Day 43: Clinical and laboratory assessments were performed including 24-hour blood sample for PK analysis.

Prior and Concomitant Therapy

All changes in medications during the course of the study were recorded in the concomitant medications section of the case report form (CRF) and the source documents.

Permitted Medications

Use of all medications administered for reasons other than the management of DG was continued provided that there was no known interaction between these and metoclopramide.

Treatment Compliance

Patients were asked to return unused study drug at the end of the study period. Assessment of the effect of patient compliance was not included in the analytical plan. The trial was conducted over a period of 5 months, (b) (6). The study duration for each patient was approximately 7 weeks that included 7-day washout from potentially interacting followed by a 6-week treatment period.

Study Endpoints

The primary efficacy endpoint was the change in the total symptom score from baseline to the end of the study. The total symptom score is the sum of the six patient-rated frequency items of SAQ and the sum of the six investigator-rated severity items of IAQ. SAQ assessed the frequency of symptoms and IAQ examined the severity.

The SAQ and IAQ questionnaires are summarized:

Symptom Assessment Questionnaire

This instrument/scale was the modification of the instrument described by Perkel and colleagues.[35] Modification to the Perkel scale included removal of redundant items, making the language simple and more precise response specification to increase inter-site consistency. The six target symptoms were nausea, vomiting, anorexia, bloating, early satiety and meal tolerance and patients assigned each symptom based on a predefined ordinal frequency score of zero to four. The maximum score would be 24 for the six symptoms.

Investigator's Assessment Questionnaire

This scale was completed by the investigator after asking the patient about severity of symptoms reported on the SAQ. The severity was calculated by the following guidelines:

- Mild: can be ignored when patient does not think about it
- Moderate: cannot be ignored
- Marked: influences concentration on daily activities
- Extreme, severe: markedly affects daily activity and/or requires the patient to rest

The inclusion criteria in the Perkel et al. study was a total score of 6 out of a maximum possible 36 score.[35] The SAQ was modified and had six categories compared to nine categories in Perkel et al. questionnaire. Furthermore, the proposed entry criteria of eight was selected for each SAQ and IAQ to enroll patients with moderate or greater grading (≥2) of at least two symptoms and varying grading on the other symptoms. The maximum score of 40 was selected because the label for Reglan® indicated that for severe symptoms, as would be expected with a score of 40 or more, IV metoclopramide should be administered.

Both questionnaires were completed at baseline and once per week during the 6-week treatment period: Days 7, 14, 21, 28, 35 and 42, respectively.

Secondary Efficacy Parameters:

- Changes from baseline in the weekly total symptom scores.
- Each individual symptom combined severity (IAQ) and frequency (SAQ) score, each combined item has a possible score of 0 to 8.

Exploratory Efficacy Parameters:

- Percentage of responders. A patient was considered a responder if his/her end-of-study reduction of the total symptom score was ≥33%, calculated as 100% x [(total score at baseline - total score at study end) / total score at baseline].
- Summary of the glycemic control, fructosamine, and HbA-lc based on the change from baseline.

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[35] Perkel, MS, et al, 1980, Metoclopramide therapy in fifty-five patients with delayed gastric emptying, Am J Gastroenterol, 74(3):231-236.

Statistical Analysis Plan

Statistical Analyses:

The primary efficacy endpoint was analyzed by an ANCOVA model including the factors for study center, treatment group, and baseline total symptom assessment score as a covariate.

Analyses of secondary endpoints, the change from baseline in weekly total symptom scores, were performed using the same ANCOVA model as used for the primary analysis, adjusted for center and the baseline total score. The means across study visits were also presented graphically by treatment groups.

All efficacy analysis in this trial were exploratory. All tests were conducted at a two-sided 0.05 significance level. There were no prespecified multiplicity adjustments to control study-wise type I error rate.

Missing Data:

In the ITT analyses, missing total SAQ and IAQ scores were handled in the following manner:

- Missing scores for either SAQ or IAQ were imputed using the LOCF method
- For the PP analysis of a given visit, patients were excluded from the analysis if either the total SAQ or total IAQ score was missing at that visit, or if either of them was obtained out of the visit window defined by the ±3 day of the scheduled date

If the total number of missing items was less than two or less than 20% of the total number of items in a questionnaire, missing scores for individual items of either questionnaire were imputed with the average of the remaining items with a valid value.

Analysis Populations:

ITT Data set: The primary analysis of efficacy was an ITT analysis where all patients who were randomized to one of the three treatments and had at least one postrandomization assessment (including SAQ and IAQ) were included. Of the 89 patients who were randomized, two patients ((b) (6) and (b) (6)) were excluded because there were no data to assess efficacy collected after they were randomized.

PP population: The secondary analysis of efficacy was a PP analysis which included all patients who completed the study per protocol. This PP analysis was performed only for the primary efficacy endpoint (i.e., the change from baseline to the end of the study in the total symptom score). Patients who did not meet the baseline SAQ/IAQ score criteria were excluded. The SAQ and IAQ taken during the time interval in which prohibited concomitant therapies were taken was also excluded from the PP analysis.

We note that the defined ITT population is not a true ITT population as it excludes patients without postrandomization assessments. Any efficacy results should be considered exploratory as the study is open-label and lacks a multiplicity adjustment.

8.1.5. Study Results

Compliance With Good Clinical Practices

The Applicant states that the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular those affording greater protection to the safety of study participants.

Financial Disclosure

The Applicant certified that, in compliance with 21 CFR 54, no financial disclosures were applicable to any of the studies conducted in support of this application. The Applicant submitted Form FDA 3454 and certified that the clinical investigators did not participate in any financial arrangement with the Applicant of the covered studies whereby the value of compensation to the Investigator for conducting the study would affect the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the Applicant of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

Patient Disposition

Patient disposition is presented for studies METO-IN-002, METO-IN-003, and 25,512-302R in the tables below. Completion rates were similar for placebo and metoclopramide 10 mg nasal spray but were lower for the metoclopramide 14 mg nasal spray group in study METO-IN-002. The 14-mg group also had higher withdrawal due to AEs. The metoclopramide 10 mg nasal spray had lower completion rates and higher withdrawal due to AEs in study METO-IN-003. The metoclopramide 20 mg nasal spray group had a similar withdrawal rate due to AEs as metoclopramide 10 mg oral tablet in study 25,512-302R and the metoclopramide 10 mg nasal spray had a lower rate of withdrawal due to AEs. Study METO-IN-004 was stopped early due to difficulty in enrollment. Only 53 subjects were randomized out of a planned sample size of 150.

Table 4: Patient Disposition METO-IN-002

		Treatment (N 192)		
Disposition	Placebo (N=95) n (%)	Metoclopramide 10 mg Nasal Spray (N=96) n (%)	Metoclopramide 14 mg Nasal Spray (N=96) n (%)	Total (N 287) n (%)
Completed	87 (91.6)	88 (91.7)	84 (87.5)	259 (90.2)
Withdrawal due to:				
Adverse event	4 (4.2)	3 (3.1)	8 (8.3)	15 (5.2)
Loss-to-follow-up	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.4)
Protocol violation	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)
Withdrawal of consent	1 (1.1)	5 (5.2)	1 (1.0)	7 (2.4)
Other	2 (2.1)	0 (0.0)	2 (2.1)	4 (1.4)

Source: Reviewers analysis created from adsl.xpt

Table 5: Patient Disposition METO-IN-003

Disposition	Placebo (N=103) n (%)	Metoclopramide 10 mg Nasal Spray (N=102) n (%)	Total (N=205) n (%)
Completed	99 (96.1)	91 (89.2)	190 (92.7)
Withdrawal due to:			
Adverse event	0 (0.0)	5 (4.9)	5 (2.4)
Loss-to-follow-up	0 (0.0)	2 (2.0)	2 (1.0)
Protocol violation	1 (1.0)	1 (1.0)	2 (1.0)
Withdrawal of consent	2 (1.9)	3 (2.9)	5 (2.4)
Other	1 (1.0)	0 (0.0)	1 (0.5)

Source: Reviewers analysis created from adsl.xpt

Table 6: Patient Disposition Study 25,512-302R

Disposition	Control Metoclopramide 10 mg Oral Tablet (N=18) n (%)	Treatment (N=71) Metoclopramide 10 mg Nasal Spray (N=35) n (%)	Treatment (N=71) Metoclopramide 20 mg Nasal Spray (N=36) n (%)	Total (N= 89) n (%)
Completed	17 (94.4)	32 (91.4)	33 (91.7)	82 (92.1)
Withdrawal due to:				
Adverse event	1 (5.6)	0 (0.0)	2 (5.6)	3 (3.4)
Loss-to-follow-up	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.1)
Protocol violation	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.1)
Withdrawal of consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (2.9)	1 (2.8)	2 (2.3)

Source: Reviewers analysis created from eos.xpt

Protocol Violations/Deviations

METO-IN-002 had 13 major protocol deviations, most were due to taking prohibited medication (7) or improper dosing of the study medication (4). One patient in the placebo group was withdrawn due to taking prohibited medication during the study.

METO-IN-003 had 22 major protocol deviations, all were related to the inclusion/exclusion criteria where subjects should have been excluded due to prohibited medication or QTcB>470. There were two patients that were withdrawn due to major protocol violations. One patient in the metoclopramide 10 mg nasal spray group took prohibited medication during screening and one patient in the placebo group had a QTcB>470.

Study 25,512-302R had one patient in the metoclopramide 10 mg nasal spray group withdrawn due to protocol violation.

Table of Demographic Characteristics

Demographic characteristics are presented for studies METO-IN-002, METO-IN-003, and 25,512-302R in the tables below. Demographic characteristics are generally balanced across treatment groups for studies METO-IN-002 and METO-IN-003 with a few exceptions. The placebo group has a slightly higher proportion of Hispanic patients and patients with a BMI≥30 compared to the treatment groups in METO-IN-002. In METO-IN-003, the placebo group has a

higher proportion of white patients and fewer African American patients than the treatment group. For study 25,512-302R, the metoclopramide 20 mg nasal spray group has a much higher proportion of females than the other two treatment groups and the dosing groups have different distributions of BMI and racial/ethnic characteristics. These imbalances can be due to the small number of patients in each treatment group.

Table 7: Demographic Characteristics for METO-IN-002

		Treatment (N=192)		
Demographic Parameters	**Placebo (N=95) n (%)**	**Metoclopramide 10 mg Nasal Spray (N=96) n (%)**	**Metoclopramide 14 mg Nasal Spray (N=96) n (%)**	**Total (N=287) n (%)**
Sex				
Male	27 (28.4)	31 (32.3)	26 (27.1)	84 (29.3)
Female	68 (71.6)	65 (67.7)	70 (72.9)	203 (70.7)
Age				
Mean years (SD)	52.4 (10.0)	51.6 (12.1)	50.4 (12.4)	51.5 (11.5)
Median (years)	53	52.5	53	53
Min, max (years)	23, 72	18, 75	19, 72	18, 75
Age group				
<65 years	85 (89.5)	81 (84.4)	83 (86.5)	249 (86.8)
≥65 years	10 (10.5)	15 (15.6)	13 (13.5)	38 (13.2)
BMI				
<18.5	1 (1.1)	1 (1.0)	0 (0.0)	2 (0.7)
≥18.5, <25	8 (8.4)	9 (9.4)	15 (15.6)	32 (11.1)
≥25, <30	18 (18.9)	24 (25.0)	24 (25.0)	66 (23.0)
≥30	68 (71.6)	62 (64.6)	57 (59.4)	187 (65.2)
Race				
White	67 (70.5)	62 (64.6)	65 (67.7)	194 (67.6)
Black or African American	23 (24.2)	28 (29.2)	31 (32.3)	82 (28.6)
Asian	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (3.2)	2 (2.1)	0 (0.0)	5 (1.7)
Multiple	2 (2.1)	3 (3.1)	0 (0.0)	5 (1.7)
Ethnicity				
Hispanic or Latino	19 (20.0)	7 (7.3)	13 (13.5)	39 (13.6)
Not Hispanic or Latino	76 (80.0)	89 (92.7)	83 (86.5)	248 (86.4)

Abbreviations: SD=standard deviation
Source: Reviewer's analysis created from adsl.xpt

Table 8: Demographic Characteristics for METO-IN-003

Demographic Parameters	Placebo (N=103) n (%)	Metoclopramide 10 mg Nasal Spray (N=102) n (%)	Total (N=205) n (%)
Sex			
Male	0 (0.0)	0 (0.0)	0 (0.0)
Female	103 (100.0)	102 (100.0)	205 (100.0)
Age			
Mean years (SD)	52.9 (11.6)	52.5 (10.9)	52.7 (11.2)
Median (years)	56	53.5	55
Min, max (years)	24, 74	27, 75	24, 75
Age group			
<65 years	90 (87.4)	87 (85.3)	177 (86.3)
≥65 years	13 (12.6)	15 (14.7)	28 (13.7)
BMI			
<18.5	0 (0.0)	2 (2.0)	2 (1.0)
≥18.5, <25	9 (8.7)	8 (7.8)	17 (8.3)
≥25, <30	21 (20.4)	18 (17.6)	39 (19.0)
≥30	73 (70.9)	74 (72.5)	147 (71.7)
Race			
White	79 (76.7)	62 (60.8)	141 (68.8)
Black or African American	20 (19.4)	37 (36.3)	57 (27.8)
Asian	2 (1.9)	0 (0.0)	2 (1.0)
American Indian or Alaska Native	1 (1.0)	2 (2.0)	3 (1.5)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	1 (1.0)	1 (1.0)	2 (1.0)
Ethnicity			
Hispanic or Latino	14 (14.6)	11 (10.8)	25 (12.2)
Not Hispanic or Latino	89 (86.4)	91 (89.2)	180 (87.8)

Abbreviations: SD=standard deviation
Source: Reviewer's analysis created from adsl.xpt

Table 9: Demographic Characteristics for Study 25,512-302R

	Control	Treatment (N=71)		
Demographic Parameters	Metoclopramide 10 mg Oral Tablet (N=18) n (%)	Metoclopramide 10 mg Nasal Spray (N=35) n (%)	Metoclopramide 20 mg Nasal Spray (N=36) n (%)	Total (N=89) n (%)
Sex				
Male	9 (50.0)	19 (54.3)	13 (36.1)	41 (46.1)
Female	9 (50.0)	16 (45.7)	23 (63.9)	48 (53.9)
Age				
Mean years (SD)	54.3 (9.7)	55.5 (11.2)	53.8 (9.6)	54.6 (10.2)
Median (years)	54	55	55.5	55
Min, max (years)	35, 70	32, 82	31, 69	31, 82
Age group				
<65 years	14 (77.8)	27 (77.1)	31 (86.1)	72 (80.9)
≥65 years	4 (22.2)	8 (22.9)	5 (13.9)	17 (19.1)
BMI				
<18.5	1 (5.6)	2 (5.7)	1 (2.8)	4 (4.5)
≥18.5, <25	1 (5.6)	4 (11.4)	2 (5.6)	7 (7.9)
≥25, <30	9 (50.0)	7 (20.0)	15 (41.7)	31 (34.8)
≥30	7 (38.9)	22 (62.9)	18 (50.0)	47 (52.8)
Race/ethnicity				
Non-Hispanic White	6 (33.3)	13 (37.1)	13 (36.1)	32 (36.0)
Black or African American	4 (22.2)	2 (5.7)	4 (11.1)	10 (11.2)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (2.8)	1 (1.1)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hispanic	8 (44.4)	20 (57.1)	18 (50)	46 (51.7)

Abbreviations: SD=standard deviation; BMI body mass index
Source: Reviewer's analysis created from demo.xpt

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

METO-IN-002 required an average daily GCSI-DD score between 2 and 4 for the week prior to randomization for inclusion in the study. The average baseline GCSI-DD scores were 2.73, 2.73, and 2.74 for the placebo group, the metoclopramide 10 mg nasal spray group, and the metoclopramide 14 mg nasal spray group, respectively.

METO-IN-003 required a mean daily GSA score for determining study eligibility between 1.4 and 3.5 during the qualification period and the baseline period for inclusion in the study. The average baseline daily GSA-E score was 2.30 in the placebo group and 2.28 in the metoclopramide 10 mg nasal spray group.

Study 25,512-302R required both an IAQ and SAQ score between 8 and 20 for study eligibility. The average baseline IAQ scores were 11.6, 11.7, and 10.9 for the metoclopramide 10 mg oral tablet group, the metoclopramide 10 mg nasal spray group, and the metoclopramide 14 mg nasal spray group, respectively. The average baseline SAQ scores were 11.3, 12.0, and 10.6 for the

metoclopramide 10 mg oral tablet group, the metoclopramide 10 mg nasal spray group, and the metoclopramide 14 mg nasal spray group, respectively.

Patients included in the trials had only mild to moderate symptoms of DG.

All the patients had prolonged medical history of (h/o) DM and other diseases such as HTN, dyslipidemia, gastroesophageal reflux disease (GERD) and were receiving several concomitant medications which may have contributed to some of the symptoms of DG.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Studies METO-IN-002 and METO-IN-003 measured treatment compliance as the number of diary entries during treatment divided by the duration of treatment.

In study METO-IN-002, 79.0% (75/95) of patients randomized to placebo had over 80% compliance, 68.8% (66/96) of patients randomized to metoclopramide 10 mg nasal spray had over 80% compliance, and 75.0% (72/96) of patients randomized to metoclopramide 14 mg nasal spray had over 80% compliance.

In study METO-IN-003, 89.3% (92/103) of patients randomized to placebo had over 80% compliance. For patients randomized to metoclopramide 10 mg nasal spray, 79.4% (81/102) of patients randomized had over 80% compliance.

Efficacy Results – Primary Endpoint

METO-IN-002

The results of Applicant's ANCOVA model for testing change in the weekly average mGCSI-DD score from baseline to Week 4 of the study were replicated by the FDA. The results are displayed in the table below. A lower score on the mGCSI-DD indicates less severe GP symptoms. There is no statistically significant difference in the change in mGCSI-DD score between the metoclopramide groups and placebo. The ANCOVA model used LOCF imputation, though the results are similar when using only observed data. The number of subjects missing evaluations at Week 4 were similar across treatment groups (13 placebo patients; 14 patients in the 10 mg metoclopramide arm; and 17 patients in the 14 mg metoclopramide arm).

Table 10: Mean Change From Baseline to Week 4 in mGCSI Score

	Placebo (n 95)	Metoclopramide 10 mg Nasal Spray (n 96)	Metoclopramide 14 mg Nasal Spray (n 96)
Baseline mean (SD)	2.77 (0.57)	2.87 (0.60)	2.82 (0.62)
Estimated change from baseline at week 4 (95% CI)	-1.01 (-1.20, -0.82)	-1.21 (-1.40, -1.02)	-1.15 (-1.35, -0.96)
Week 4 difference versus placebo (95% CI)		-0.20 (-0.47, 0.07)	-0.14 (-0.42, 0.13)
p-value		0.149	0.298

Abbreviations: SD=standard deviation; CI confidence interval
Source: Reviewer's analysis created from adqs.xpt

The SAP prespecified conducting supportive subgroup analyses on the primary endpoint. A total of six baseline factors, including gender, were used to create twelve subgroups. With 2 dose

groups, a total of 24 hypotheses could be tested. The subgroup analyses did not include any adjustment for multiplicity; therefore, the type I error inflation could be substantial. As an example, if there are 24 tests to be conducted and the test statistics are independent, then there is a >70% chance of observing at least one p-value less than 0.05 even when the null hypothesis of no treatment difference is true.

The Applicant's subgroup analyses nominally showed a statistically significant treatment effect in females. The results of the ANCOVA analysis in females are presented in the table below. Additionally, the average mGCSI-DD score is lower at baseline among placebo patients compared to the treatment groups and the difference in the change in mGCSI-DD score between placebo and treatment may be partially attributable to regression to the mean for the treatment groups. The differences in the mGCSI-DD scores (unadjusted for baseline) between metoclopramide 10 mg and metoclopramide 14 mg and placebo are -0.28 and -0.27. Regardless, the subgroup analysis in females can only be considered exploratory.

Table 11: Mean Change From Baseline to Week 4 in mGCSI Score (Females Only)

	Placebo (n 68)	Metoclopramide 10 mg Nasal Spray (n 65)	Metoclopramide 14 mg Nasal Spray (n 70)
Baseline mean (SD)	2.72 (0.54)	2.89 (0.62)	2.92 (0.62)
Estimated change from baseline at week 4 (95% CI)	-0.85 (-1.08, -0.61)	-1.23 (-1.46, -0.99)	-1.23 (-1.46, -1.00)
Week 4 difference versus placebo (95% CI)		-0.38 (-0.71, -0.05)	-0.38 (-0.71, -0.06)
p-value		0.0243	0.0212

Abbreviations: SD=standard deviation; CI confidence interval
Source: Reviewer's analysis created from adqs.xpt

The same subgroup analysis was replicated for male patients. The results are displayed in the table below. Although it was not statistically significant, the placebo group performed better than both treatment groups in the change in mGCSI-DD score.

Table 12: Mean Change From Baseline to Week 4 in mGCSI Score (Males Only)

	Placebo (n 27)	Metoclopramide 10 mg Nasal Spray (n 31)	Metoclopramide 14 mg Nasal Spray (n 26)
Baseline mean (SD)	2.88 (0.63)	2.83 (0.54)	2.55 (0.56)
Estimated change from baseline at week 4 (95% CI)	-1.35 (-1.70, -1.00)	-1.17 (-1.50, -0.84)	-1.03 (-1.39, -0.67)
Week 4 difference versus placebo (95% CI)		0.18 (-0.30, 0.66)	0.32 (-0.19, 0.83)
p-value		0.450	0.217

Abbreviations: SD=standard deviation; CI confidence interval
Source: Reviewer's analysis created from adqs.xpt

The ANCOVA model for the overall study population showed a nominally significant interaction effect between treatment and gender (p=0.038).

METO-IN-003

The Applicant's primary analysis for testing the change in the weekly average GSA total score from baseline to Week 4 of the study was replicated. The results are presented in the table below. A lower score on the GSA total score indicates less severe GP symptoms. There is no

statistically significant difference in the change in GSA total score between the metoclopramide groups and the placebo group, and the p-value is quite large (p=0.881). The p-value was computed using a rank ANCOVA model due to the statistical significance of the Shapiro-Wilk test; however, the p-value from the ANCOVA model was similar (p=0.807). The ANCOVA model used baseline observation carried forward, though the results are similar when using only observed data. The number of subjects missing evaluations at Week 4 was quite small (4 placebo patients and 9 metoclopramide 10 mg patients). Study METO-IN-003 only enrolled female patients and failed to confirm the observation from the exploratory subgroup analysis in METO-IN-002 that suggested a potential treatment effect in female patients.

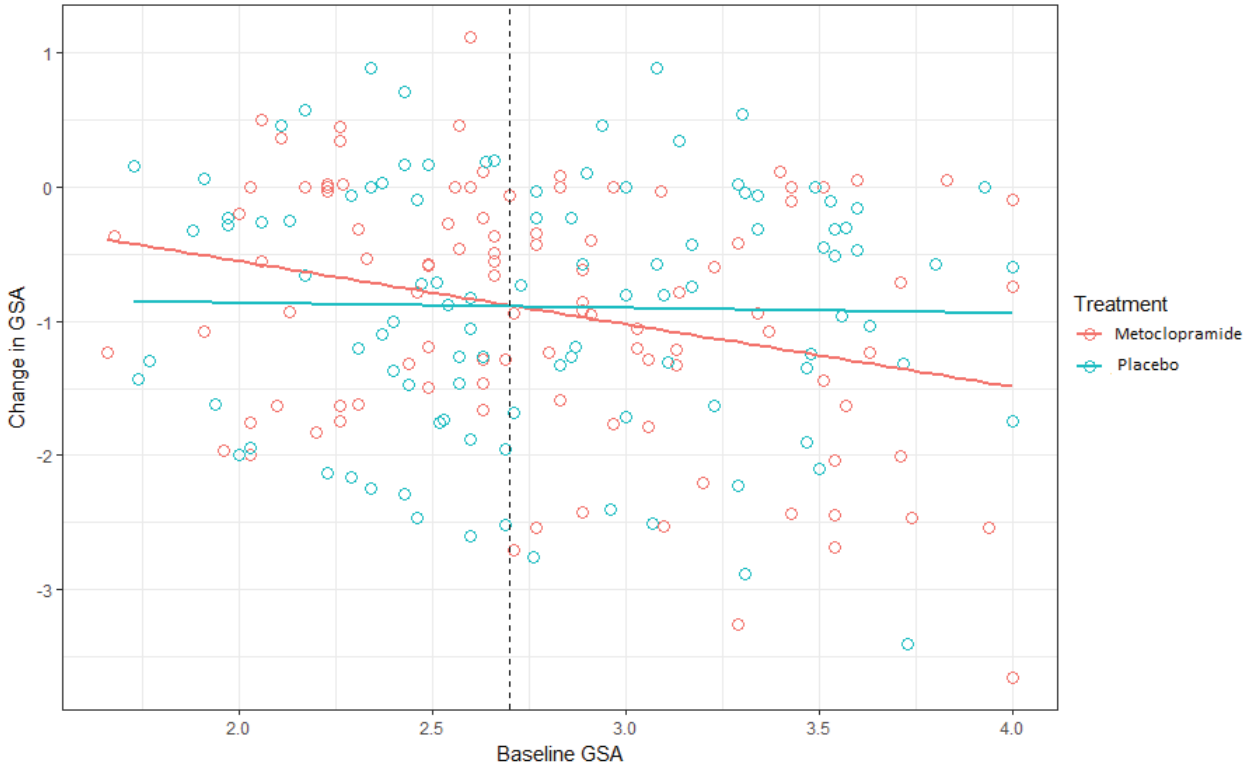
Table 13: Mean Change From Baseline to Week 4 in GSA Total Score

	Placebo (n 103)	**Metoclopramide 10 mg Nasal Spray (n 102)**
Baseline mean (SD)	2.81 (0.56)	2.80 (0.57)
Estimated change from baseline at week 4 (95% CI)	-0.89 (-1.08, -0.71)	-0.93 (-1.11, -0.74)
Week 4 difference from placebo (95% CI)		-0.032 (-0.29, 0.22)
p-value		0.881

Abbreviations: SD=standard deviation; CI confidence interval
Note: P-value computed from a rank ANCOVA model adjusted for baseline GSA
Source: Reviewer's analysis created from adqs.xpt

The SAP stated that the Applicant would explore a baseline-by-treatment interaction and see if the regression lines for the two treatment groups crossed within the observed range of the baseline GSA values. Based on this analysis, the Applicant determined that the regression lines crossed just above the baseline GSA total score value of 2.7. The Applicant conducted a post hoc analysis using a baseline GSA total score >2.7 to and ≤2.7 to define subgroups. The figure below shows a scatterplot with regression lines for change in GSA total score at Week 4 versus baseline GSA total score by treatment group. The dotted vertical line corresponds to a baseline value of 2.7. In the subgroup defined by baseline GSA total score ≤2.7, the placebo group has a larger decrease in GSA total score than the metoclopramide group; however, metoclopramide is favored in the subgroup with a baseline GSA total score >2.7.

Figure 1: Change in GSA Total Score vs. Baseline GSA Total Score



Source: Reviewer's analysis created from adqs.xpt

The Applicant's post hoc subgroup analysis for patients with a baseline GSA total score >2.7 has been reproduced and the results are displayed below. The p-value for the treatment difference is not significant at the 0.05 two-sided level, though it is close. The p-value was computed using a rank ANCOVA model due to the statistical significance of the Shapiro-Wilk test. The p-value from the ANCOVA model was similar (0.056), but still not significant. Results from this post hoc analysis can only be considered exploratory.

Table 14: Mean Change From Baseline to Week 4 in GSA Total Score (Baseline GSA Total Score >2.7)

	Placebo (n 53)	Metoclopramide 10 mg Nasal Spray (n 52)
Baseline mean (SD)	3.26 (0.35)	3.25 (0.38)
Estimated change from baseline at week 4 (95% CI)	-0.86 (-1.12, -0.59)	-1.22 (-1.49, -0.95)
Week 4 difference from placebo (95% CI)		-0.36 (-0.73, 0.01)
p-value		0.085

Abbreviations: SD=standard deviation; CI confidence interval
Note: P-value computed from a rank ANCOVA model adjusted for baseline GSA
Source: Reviewer's analysis created from adqs.xpt

In this instance, the ANCOVA lines intersect very close to the cutoff value for the baseline GSA total score that would produce the smallest p-value in favor of the study drug. The lines intersect at 2.73 and the smallest p-value in favor of metoclopramide, based on the ANCOVA model, occurs in the subgroup for GSA total score >2.76.

We performed an exploratory analysis to determine how often a nominal p-value of less than 0.05 could be obtained from creating two subgroups based on the baseline GSA total score under the null hypothesis. The baseline GSA total score and change in GSA total score were fixed to preserve their relationship and avoid distributional assumptions; however, the treatment assignments were randomly permuted. After the treatment permutation, two subgroups were created based on a baseline GSA value greater than a cutoff value or less than or equal to that cutoff. The p-value is then reported for the subgroup where the treatment outperforms the placebo. The smaller of the two p-values is selected if the treatment outperforms the placebo in both subgroups. The cutoff value is selected to minimize the p-value across all possible subgroups. Based on this analysis, there is approximately a 24% chance that a subgroup that produces a p-value less than 0.05 in favor of the treatment can be found even when the null hypothesis is true. This analysis is only based on a single baseline factor. As the analysis was not prespecified, there are multiple baseline factors which could have been used to select subgroups. Selecting post hoc subgroups based on baseline characteristics can substantially inflate the type I error rate. Therefore, the post hoc subgroup analysis does not provide evidence of efficacy.

METO-IN-004

The study was stopped early due to difficulty in enrollment. The study stopped with 27 placebo patients and 26 metoclopramide patients. None of the primary and secondary endpoints were statistically significant.

Study 25,512-302R

The table below presents the estimated treatment difference between the treatment groups and control for the change in total symptom scores from baseline to the end of study (Week 6). The table includes the primary analysis used by the Applicant and some sensitivity analyses. Smaller values of the total symptom scores are better. The primary analysis used by the Applicant for change in total symptom scores using the ANCOVA model shows a nominally significant treatment difference (p=0.026) for the metoclopramide 20 mg nasal spray compared to the 10-mg oral tablet and a p-value of 0.132 for the treatment difference between the 10-mg nasal spray and the 10-mg oral tablet. No multiplicity adjustment was specified, and the 20-mg nasal spray would not be significant if a Bonferroni adjustment were used.

There were 18 patients randomized to metoclopramide 10-mg oral tablet, 35 randomized to metoclopramide 10-mg nasal spray, and 36 randomized to metoclopramide 20-mg nasal spray. Two randomized patients (1 metoclopramide 10-mg nasal spray and 1 metoclopramide 20-mg nasal spray) were excluded from the primary analyses because they had no postbaseline data. Using the primary imputation of LOCF for these patients (in this case equivalent to baseline observation carried forward) and including these patients in the ANCOVA analysis greatly alters the results, with the treatment differences no longer approaching significance. Further examination showed that one patient randomized to metoclopramide 10-mg oral tablet ((b) (6)) experienced a large increase in GP symptoms at the last visit compared to the previous visits. This patient appears to have been an outlier compared to other patients in the metoclopramide 10-mg oral tablet group. Removing this patient from the ANCOVA analysis also alters the efficacy conclusions. The efficacy results are not robust because they can be altered by changing the outcomes in one or two patients.

Table 15: Results From ANCOVA Model for Mean Change in Total Symptom Scores

	Metoclopramide 10-mg Spray Difference from Oral Tablet Estimate (95% CI) p-value	Metoclopramide 20-mg Spray Difference from Oral Tablet Estimate (95% CI) p-value
Primary analysis	-2.5 (-5.8, 0.8) p=0.132	-3.8 (-7.1, -0.5) p=0.026
All randomized patients	-2.0 (-6.9, 3.0) p=0.348	-2.6 (-7.5, 2.4) p=0.219
Excluding 05/008	-1.2 (-4.9, 2.5) p=0.437	-2.7 (-6.4, 1.0) p=0.083

Abbreviations: CI=confidence interval
Source: Reviewer's Analysis created from SAQ.xpt and IAQ.xpt

An ANCOVA model using LOCF imputation is not ideal for handling missing data and dropout. The data was reanalyzed by the FDA using a MMRM with the same covariate and factors as the ANCOVA model, but with an added categorical variable for visit and visit-by-treatment interaction. An unstructured covariance matrix was specified. The MMRM can handle data that are missing at random, which, while not likely to be completely accurate, is a more appropriate missing data assumption than LOCF. The MMRM also shows the estimated treatment effect at every study visit, which provides more information than only examining the treatment effect at the final visit. The estimated treatment difference and 95% CI for each visit are presented in the table below. The metoclopramide 20-mg nasal spray is only significantly different from the metoclopramide 10-mg oral table at the final visit of the treatment period. The metoclopramide 10-mg nasal spray is never significantly different from the oral tablet. This analysis excluded the two randomized patients with missing postbaseline data.

Table 16: Results From MMRM Model for Mean Change in Total Symptom Scores

	Metoclopramide 10-mg Spray Difference from Oral Tablet Estimate (95% CI)	Metoclopramide 20-mg Spray Difference from Oral Tablet Estimate (95% CI)
Visit 4	0.60 (-3.11, 4.31)	-0.86 (-4.54, 2.82)
Visit 5	-0.66 (-4.74, 3.42)	-1.41 (-5.47, 2.64)
Visit 6	-1.26 (-4.80, 2.28)	-3.25 (-6.79, 0.29)
Visit 7	-0.18 (-3.97, 3.60)	-0.21 (-3.99, 3.57)
Visit 8	-0.87 (-4.29, 2.54)	-2.78 (-6.20, 0.64)
Visit 9	-2.65 (-5.97, 0.66)	-3.78 (-7.10, -0.45)

Abbreviations: CI=confidence interval
Source: Reviewer's Analysis created from SAQ.xpt and IAQ.xpt

Efficacy Results – Secondary and Other Relevant Endpoints

METO-IN-002

The secondary endpoints were analyzed with an ANCOVA model similar to the primary endpoint. Results are presented in the table below. Only nausea showed a nominally significant difference from placebo for the 14-mg group at α 0.05; however, nausea could not be formally tested due to the failure of the primary endpoint earlier in the testing hierarchy.

Table 17: Mean Difference From Placebo for GCSI-DD Individual Item Scores in METO-IN-002

	MCP 10-mg Nasal Spray	MCP 14-mg Nasal Spray
Nausea		
Difference from placebo	-0.23	-0.38
(95% CI)	(-0.52, 0.07)	(-0.68, -0.08)
Bloating		
Difference from placebo	-0.19	-0.12
(95% CI)	(-0.55, 0.17)	(-0.48, 0.24)
Early satiety		
Difference from placebo	-0.15	0.04
(95% CI)	(-0.47, 0.16)	(-0.27, 0.35)
Upper abdominal pain		
Difference from placebo	-0.25	-0.15
(95% CI)	(-0.56, 0.06)	(-0.46, 0.16)

Abbreviations: CI confidence interval
Source: Reviewer's analysis created from adqs.xpt

METO-IN-003

The secondary endpoints were analyzed with a similar ANCOVA model to the primary endpoint. Results are presented in the table below. None of the secondary endpoints were statistically significant.

Table 18: Mean Difference From Placebo for GSA Individual Item Scores in METO-IN-003

	MCP 10-mg Nasal Spray
Nausea	
Difference from placebo	-0.13
(95% CI)	(-0.42, 0.16)
Upper abdominal pain	
Difference from placebo	-0.08
(95% CI)	(-0.37, 0.20)
Prolonged fullness	
Difference from placebo	-0.02
(95% CI)	(-0.31, 0.27)
Bloating	
Difference from placebo	0.09
(95% CI)	(-0.19, 0.37)
Early satiety	
Difference from placebo	-0.02
(95% CI)	(-0.30, 0.26)

Abbreviations: CI=confidence interval; MCP=metoclopramide
Source: Reviewer's analysis created from adqs.xpt

Data Quality and Integrity

The data quality was sufficient for analysis and there were no identified issues with data quality that impeded the review.

Dose/Dose Response

For Study 25,512-302R, the primary analysis used by the Applicant for change in total symptom scores showed a slight dose response between the metoclopramide 20 mg and 10 mg nasal spray compared to the 10 mg oral tablet. However, the efficacy results are not robust because they can be altered by changing the outcomes in one or two patients. There was no clear dose-response in the other clinical trials. Since the clinical trials did not evaluate the dose proposed by the Applicant for labeling, any dose-response or lack thereof is not applicable.

Durability of Response

The clinical trials failed to demonstrate efficacy on the primary endpoint and did not evaluate the dose proposed by the Applicant for labeling; therefore, the durability of response is not applicable.

Persistence of Effect

The clinical trials failed to demonstrate efficacy on the primary endpoint and did not evaluate the dose proposed by the Applicant for labeling; therefore, the persistence of effect is not applicable.

8.1.6. Summary Assessment of Effectiveness

Both double-blind studies, METO-IN-002 and METO-IN-003, failed to achieve statistical significance in their primary endpoints, so formal statistical hypothesis testing was stopped. Among four secondary endpoints and two dose groups, only one secondary endpoint (nausea) was nominally significant ($p<0.05$) for metoclopramide 14-mg nasal spray in METO-IN-002 and no secondary endpoints were nominally significant for METO-IN-003. The Applicant's subgroup analyses do not have proper type I error rate control and cannot be used to establish efficacy. Furthermore, the subgroup analysis of METO-IN-002 was not replicated on METO-IN-003. METO-IN-004 was stopped early due to difficulty in enrollment. The study stopped with 27 placebo patients and 26 metoclopramide patients; none of the primary and secondary endpoints were statistically significant.

While the efficacy results appear more promising for study 25,512-302R, the results are potentially biased due to the trial being open-label. The efficacy results can only be considered supportive/exploratory. Additionally, the sample size is small in study 25,512-302R, the efficacy results are driven by a few subjects, and there is no significant difference between treatment groups for most of the treatment period.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of Gimoti was primarily ascertained through the evaluation of reported AEs, physical examination findings, and laboratory data in the two phase 3 clinical trials (METO-IN-003, and METO-IN-004) and one phase 2b trial (METO-IN-002). Safety information for each trial was assessed independently. Adverse events based on system organ class (SOC) and preferred term (PT) were compared against the placebo.

8.2.2. Review of the Safety Database

The review was based on this reviewer's independent analysis of the data sets provided by the Applicant, and on the Applicant's study reports. The overall design of the clinical trials are summarized below:

METO-IN-002: A phase 2b dose-ranging, safety and efficacy study in female and male patients with DG randomized to receive Gimoti 10 mg or 14 mg or placebo (95 each) in a 1:1:1 ratio for 4 weeks.

METO-IN-003: A phase 3 study that evaluated efficacy and safety of IN Gimoti 10 mg QD for 4 weeks compared to placebo in 205 female patients with DG. This trial enrolled female patients only.

METO-IN-004: A phase 3 study that evaluated efficacy and safety of IN Gimoti 10 mg QD for 4 weeks compared to placebo in 53 male patients with DG. The study was stalled due to low enrollment and terminated prematurely. This trial enrolled male patients only.

Metoclopramide is known to have CNS related extrapyramidal reactions including acute dystonic reactions, parkinsonian-like symptoms, akathisia, and TD. The labeling for the currently approved oral formulation, Reglan, includes a boxed warning for TD, a serious movement disorder that is often irreversible. The IN administration of the drug may have the potential for direct CNS delivery via the IN route, and therefore, increased safety implications for a drug known to cause CNS AEs. Therefore, the narratives of patients with serious AEs, and special interest AEs including neurological AEs and nasopharyngeal AEs were also reviewed.

The adequacy of the current safety database for Gimoti as well as the potential safety implications of the IN administration for a drug known to cause CNS AEs were discussed with the Safety Outcome Subcommittee of the Medical Policy Council comprised of senior CDER management. Based on the discussion, the Division determined that the application may be fileable, however, the Division identified significant safety and efficacy concerns that will be review issues. The Applicant's proposed (b) (4) (b) (4) The Division recommended that the Applicant should include a proposal for a randomized postmarketing safety trial with an active comparator to assess CNS events (not limited to TD).

Additional supportive safety data from a phase 2 study 25,512-302R and legacy studies were also evaluated. As stated in Section 8.1.4, study 25,512-302R was conducted by another sponsor under IND 025512 (b) (6); a different metoclopramide IN formulation ((b) (4) metoclopramide nasal spray formulation) was used to evaluate 10- and 20-mg IN metoclopramide compared to oral 10-mg metoclopramide for the duration of 6 weeks. The legacy studies were conducted between (b) (6) and they utilized different IN formulation for other indications (other than DG). For details, see Appendix 15.4.1.

The safety analyses included the proportion of patients with SAEs, discontinuation due to treatment emergent adverse events (TEAEs) and special interest AEs related to the CNS, psychiatry, nasal, and cardiovascular TEAEs. CRFs of the patients were reviewed to ascertain

the plausibility of relatedness of TEAEs with the administration of Gimoti since the trial population had several coexisting illnesses and were taking several concomitant medications. Tables created to compare the TEAEs show the proportion (%) of patients in each group. It is noted that many patients had more than one TEAE; therefore, the number of patients in the SOC or main group may not match the total number of patients as per PT.

The abbreviated safety data from the METO-IN-004 is presented separately. It is stated by the Applicant that the efficacy was not achieved in male patients because their drug levels were lower than the female patients. Therefore, the safety analyses were performed separately as the male patients were less likely to have the TEAEs and combining their results may dilute the safety signal/trend/observation in the female patients.

The clinical laboratory evaluations including hematology, biochemistry, and vitals for the three studies (METO-IN-002, METO-IN-003, and METO-IN-004) were pooled. A treatment emergent, potentially clinically significant laboratory abnormality was defined as any potentially clinically significant event that occurred at any postbaseline visit and had a value that was out of range based on a predefined threshold.

The results of the ECGs done during the clinical studies and a thorough ECG (QT study) study (METO-IN-005), reviewed by the QT study team, are summarized.

Additional Safety Analyses

Additional safety data from other trials were also reviewed. The to-be-marketed formulation was not used in these clinical trials, and the clinical data are not informative because the 15-mg dose was not evaluated; therefore, additional analyses are provided in Appendix 15.4.

Overall Exposure

The safety population included 543 patients for the IN-Gimoti and 89 patients for the previous IN-metoclopramide formulation. Of the 543 patients in the three studies (METO-IN-002, METO-IN-003, and METO-IN-004), 223, 95, and 225 patients received 10-mg metoclopramide, 14-mg metoclopramide, and placebo respectively. Of the 89 patients in IN-metoclopramide group (25,512-302R), 35, 36, and 18 patients received 10-mg metoclopramide, 20-mg metoclopramide, and placebo, respectively (Table 19**)**.

Table 19: Safety Population

Study Number/ Study Design Population	Safety Population Gimoti IN/ Metoclopramide Oral/Placebo QID for 4 weeks					Safety Assessments
	10 mg IN (n 258)	14 mg IN (n 95)	20 mg IN (n 36)	10 mg Oral (n 18)	Placebo (n 225)	
METO-IN-003 Phase 3, R, MC, DB, PC, PG. Female patients only	102	-	-	-	103	AEs, labs, PE, vitals, ECGs
METO-IN-004 Phase 3, R, MC, DB, PC, PG. Male patients only	26	-	-	-	27	AEs, labs, PE, vitals, ECGs
METO-IN-002 Phase 2b, DR, R, MC, DB, PC, PG. Male and female patients	95	95	-	-	95	AEs, labs, PE, vitals, ECGs
25.512-302R Phase 2, OL, AC, R, PD, PK and safety study. Male and female patients	35	-	36	18	-	AEs, labs, PE, vitals, ECGs

Abbreviations: PC placebo control; R=randomized; DB=double blind; OL open label; AC=active control; MC=multi center, PG=parallel group; PK pharmacokinetic; DR=dose ranging; PE=Physical Exam; ECG electrocardiogram; AE=adverse event; QID four times a day; PD pharmacodynamic; IN intranasal
Note: "n" is the sum of all available numbers from the columns below
Source: Adapted from Table 1 of the Applicants summary of clinical safety

Drug Exposure in Individual Studies

Table 20 shows study overall drug exposure compared to placebo in males and females, based on the duration of treatment and compliance, in studies METO-IN-002, METO-IN-003, and METO-IN-004.

Table 20: Overall Drug Exposure

Duration of Treatment / Compliance	Females		Males		All Subjects (Total)	
	Gimoti N 236	Placebo N=171	Gimoti N=82	Placebo N=54	Gimoti N=318	Placebo N=225
Duration of treatment (days)						
Mean (SD)	27.1 (6.85)	27.6 (5.63)	28.3 (4.84)	28.0 (5.09)	27.4 (6.40)	27.7 (5.50)
Median	29	29	29	29	29	29
Min, max	1, 40	1, 35	1, 43	1, 33	1, 43	1, 35
Duration of treatment - %						
>21-28 days	24	23	19	18	23	22
28 days	66	71	76	76	69	72
Diary compliance - %						
<80	36	19	25	18	33	19
>80	63	78	75	80	66	78

Abbreviations: SD=standard deviation
Source: Applicant's NDA submission, Table 3 of clinical safety summary, page 18, 6/1/2018

The overall mean duration of treatment in the pooled Gimoti studies was similar between the Gimoti and placebo patient groups. Furthermore, the mean duration of exposure was also similar between female and male subjects, ranging from 27.1 to 28.3 days across treatment groups. Over 90% of patients (92% of Gimoti and 94% of placebo) received treatment for more than 21 days, and 69% of the Gimoti group and 72% of the placebo group received treatment for more than 28 days.

Review of the individual studies showed that the exposure and compliance were lower in the Gimoti group compared to the placebo group in the phase 3 study (METO-IN-003) supportive of the proposed indication that enrolled only female patients. The drug exposure and compliance for individual studies are shown in Table 20, Table 21, and Table 22.

Study METO-IN-002

The mean duration of treatment was similar for all treatment groups, 27.3 or 27.4 days, with a range from 1 to 43 days (Table 21).

Table 21: Study METO-IN-002 - Drug Exposure

Duration of Treatment (Days)	Placebo (N=95)	Metoclopramide 10 mg (N=95)	Metoclopramide 14 mg (N=95)
Mean (SD)	27.3 (6.31)	27.4 (6.32)	27.4 (6.97)
Median	29	29	29
Min, max	1, 33	1, 37	1, 43

Abbreviation: SD standard deviation
Source: Applicant's NDA submission, Table 26 Study Drug Exposure of the CSR METO-IN-002

Study METO-IN-003

The mean duration of treatment appears similar in the placebo and 10-mg Gimoti groups (28.2 and 27.0 days respectively). However, the proportion of patients who completed at least 22 days of treatment was slightly lower in the 10-mg Gimoti group (91%) than the placebo group (97%). This was further supported by the Gimoti group's low compliance rate (79% at >80%) compared to the placebo group (89% at >80%) (Table 22).

Table 22: Study METO-IN-003 - Drug Exposure

	Placebo (N=103)	Gimoti 10 mg (N=102)
Duration of treatment days		
Mean (SD)	28.2 (4.7)	27 (7)
Median	29	29
Min, max	1, 35	1, 38
Duration - %		
1 – 7 days	3	6
≥22 days	97	91
Diary compliance - %		
<80	9	18
>80	89	79

Abbreviation: SD standard deviation
Source: Adapted from Applicant's NDA submission, Tables 11 and 23 of the CSR METO-IN-003

The duration of drug exposure/compliance was low in the Gimoti group compared to the placebo group. The lower rates in Gimoti group could possibly be related to the higher AEs (systemic and/or local; however, other possibilities include lower efficacy and/or suboptimal dosing).

There is potential for either increased or decreased absorption of drug due to changes occurring in nasal mucosa over time with repeated administrations. This product is intended to be administered QID, and because GP is a chronic condition, patients will likely take this product long-term. The clinical trials were limited to 4 weeks in duration; therefore, the effect on the nasal mucosa for longer durations is unknown.

Study METO-IN-004

The overall mean duration of treatment is similar in the placebo and 10-mg Gimoti groups (27 and 29 days, respectively). However, the proportion of patients who completed at least 22 days of treatment was higher in the 10-mg Gimoti group (100%) than the placebo group (89%). This was further supported by a numerically high compliance rate (at >75%) in Gimoti group (96%) compared to placebo (89%).

Adequacy of the Safety Database

The majority of the safety data include data from patients who received the 10-mg dose QID for 4 weeks (i.e., 2/3 of the proposed 15-mg QID dose). Therefore, the safety data from the clinical trials are not informative for the safety of the proposed 15 mg dose.

Overall, 389 patients with DG and 454 healthy volunteers received metoclopramide in the clinical development program that includes phase 1, phase 2 and phase 3 studies. Of the 389 patients with DG, 95 (70 females, 25 males) patients received the (b) (4) formulation at a dose of 14 mg QID, which is approximate but still lower than the proposed 15-mg clinical dose. Of the 454 healthy volunteers, 165 (75 females, 90 males) subjects received a single dose of ≥15 mg.

The safety data are based on 70 female patients with DG treated with Gimoti at a dose of 14 mg (lower than the proposed dose of 15 mg) administered for 4 weeks. Additionally, 23 females were treated with 20 mg, another formulation, for 6 weeks in an open-label, active-controlled trial with 10-mg Reglan oral tablet.

The data that directly compared the safety of the proposed IN formulation to the listed drug are limited. As previously noted, the proposed dose of 15-mg Gimoti QD in the application has not been evaluated for neither safety nor efficacy in any clinical trial submitted by the Applicant.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

The Applicant's process for recording, coding, and categorizing AEs appeared to be reasonable.

An AE was defined as the development of an undesirable and unintended medical condition in a patient administered study medication, whether or not considered causally related to the study drug. An AE could be a symptom (e.g., nausea, chest pain), a sign (e.g., tachycardia, enlarged liver), or an abnormal laboratory result. A TEAE was defined as an AE that began or worsened in severity after at least one dose of study drug was administered. Nontreatment-emergent AEs were the AEs that occurred prior to the first dose of study drug at Visit 4/Day 0. An adverse drug reaction was any untoward and unintended response in a subject to an investigational medicinal product which was related to any dose administered to that patient.

An SAE was defined as any AE that resulted in any of the following: death; immediate life-threatening event; persistent or significant disability or incapacity; a congenital abnormality or birth defect; required inpatient hospitalization or a prolonged existing hospitalization; and an

important medical event that could have jeopardized the subject or required medical intervention to prevent one of the outcomes listed above.

The AEs were reported spontaneously by the patients either in response to an open-ended question or as observations recorded on the appropriate electronic case report form. Any abnormal laboratory value that constituted an SAE or led to discontinuation of the study drug was recorded as an AE. The investigator evaluated each AE and reported the onset (date and time), intensity (mild, moderate, severe, or life threatening), causality (none, unlikely, possible, or probable), action taken, serious outcome (if applicable), resolution (date and time), and whether or not the AE caused the subject to be discontinued from the study.

All SAEs that occurred up to 30 days after receiving the last dose of study drug were documented and reported to the safety monitoring vendor and to the Evoke Pharma Medical Monitor as soon as possible, but no later than 24 hours of knowledge of the event. This report included all information available at the time of notification. The safety monitoring vendor and the investigator were responsible for notifying the relevant regulatory authorities of certain events. The investigator was responsible for notifying the IRB of all SAEs that occurred at his or her site.

Routine Clinical Tests

Complete blood counts with differentials and a full chemistry panel including creatinine, magnesium, aspartate aminotransferase/alanine aminotransferase, bilirubin, HbA1C, and total cholesterol were collected during the screening visits and at Day 28. Serum and urine pregnancy tests were performed for female subjects of childbearing potential at different visits, which included screening, randomization, and end of the study. A 12-lead ECG was performed at screening, randomization, and end of the study. Laboratory parameters were summarized for each treatment group using descriptive statistics at baseline and at the final visit (Day 28 or end of treatment).

8.2.4. Safety Results

Deaths

No deaths occurred during any of the three clinical trials, METO-IN-002, METO-IN-003, or METO-IN-004.

Serious Adverse Events

Study METO-IN-002

Two patients in the 14-mg Gimoti group and three patients in placebo group reported SAEs as shown in Table 23. The TEAEs of two patients in the Gimoti group included worsening of GP and acute cholecystitis, and the TEAEs of three patients in placebo group included diabetic ketoacidosis (DKA), kidney infection, and chronic obstructive pulmonary disease (COPD) exacerbation/non-cardiac chest pain (NCCP). None of these TEAEs were related to the study drug administration. In addition, one patient ((b) (6)) is not included in the list of treatment-emergent SAEs. This patient had syncope and was hospitalized after signing the informed consent but before undergoing randomization. However, he was enrolled in the IN 10-mg group 2 months later and completed the study.

Table 23: Study METO-IN-002 - SAEs

Group	Patient ID	SAE Type (Severity)	Treatment Relationship	Action Taken	Outcome
Gimoti 14 mg	(b) (6) (65 F)	Worsening of GP (severe)	None	Dose not changed	Recovered
	(41 F)	Acute cholecystitis (severe)	None	Drug withdrawn	Recovered
Placebo	(43 F)	DKA (severe)	None	Drug withdrawn	Recovered
	(43 F)	Kidney infection (mod)	None	Drug withdrawn	Recovered
	(60 F)	COPD (moderate) NCCP (mild)	None	Dose not changed	Recovered

Abbreviations: DKA diabetic ketoacidosis; COPD chronic obstructive pulmonary disease; NCCP non-cardiac chest pain; GP=gastroparesis; SAE serious adverse event
Note: The AEs in the placebo group are categorized as mild to severe in the AESEV column but all are rated as SESER column.
Source: Adapted from Table 17, and review of CFRs of the CSR METO-IN-002

For brief narratives for the SAEs see Appendix 15.4.2.

Overall, our review of the narratives provided by the Applicant and CRFs suggest that the SAEs appeared to be unrelated to the study drug administration.

Study METO-IN-003

Three patients in the Gimoti group and two patients in placebo group reported SAEs as shown in Table 24. Patients in the Gimoti group had orthostatic hypotension, cellulitis, and chalazion, and patients in the placebo group had worsening of anxiety disorder and NCCP.

Table 24: Study METO-IN-003 - SAEs

	Patient ID	SAEs	Start Day/ Stop Day	Comments	Action Taken
Gimoti	(b) (6)	Orthostatic hypotension, and hypoglycemia	6/13	Unlikely	Drug withdrawn
		Cellulitis right index finger	5/17	Unlikely	Dose not changed
		Chalazion	15/16	Unlikely	Dose not changed
Placebo		Worsening of anxiety disorder	26/27	None	Drug withdrawn
		Non-cardiac chest pain	15/17	None	Drug interrupted, continued

Abbreviations: SAE serious adverse event
Source: Adapted from Appendix 16.2.7, Listing 21 of the CSR METO-IN-003

For brief narratives of the patients with SAEs, see Appendix 15.4.2. Overall, our review of the narratives provided by the Applicant and CRFs suggest that the SAEs appeared to be unrelated to the study drug administration.

Study METO-IN-004

Two patients in the placebo group reported three SAEs of worsening of GP, inadequate diabetic control, and local infection in shin. These SAEs were considered unlikely to be related to study drug.

All SAEs resolved in 2 to 5 days (Table 25).

Table 25: Study METO-IN-004 - SAEs

	Patient ID	Start Treatment	SAEs	Start Day	Stop Day	Relationship	Action Taken
Gimoti	-		-	-		-	-
Placebo	(b) (6)	6/24/2014	Worsening of GP. Inadequate diabetic control	7/7/2014 (13/18) 7/10/2014 (16/18)	7/12/2014 7/12/2014	None	Drug withdrawn
		10/22/2014	Staphylococcal infection, left shin.	11/20/2014 (29/31)	11/22/2014	None	Drug withdrawn

Abbreviations: SAE=severe adverse event; GP=gastroparesis
Source: Adapted from section 14.3.2 and Appendix 16.2.7, listing 21 of the CSR METO-IN-004

For brief narratives of the SAEs, see Appendix 15.4.2.

Overall Summary of the SAEs

The SAEs were comparable between the treatment groups in studies METO-IN-002, METO-IN-003, and METO-IN-004 and appeared unrelated to the study drug administration:

- In study METO-IN-002, two patients in the Gimoti group were reported to have worsening of GP and acute cholecystitis, and three patients in the placebo group had DKA, kidney infection, and COPD exacerbation/NCCP. None of the TEAEs were related to the study drug administration.

- In study METO-IN-003, three patients in the 10-mg Gimoti group were reported to have orthostatic hypotension, cellulitis, and chalazion, and two patients in the placebo group were reported to have worsening of anxiety disorder and NCCP. The patient who developed orthostatic hypotension had many coexisting medical conditions and was taking several concomitant medications. It is difficult to clearly conclude that TEAE was related to the study drug; however, the study drug may have contributed to the AE of hypotension which is listed in the labeling of the listed drug.

- In study METO-IN-004, two patients in the placebo group reported SAEs of worsening GP and a local infection in shin.

Dropouts and/or Discontinuations Due to Adverse Effects

Study METO-IN-002

The patients that discontinued the Gimoti due to the AEs in the 10- and 14-mg treatment groups are listed in Table 26. Five patients discontinued from the placebo group and included 1 patient each for diabetic ketoacidosis and pneumonia, constipation, depression and 2 patients for mild prolongation of QT interval.

Table 26: Study METO-IN-002 - Discontinuations Due to Adverse Events

PT ID (Dose)	Treatment Start Date	Adverse Events (AE)	AE Start Date	AE End Date	Causality	Action Taken	Conc Illnesses, Medications
Females - Gimoti 10 mg							
METO-IN- (b) (6)	(b) (6)	Extreme drowsiness	(b) (6)	(b) (6)	Probable	Drug withdrawn	DG, HTN, IBS, GERD, high

PT ID (Dose)	Treatment Start Date	Adverse Events (AE)	AE Start Date	AE End Date	Causality	Action Taken	Conc Illnesses, Medications
		and eye discomfort (B/L)				(b) (6)	cholesterol Synthroid, Benicar, insulin, aspirin, Nexium, Lipitor
METO-IN- (b) (6)	(b) (6)	Decreased memory, tunnel vision, fatigue Unsteady gait, upper gaze nystagmus, myoclonic jerks resting tongue	(b) (6) (b) (6)	(b) (6)	Possible Probable	Drug withdrawn (b) (6)	HTN, vertigo, ulcers. Avapro, levothyroxine, glipizide, and several supplements
METO-IN- (b) (6)	(b) (6)	Flu symptoms	(b) (6)	Not recovered	None	Drug withdrawn (b) (6)	HTN, hypothyroid, MI, depression, CCF, CABG. Zetia, Crestor, Digoxin, metoprolol, Lasix, levothyroxine, amlodipine, aspirin, Avandia, allopurinol, lisinopril
METO IN- (b) (6)	(b) (6)	Anxiety (pre-existing since (b) (6) Nausea	(b) (6)	(b) (6)	Possible	Drug withdrawn (b) (6)	HTN, gout, insomnia. Losartan,/HCTZ, amlodipine, warfarin, temazepam, diazepam
Females - Gimoti 14 mg							
METO-IN- (b) (6)	(b) (6)	Elevated BP dizziness, Nausea and diarrhea	(b) (6) (b) (6)	(b) (6) (b) (6)	Possible	Drug withdrawn (b) (6)	HTN, anxiety, fatty liver, IBS, stomach ulcer Vasotec, Celexa, metformin, Provera, NTG, saline, Phenergan
METO-IN- (b) (6)	(b) (6)	Drowsiness	(b) (6)	(b) (6)	Possible	Drug withdrawn (b) (6)	HTN, high lipids, insomnia Metformin only

PT ID (Dose)	Treatment Start Date	Adverse Events (AE)	AE Start Date	AE End Date	Causality	Action Taken	Conc Illnesses, Medications
METO-IN- (b) (6)	(b) (6)	Irritability	(b) (6)	(b) (6)	Possible	Drug withdrawn (b) (6)	Ablation, IBS, GERD, AFib, depression. Insulin, Cytotec, lorazepam, metformin, Cymbalta, lisinopril, Lyrica
		Nose bleed	(b) (6)	(b) (6)			
METO-IN- (b) (6)	(b) (6)	Nose bleed and headache	(b) (6)	(b) (6)	Probable	Drug withdrawn (b) (6)	IBS, GERD, High cholesterol. Metformin, Lipitor,
METO-IN- (b) (6)	(b) (6)	Acute cholelithiasis	(b) (6)	(b) (6)	None	Drug withdrawn (b) (6)	HTN, high cholesterol, GERD, neuropathy Lisinopril, Prozac, insulin, Lasix
METO-IN- (b) (6)	(b) (6)	Numbness and tingling left arm and tachycardia, increased blood sugar	(b) (6)	Not known	Probable	Drug withdrawn (b) (6)	High lipids, HTN, hypothyroid, endometriosis, gastritis. Lipitor, Hyzaar, aspirin, Synthroid, Amaryl, Janumet
		Fatigue	(b) (6)				
Males – 10 mg							
METO-IN- (b) (6)	(b) (6)	Stomach flu	(b) (6)	(b) (6)	None	Drug withdrawn (b) (6) shown as WD but finished study.	CABG, Ca prostate, gall stones, GERD, HTN, high cholesterol, hypothyroid, Glimepiride, clopidogrel, digoxin, metoprolol, Levoxyl, simvastatin, metformin, aspirin, niacin
		Diarrhea	(b) (6)	(b) (6)			
Males – 14 mg							
METO-IN- (b) (6)	(b) (6)	Fatigue	(b) (6)	(b) (6)	Possible	Drug withdrawn (b) (6)	HTN, depression, ADHD, IBS, dyslexia, sleep

PT ID (Dose)	Treatment Start Date	Adverse Events (AE)	AE Start Date	AE End Date	Causality	Action Taken	Conc Illnesses, Medications
							apnea Cymbalta, metformin, glipizide, lisinopril
METO-IN- (b) (6)	(b) (6)	Dizziness, worsening of nausea and vomiting	(b) (6)	(b) (6)	Possible	Drug withdrawn (b) (6)	HTN, GERD, sleep apnea. Nexium, lisinopril/HCTZ, insulin, Lasix, levothyroxine

[1] Includes all events reported with possible or probable relationship to study drug
Abbreviations: B/L=bilateral; DG=diabetic gastroparesis; HTN hypertension; IBS=irritable bowel syndrome; GERD=gastroesophageal reflux disease; MI=myocardial infarction; CCF congestive cardiac failure; CABG coronary artery bypass grafting; AFib=atrial fibrillation; ADHD=Attention-Deficit/Hyperactivity Disorder; HCTZ=hydrochlorothiazide; NTG=nitroglycerin; AE=adverse event
Source: Compiled from ADAE data sets and CRFs: overview of treatment-emergent adverse events of the CSR METO-IN-002

- In the study drug (Gimoti) treatment arm, the number of female patients who were withdrawn as a result of CNS and nasal AEs (n=10) was higher than the number of male patients who were withdrawn (n=3); however, there were more female patients than males enrolled in the trial. Four and six female patients were withdrawn from the Gimoti 10- and 14-mg dose groups, respectively.

- The CNS and nasal AEs that lead to the discontinuation of Gimoti included:
  - drowsiness (n=2)
  - anxiety (n=1)
  - tingling and numbness of arm (n=1)
  - tunnel vision, fatigue, unsteady gait, upper gaze nystagmus, myoclonic jerks of resting tongue (n=1)
  - nausea/vomiting/diarrhea (n=2)
  - nose bleed (n=2)

Although tunnel vision, fatigue, unsteady gait, upper gaze nystagmus, and myoclonic jerks of resting tongue occurred in only one patient, they are significant as they may be suggestive of early involvement of the extra-pyramidal system. A majority of the AEs observed in females appear to be severe compared to the AEs in males, and they were considered probably and possibly related to Gimoti except diarrhea, flu symptoms, and acute cholecystitis. The AEs in male patients that led to the discontinuation of Gimoti included nausea/vomiting, diarrhea, and fatigue.

It is important to note that these patients had comorbid medical conditions and were taking concomitant medications. Furthermore, it is difficult to assess whether the incidence of AEs for the IN formulation is higher or comparable to the oral formulation of Reglan. The limitations for

interpreting the safety data include the small number of events and the absence of safety data for the oral formulation, which was not used as a comparator in the clinical trials. A majority of the AEs observed are listed in the labeling information of the Reglan. No new AEs were observed.

Study METO-IN-003

In this study, a higher proportion of patients in the Gimoti group discontinued drug treatment due to AEs compared to the placebo group. Eight patients discontinued the drug- six in the Gimoti group and two in placebo group (Table 27). Six patients in the 10-mg Gimoti group experienced somnolence, orthostatic hypotension, anxiety, tremor, hypoesthesia/muscle spasm, and palpitations. In two of the six patients who discontinued the drug, the AEs were considered SAE and are also listed in Table 24 for SAE. Other than the orthostatic hypotension, the TEAEs in five patients were assessed as possibly or probably related to study drug.

Table 27: Study METO-IN-003 - TEAEs Leading to Discontinuation of Study Drug and if Applicable, Study Withdrawal

Treatment	Subject ID	Preferred Term	Start Day/ Stop Day	Relationship	Study Withdrawal
Gimoti 10 mg	(b) (6)	Somnolence	½	Possible	Yes
		Orthostatic hypotension	6/13	None	Yes
		Anxiety	1/3	Probable	No
		Tremor	8/15	Possible	Yes
		Hypoesthesia/muscles spasm	1/1	Possible	Yes
		Palpitations	6/10	Probable	Yes
Placebo		Worsening of anxiety disorder	26/27	Possible	No
		Auditory hallucination	20/29	Probable	No
		Nasal discomfort	22/27	Probable	
		Epistaxis	25/25	Probable	

Abbreviations: TEAE treatment emergent adverse event
Source: Adapted from Table 29 of the CSR MET-IN-003

For brief summaries of the patients that discontinued see Appendix 15.4.3.

Study METO-IN-004

The study drug was withdrawn after 53/150 were randomized due to low enrollment. Only one patient ((b) (6)) from the placebo group developed AEs of worsening of GP and depression. The narratives for this patient is provided under the SAE section.

Significant Adverse Events

All severe AEs were also deemed as serious AEs and were discussed above.

Treatment Emergent Adverse Events and Adverse Reactions

Study METO-IN-002

Table 28 shows the overall TEAEs and TEAEs in the treatment groups compared to the placebo.

Table 28: Study METO-IN-002 - Overview of TEAEs

	All Patients		
TEAEs	Placebo (N=95)	MCP 10 mg IN (N=95)	MCP 14 mg IN (N=95)
Subjects with TEAE(s)	58%	57%	60%
TEAEs	137	120	130
Subjects with treatment-related TEAE(s)[1]	18%	38%	36%
Subjects with SAEs	3%	0	2%
Discontinuation due to TEAEs	5%	3%	8%

[1] Includes all events reported with possible or probable relationship to study drug
Abbreviations: TEAE treatment emergent adverse event; SAE serious adverse event; MCP=metoclopramide; IN=intranasal
Source: CRFs and Table 12, overview of treatment-emergent adverse events of the CSR METO-IN-002

Table 29 shows the TEAEs observed in female and male subjects.

Table 29: Study METO-IN-002 - Overview of TEAEs by Sex

	Females			Males		
TEAEs	Placebo (N=68)	MCP 10 mg IN (N=64)	MCP 14 mg IN (N=70)	Placebo (N=27)	MCP 10 mg IN (N=31)	MCP 14 mg IN (N=25)
Subjects with TEAE(s) (%)	62	56	60	41	68	68
TEAEs	113	82	95	25	48	40
Subjects with treatment related TEAE(s)[1] (%)	22	34	30	7	45	56
Subjects with SAEs (%)	4	0	3	0	0	0
Discontinuation due to TEAEs (%)	6	6	9	0	3	8
TEAE of special interest (%)						
Central nervous system disorders	18	27	31	0	32	44
Psychiatric disorders	4.5	6	0	0	6	4
Cardiovascular disorders	7	3	3	0	3	4
Nasal events	4.5	6	9	0	13	16

[1] Includes all events reported with possible or probable relationship to study drug
Abbreviations: TEAE treatment emergent adverse event; SAE serious adverse event; MCP=metoclopramide; IN=intranasal
Source: Compiled from ADAE data sets: overview of treatment-emergent adverse events of the CSR METO-IN-002

- The overall TEAEs appeared similar for placebo, 10-mg, and 14-mg groups (57%, 58%, and 60%, respectively; Table 28). However, subgroup analysis based on sex showed that male patients had more TEAEs as well as treatment-related AEs at both 10-mg and 14-mg doses. The reason(s) for numerically higher TEAEs and treatment-related AEs in male patients are unclear.

- The TEAEs related to the CNS were higher in both dose arms compared to placebo, and higher in the 14-mg group than in the 10-mg treatment group for females. The TEAEs related to the CNS in males were higher than those in females at the 10-mg dose but similar at 14-mg dose. Similar observation was made for the nasal AEs. The special interest AEs related to psychiatry and the cardiovascular system were few and appeared to be similar between the two groups.

- Three female patients in the 14-mg group had SAE compared to none in the male group.

Study METO-IN-003

Table 30 shows the proportion of patients with TEAEs, SAEs, TEAEs leading to discontinuation and AEs of special interest.

Table 30: Study METO-IN-003 - Overall Percentage of Subjects Reporting TEAEs

	All Patients	
TEAEs	**Placebo (N=103)**	**Gimoti 10 mg IN (N=102)**
Subjects with TEAE(s) (%)	35	36
TEAEs	79	80
Subjects with treatment-related TEAE(s)[1] (%)	20	17
Serious TEAE[2] (%)	2	3
TEAE with outcome of death	0	0
TEAE leading to study drug withdrawal (%)	0	5
TEAE of special interest		
Central nervous system disorders (%)	15	11
Psychiatric disorders (%)	3	4
Cardiovascular disorders (%)	0	5
Nasal event (%)	18	8

[1] Includes all events reported as Possible or Probable or with missing relationship to study drug
[2] Includes all events identified as serious by the Investigator based on the protocol-specified definition
Abbreviations: TEAE treatment emergent adverse event; IN intranasal
Source: Table 24-Overall summary of number and percentage of subjects reporting treatment-emergent adverse events (safety population) CSR METO-IN-003 and AE data sets

Overall, TEAEs, including special interest AEs, were similar in the placebo and IN 10-mg groups except the nasal events, which were higher in the placebo group compared to the 10-mg Gimoti group. However, a higher proportion of patients in the Gimoti group discontinued due to TEAEs than those in the placebo group.

Study METO-IN-004

Table 31 shows proportion of patients who experienced TEAEs and AEs of special interest in METO-IN-004.

Table 31: Study METO-IN-004 - Overall Percentage of Subjects Reporting TEAEs

	All Patients	
TEAEs	**Placebo (N=27)**	**Gimoti 10 mg IN (N=26)**
Subjects with TEAE(s), n (%)	8 (30)	7 (27)
TEAEs	25	11
Subjects with treatment-related TEAE(s), n (%)	1 (4)	2 (8)
Serious TEAE, n (%)	2 (7)	0
TEAE with outcome of death	-	-
TEAE leading to study drug withdrawal, n (%)	1 (3.5)	0
TEAE of special interest (%)		
Central nervous system disorders.	4	0
Psychiatric disorders	4	0
Cardiovascular disorders	4	0
Nasal and oropharyngeal events	11	8

Abbreviations: TEAE treatment emergent adverse event; IN intranasal
Source: Compiled from the ADAE datasets of CSR METO-IN-004

Study METO-IN-004 was discontinued due to low enrollment and randomized only 53 of the 153 planned patients. Limited safety assessment shows that overall TEAEs appear to be similar in the two treatment groups. However, it should be noted that a number of TEAEs, including special interest AEs, are small and therefore are difficult to make meaningful comparisons between the two treatment groups.

8.2.4.1. Adverse AEs of Special Interest

Special interest AEs including CNS, psychiatric, cardiovascular and nasal categories are presented for each treatment group using clinical relevant PT for study METO-IN-002, METO-IN-003, and METO-IN-004.

Study METO-IN-002

Table 32 show the TEAEs of special interest categories as per SOC and PT in study METO-IN-002.

Table 32: Study METO-IN-002 - AEs of Special Interest Categories as per SOC and PT

	Placebo		Meto 10 mg		Meto 14 mg	
System Organ Class/ Preferred Term	**Males (N=27) %**	**Females (N=68) %**	**Males (N=31) %**	**Females (N=64) %**	**Males (N=25) %**	**Females (N=70) %**
Subjects reporting at least one adverse event/events (%)	41	62	68	52	68	57
Nervous system disorders (%)	0	18	32	27	44	31
Dysgeusia	0	6	13	12	28	10
Headache/tension headache	0	6	10	6	8	11.5
Fatigue	0	4.5	6	6	8	6
Dizziness, syncope, lightheadedness	0	3	6	6	8	1.5
Somnolence/sedation	0	0	3	1.5	0	4
Tremor, shakiness, irritability	0	0	0	0	0	4
Carpal tunnel syndrome	0	1.5	0	0	0	0
Cervicobrachial syndrome	0	1.5	0	0	0	0
Facial palsy	0	0	0	0	0	1.5
Loss of consciousness	0	1.5	0	0	0	0
Inability to focus, and jitteriness, and disturbance attention (070-01)	0	0	0	1.5	0	0
Myoclonus jerking tongue, upper gaze nystagmus, unsteady tandem gait, tunnel vision, memory impairment, and right thumb weakness (All in 1 patient: (020-09)	0	0	0	1.5	0	0
Numbness/tingling left arm	0	0	0	0	0	1.5
Restless legs syndrome	0	0	0	1.5	0	0
Burning sensation cheek	0	1.5	0	0	0	0
Psychiatric disorders	0	4.5	3	6	4	0
Anxiety/depression	0	3	0	3	4	0
Depression	0	1.5	0	0	0	0
Insomnia	0	0	3	1.5	0	0
Depressed mood	0	0	0	1.5	0	0

System Organ Class/ Preferred Term	Placebo		Meto 10 mg		Meto 14 mg	
	Males (N=27) %	Females (N=68) %	Males (N=31) %	Females (N=64) %	Males (N=25) %	Females (N=70) %
Nasal and oropharyngeal	11	18	19	11	32	17
Nasal	0	4.5	13	6	16	9
Nasal soreness, burning, irritation, bleeding, sensitivity, desquamation	0	4.5	0	6	16	9
Oropharyngeal	11	14	6	5	16	10
Cough	0	3		0	0	4
Dry throat, mouth	4	0	3	3	0	3
Pharyngitis, URTI, sore throat	4	9	3	0	12	1.5
Bronchitis, hoarseness		1.5	0	0	0	0
Acute sinusitis, sinus pressure, infection, post nasal drip	7	3	0	0	0	3
Worsening of seasonal allergies	0	4.5	0	0	0	0
Sneezing	0	0	0	0	0	0
Ear ache, TM injection	0	0	0	1.5	4	1.5
Cardiovascular disorders	0	7	3	3	4	3
Tachycardia, supraventricular bigeminy	0	3.5	0	0	0	1.5
Bradycardia	0	0	0	1.5	0	0
Palpitations	0	0	0	0	4	0
Ventricular extrasystoles	0	0	3	0	0	0
Prolonged QT	0	3.5	0	1.5	0	0
Hypertension	0	1.5	0	0	0	1.5

Abbreviations: URTI=upper respiratory tract infection; TM=tympanic membrane
Source: Compiled from the ADAE data sets of the CSR METO-IN-002

- CNS related AEs: The TEAEs related to the CNS occurred in 44% at 10 mg and 31% at 14 mg in males compared to 27% in males in the placebo group. There were 18% at 10 mg and 32% at 14 mg in females compared to 0% in females in the placebo group. The most common TEAEs were:
  - Dysgeusia (bad, metallic, or bitter taste): AEs of dysgeusia in males were comparable to female patients at the 10-mg dose (13% vs. 12%) and numerically higher at the 14-mg dose (28% vs. 10%) compared to the placebo (0% vs. 6%).
  - Headache: AEs of headache in males were comparable to female patients at the 10-mg dose (10% vs. 6%) and 14-mg dose (8% vs. 12%) compared to the placebo (0% vs. 6%).
  - Fatigue: AEs of fatigue in males were comparable to female patients at the 10-mg dose (6% vs. 6%) and the 14-mg dose (8% vs. 6%) compared to the placebo (0% vs 4.5%).
- AEs suggestive of EPS, a labeled adverse reaction of metoclopramide, were noted in four female patients who only received Gimoti. Two patients who developed symptoms suggestive of EPS at the 10-mg dose were:
  - Patient (b) (6): Patient with past medical h/o HTN, vertigo and ulcers taking concomitant medications of levothyroxine, glipizide, Avapro, and several supplements was started on study drug (Gimoti) on (b) (6) and developed decreased memory, tunnel vision, and fatigue on the same day. The study drug was

continued, and patients developed unsteady gait, upper gaze nystagmus, and myoclonic jerks resting tongue on (b) (6) when the study drug was discontinued. The AEs were considered possibly and probably related to the study drug.

- Patient (b) (6): Patient with past medical h/o high lipids, B12 deficiency, and GERD taking the following concomitant medications: Insulin, Prevacid, Zoloft, aspirin, Altace, Crestor, Singulair was started on study drug (Gimoti) on (b) (6). AEs of jitteriness, restlessness, anxiety, and inability to focus/concentrate were reported from (b) (6). The dose was reduced, and patient completed the study.
- Two patients reported AEs of shakiness/tremors at 14-mg dose.

- Nasal and oropharyngeal AEs: The TEAEs related to the nasal administration in males were higher than those in females at the 10-mg dose (13% vs 6%) as well as 14-mg dose (16% vs 9%) compared to the placebo (0% vs 4.5%).

- The special interest AEs related to psychiatry and cardiovascular system were few and appeared to be similar between males and females in all the groups.

Study METO-IN-003

Table 33 shows the TEAEs of special interest categories as per SOC and PT in Study METO-IN-003.

Table 33: Study METO-IN-003 - AEs of Special Interest Categories as per SOC and PT

	All Patients	
TEAE of Special Interest Category	**Placebo IN (N=103)**	**Gimoti 10 mg IN (N=102)**
SOC/Preferred Term	**Events/No. of Patients**	**Events/No. of Patients**
Nervous system disorders	18/16	26/11
Headache/occipital headache	9/7	8/5
Muscle twitching	1/1	3/2
Numbness, numbness of the tongue, numbness around mouth, fingers	2/2	3/3
Nausea	0	5/1*
Fatigue	1/1	2/2
Burning sensation in arms B/L	1/1	0
Dizziness, syncope	2/2	0
Sleepiness	0	1
Dysarthria	0	1
Generalized muscle cramps	0	1
Tremor rt leg	0	1
Worsening of diabetic neuropathy	1/1	1
Right hand grip weaker than left	1/1	0
Psychiatric disorders	4/3	4/4
Anxiety, worsening of anxiety disorder	2/1	1
Depression	1/1	0
Auditory hallucination	1/1	0
Insomnia	0	1
Panic attack	0	1
Restlessness	0	1

TEAE of Special Interest Category SOC/Preferred Term	All Patients	
	Placebo IN (N=103)	Gimoti 10 mg IN (N=102)
	Events/No. of Patients	Events/No. of Patients
Nasal and oropharyngeal	26/18	14/8
Nasal	9/6	4/3
Nasal soreness, burning, irritation, bleeding, sensitivity, desquamation	9/6	4/3
Oropharyngeal	17/12	10/5
Cough	4/4	1/1
Dry throat, mouth	2/2	1/1
Pharyngitis, URTI, post nasal drip, sore throat	5/5	44
Bronchitis, hoarseness	2/2	1/1
Acute sinusitis, sinus pressure, infection,	3/3	1/1
Sneezing	1/1	0
Ear ache	-	2/2
Cardiovascular disorders	1/1	6/5
Possible anterior infarct	1/1	0
Palpitations	0	1
ECG PR prolongation	0	1
Worsening hypertension	0	1
Orthostatic hypotension	0	2/1
Worsening chest pain	0	1

Abbreviations: IN intranasal; TEAE treatment emergent adverse event; SOC=system organ class; URTI upper respiratory tract infection; B/L Bilateral; ECG=electrocardiogram

Note: One patient could have more than one AE. * one patient had 5 events of nausea

METO-IN-003 (b) (6): This patient has been listed at 2 places: muscles twitching and dysarthria (Gimoti group)
METO-IN-003 : Listed at 2 places for gen muscle cramps and numbness
METO-IN-003 : Listed at 2 places for syncopal event (Neuro AE) and worsening of AD (Psych AE)
METO-IN-003 : Patient has 3 AEs numbness AE (neuro), audio hallucination (Psych), and AE nasal soreness and bleeding (nasal)
METO-IN-003 : Patient has AE at 2 places: burning sensations arms (Neuro) and AE burning sensation nose (Nasal)

Source: Compiled from the ADAE data set of the CSR METO-IN-003. Note: Some patient had ≥1 AEs

AEs related to the special interest by SOC and PT (CNS, psychiatry, cardiovascular and nasal AE related to the local spray of the study drug) are summarized below:

- **CNS-Related AEs:** Although overall the CNS AEs appear to be similar between the two treatment groups (i.e., placebo and Gimoti 10 mg (16% vs 11%)), it is noteworthy that CNS AEs that could have been associated with extrapyramidal system (muscle twitching (n=1), dysarthria (n 1), muscles cramps (n=1), and tremors (n=1)) were observed in the Gimoti group and not in the placebo group. CRF reviews showed that these AEs were transient, and the study drug was continued except in one patient ((b) (6)) who developed generalized muscle cramps and numbness 1 day after the start of the study drug. The study drug was withdrawn the same day and AEs resolved.

- **Psychiatric AEs:** There were 4% psychiatry-related AEs in the Gimoti group (insomnia, panic attack, anxiety, and restlessness compared to 3% of such AEs in the placebo group (anxiety disorder, depression, and auditory hallucinations). As per CRFs, the three patients in the placebo group had preexisting psychiatric illnesses and were on psychiatric medications. The AEs observed in three patients in the Gimoti group are summarized:
  - (b) (6): Patient had no previous h/o psychiatric illness, had an episode of anxiety for 1 day; study drug was continued.

- [redacted]: Patient started study drug on July 30, 2014 and developed AE of worsening depression on [redacted]. Patient was already taking Cymbalta, trazodone, Lyrica, and Klonopin. Completed study on [redacted]
- [redacted]: Patients was started on study drug on [redacted] developed AE between [redacted], had h/o anxiety/depression and was taking citalopram. Completed the study on [redacted]

It appears most of the patients in Gimoti group also had preexisting psychiatric illness and were taking antipsychiatric medication. The AEs observed do not appear to be related to Gimoti; however, the possibility of aggravation of the preexisting illness as a result of the study drug cannot be ruled out with certainty.

- **Cardiovascular AEs:** The number of cardiovascular AEs (5%) observed was higher in the Gimoti group than in the placebo group (1%). Majority of the patients with AEs had preexisting medical conditions such as HTN, hyperlipidemia, anxiety, hypothyroidism and were receiving concomitant medications; the study drug was continued except in one patient. Patient ([redacted]) developed palpitations 3 days after starting the study drug, continued for next 3 days when the study drug was withdrawn. The AE resolved next day after discontinuing the study drug.

- **Nasal and oropharyngeal AEs:** The number of nasal AEs observed was higher in the placebo group (6%) than in the Gimoti group (3%).

Study METO-IN-004

Table 34 shows the TEAEs of special interest categories as per SOC and PT in study METO-IN-004.

Table 34: Study METO-IN-004 - AEs of Special Interest Categories as per SOC and PT

	All Patients	
TEAE of Special Interest Category SOC/Preferred Term	**Placebo IN (N=27) (%)**	**Gimoti 10 mg IN (N=26) (%)**
Nervous system disorders	4%	0
Headache/occipital headache	4%	0
Psychiatric disorders	4%	0
Depression	4%	0
Nasal and oropharyngeal	11%	7.5%
Nasal		
Nasal soreness, burning, irritation, bleeding, sensitivity, desquamation	4%	3.5%
Oropharyngeal	11%	3.5%
Pharyngitis, URTI, post nasal drip, sore throat	11%	3.5%
Cardiovascular disorders	4%	0
Worsening hypertension	4%	0

Abbreviations: TEAE=treatment emergent adverse events; SOC system organ class; IN intranasal; URTI upper respiratory tract infection
Source: Compiled from the ADAE datasets of CSR METO-IN-004

No patient in the Gimoti group was observed to have CNS or cardiovascular-related AEs. The number of nasal AEs was comparable between the two treatment groups (one patient in each

group). No trend on the TEAEs related to the treatment arms was observed in this study, although this analysis was limited by the small number of events and the total number of patients.

AEs for Other Systems as per SOC and PT

Other common AEs (other than AEs of special) are summarized in Appendix 15.4.4.

Study METO-IN-002

The most common TEAE was diarrhea. The proportion of patients with an AE of diarrhea was similar between male and female patients in the 10-mg (3% vs. 3%) and 14-mg (4% vs. 3%) Gimoti groups compared to the placebo group (11% vs. 10%). There were very few instances of other AEs per PT and no trend or causality could be ascertained based on the temporal or plausibility basis.

Study METO-IN-003

The most common TEAE was diarrhea, which was reported in 4% of patients in the Gimoti group and was not reported in the placebo group. No trend or causality could be ascertained based on the small number of AEs for the PTs.

Study METO-IN-004

The most common AE was diarrhea; 4% of the patients in the Gimoti group had diarrhea and nausea/heart burn/bloating compared to none in the placebo group. There were very few instances of other AEs per PT and no trend or causality could be ascertained based on the temporal or plausibility basis.

Laboratory Findings

The pooled analysis of safety data from studies METO-IN-002, METO-IN-003, and METO-IN-004 did not show clinically meaningful changes in the post baseline vitals, hematology (CBC) and biochemistry (aspartate aminotransferase/alanine aminotransferase, BUN, creatinine, sodium, potassium, and glucose) results at Day 28/early termination compared to the baseline.

Electrocardiograms

Machine-read ECG interpretations were performed at screening, predose, 1–1.5 hrs and 2.5 hrs postdose, and Day 28/early termination in Studies METO-IN-002, METO-IN-003, and METO-IN-004. In addition, centrally read ECGs were also performed for the study METO-IN-003.

Study METO-IN-002

No patient had a shift in ECG evaluation from normal at baseline to abnormal and clinically significant change during postdose period. A shift from abnormal and not clinically significant at baseline to abnormal and clinically significant ECG was reported in two patients in the placebo group 1-hour postdose and one patient in the 10-mg Gimoti group at Day 28. One patient in the Gimoti group was observed to have abnormal but not clinically significant ECG findings at each

of the study assessments including baseline. Some of the relevant information for the four patients is summarized below:

- A 39-year-old female (Patient: (b) (6)), in the placebo group, had an ECG reported as "Normal sinus rhythm, possible left atrial enlargement, prolonged QT (QTcB (QTc interval corrected using Bazett's formula) 465 ms)."The AE of prolonged QT was considered mild and not related to the study drug. The subject was withdrawn due to prolonged QTc interval, and the event resolved.

- A 63-year-old female (Patient: (b) (6)) in the placebo group, had an ECG reported as QTc prolonged, at 1-hour postdose. Prolonged QTc was considered moderate and probably related to the study drug. The subject was withdrawn due to prolonged QTc interval, and the event resolved.

- A 53-year-old male (Patient: (b) (6)) in the 10-mg Gimoti group had an ECG reported as premature ventricular complexes on Day 28 which was considered mild and possibly related to the study drug. The event was ongoing at the last follow-up.

- A 64-years-old female (Patient: (b) (6)) in the Gimoti group was observed to have abnormal but not clinically significant ECG findings at each of the study assessment; however, prolonged QTc was observed at Day 28 which was considered mild and possibly related to the study drug. The patient had completed the study, although the TEAE was ongoing at the last follow-up.

Overall, no safety signal related to the ECG findings were observed; the ECG results were generally similar between the Gimoti and placebo groups.

Study METO-IN-003

Observed changes in QTc, heart rate, PR interval, and QRS interval were small and consistent with spontaneous variation. Outlier values and abnormal ECG diagnostic statements were similar in frequency and distribution in the Gimoti 10 mg and placebo groups. These are summarized below:

- QTcF: The proportion of frequencies where QTcF exceeded 450 ms were similar in the Gimoti and placebo groups (4.9% and 5.9%, respectively), and the on-treatment frequencies were similar to predose, for both groups. The QTcF was >480 (and ≤500 ms) in one instance in the placebo group predose and in one instance in the 10-mg Gimoti group on Day 28. There was a single instance of a QTcF >500 ms observed. However, AE occurred predose in the 10-mg Gimoti group and was due to an error in calculating heart rate (which was actually 73 and not 147 used for calculation). After correction, the actual QTcF value was 460 ms rather than the recorded 580 ms.

- Heart rate: One patient in the Gimoti group had HR >100 bpm with at least 25% increase from the baseline on Day 28; no patient in the placebo group showed an increase in heart rate.

- PR interval: One instance of PR >200 ms with a 25% increase from baseline on Day 0, and two instances on Day 28 were reported in the 10-mg Gimoti group compared to no patient in the placebo group.

- QRS interval: One patient in the placebo group had QRS interval exceeding 110 ms with a ≥25% increase from baseline in the placebo group compared to no patient in the Gimoti group.

One patient (Patient (b) (6)) had PR prolongation starting at 1.5 hours after the first dose of 10-mg Gimoti on Day 0 (PR 259 ms predose, 266 ms 1.5 hours postdose, and 270 ms 2.5 hours postdose). The ECG assessments were abnormal and not clinically significant on Day 0 (at the time of randomization), abnormal and clinically significant on Day 14 (unscheduled visit), and abnormal and not clinically significant on Day 29 (Day 28/end of treatment). All ECG interpretations showed sinus rhythm with first-degree atrioventricular block. The TEAE of PR prolongation was assessed as moderate, and it was not recovered/not resolved at the end of the study.

Study METO-IN-004

All ECG interpretations were assessed as normal or abnormal and not clinically significant.

QT Study

Study METO-IN-005 was a randomized, double blind, double dummy, 4-period cross over, thorough ECG study conducted in healthy male and female volunteers to evaluate ECG effects of metoclopramide nasal spray using a clinical and supra-therapeutic Gimoti dose compared with placebo and moxifloxacin (positive control).

The study did not show any significant QTc prolongation effect of metoclopramide at a therapeutic (20-mg) or a supra-therapeutic (80-mg) dose. The largest upper bounds of the two-sided 90% CI for the mean difference between metoclopramide (20 mg and 80 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in International Council for Harmonisation E14 guidelines. The active comparator, moxifloxacin, was demonstrated to be adequate for comparison.

For details please see review by the Interdisciplinary Review Team for QT Studies, under IND 025512, dated June 23, 2016.

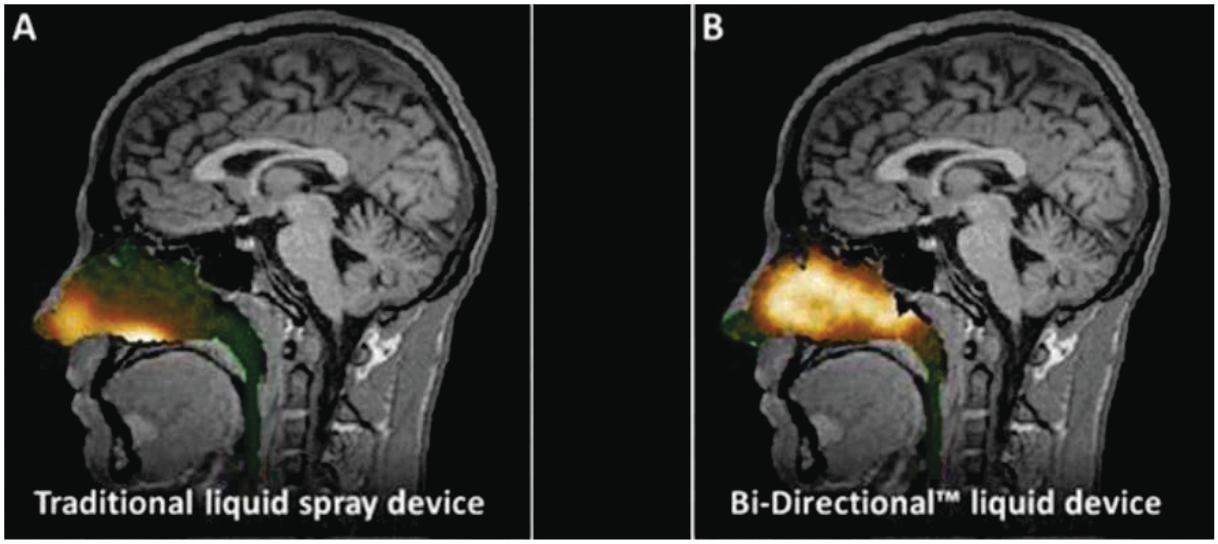
Analysis of Submission-Specific Safety Issues

There is a theoretical concern for increased CNS toxicity, including TD, in patients administered IN Gimoti given the IN route of administration. The Applicant submitted a rationale based on the droplet size of the nasal spray and local distribution to support that Gimoti nasal spray is unlikely to cause higher CNS toxicity. The Applicant states that based on the droplet size of the Gimoti spray, (b) (4)% of the spray volume is distributed in the range of (b) (4) µm with a median droplet size of (b) (4); thus, the majority of the spray consists of large droplets which facilitate local deposition. However, there is a possibility of smaller size droplets being inhaled up in the nose beyond the squamous lined lower intended anterior region of the nasal cavity.

While the Applicant did not directly evaluate the drug distribution within the nasal cavity for their formulation, they compared the drug distributions from two different (traditional and bi-directional) IN spray devices (Figure 2). Based on an illustration of the traditional spray pump similar to (b) (4) used in the clinical trials, the Applicant states that approximately 83% of the Gimoti dose will be deposited in the front and along the floor of the nasal cavity. The Applicant states the (b) (4) nasal spray pump is a traditional or conventional liquid spray device designed to deliver very small (microliter) volumes to the lower anterior regions of the nose; also, the relatively wide plume angle of the mist reduces the distance that the drug particles travel and causes the drug to impact the sides of the nose. Therefore, there is minimal risk of drug reaching the olfactory area and traversing directly to the brain. These conventional spray pumps have been used in many marketed nasal spray products, including Flonase®.

It is noted that the Applicant has not performed the drug distribution for the study drug (Gimoti). Even with the supportive information, up to 17% of the drug may not be absorbed in the lower portions of the nose, and there is a potential for getting absorbed proximally and reaching brain or systemic circulation, bypassing first-pass metabolism, and achieving higher concentration in the CNS.

Figure 2: Gamma Camera Image Information of Drug Distribution From the Nasal Cavity



The Gamma camera image information (logarithmic "hot iron" intensity scale) from the nasal cavity is superimposed on the corresponding sagittal MRI section. The images are from the same subject and present deposition 2 minutes after delivery using (A) a traditional liquid spray and (B) the breath-powered Bi-Directional™ liquid spray device incorporating the same spray pump as used in A.
Source: Applicant's clarification response submission dated 12/04/2017, pg. 8

There is a theoretical concern that direct absorption of Gimoti through the nasal mucosa to the CNS may result in higher CNS AEs, including TD. TD is a rare adverse reaction that is not expected to occur with short-term use; therefore, the duration of the clinical trials would not have detected this event. The other factors that are likely to play a role in higher absorption to the CNS include drug characteristics and other routes of absorption in the nasal cavity. The higher direct absorption may occur through venous drainage, lymphatics, olfactory/trigeminal nerves and cribriform plate. It is likely that a combination of these pathways is responsible, although one pathway may predominate depending on the properties of the therapeutic, the characteristics

of the formulation, and the delivery device used.

An adequate assessment of safety for the proposed IN formulation is therefore an important issue, especially given that metoclopramide labeling already carries warnings regarding CNS AEs.

8.2.5. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

N/A

8.2.6. Safety Analyses by Demographic Subgroups

Majority of the patient population in the pivotal METO-IN-003 study (females only) were less than 65 years old and white Caucasian. Overall, 78/205 (38%) patients developed TEAEs: Gimoti 38 (37%) and placebo 40 (36%). Safety analyses based on the age and race are summarized (Table 35):

- Age: Incidence of patients experiencing ≥1 TEAEs was similar between patients aged <65 years and ≥65 years in the Gimoti (37% and 40% respectively) and placebo groups (39% and 38% respectively).

- Race: The number of patients experiencing ≥1 TEAEs was lower among African American patients in both the Gimoti and the placebo groups (27% and 25% respectively) than among white Caucasian patients (42% and 40%). However, it should be noted that number of African American patients was smaller, and it may be difficult to draw a firm conclusion regarding lower incidence of TEAEs in African American patients.

Table 35: Incidence of TEAEs as per Age and Race

	Age			
	<65 years		≥65 years	
Number of patients	Gimoti (87)	Placebo (90)	Gimoti (15)	Placebo (13)
TEAEs: number of patients, (%)	32/87 (37)	35/90 (39)	6/15 (40)	5/13 (38)
	Race			
	White Caucasians		African Americans	
Number of patients	Gimoti (62)	Placebo (79)	Gimoti (37)	Placebo (20)
TEAEs: number of patients, (%)	26/62 (42)	32/79 (40)	10/37 (27)	5/20 (25)

Abbreviations: TEAE treatment emergent adverse event
Note: Study METO-IN-003 included very few patients (3 in Gimoti and 4 in placebo group) of other races (i.e. Asian, American Indians, multiple).
Source: compiled from the demographic and AEs datasets

8.2.7. Specific Safety Studies/Clinical Trials

N/A

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

N/A

Human Reproduction and Pregnancy

N/A

Pediatrics and Assessment of Effects on Growth

N/A

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The approved label for Reglan (metoclopramide) includes the following information about overdose:

- Manifestations of metoclopramide overdosage included drowsiness, disorientation, extrapyramidal reactions, other adverse reactions associated with metoclopramide use (including, e.g., methemoglobinemia), and sometimes death. Neuroleptic malignant syndrome (NMS) has been reported in association with metoclopramide overdose and concomitant treatment with another drug associated with NMS.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

N/A

Expectations on Safety in the Postmarket Setting

N/A

8.2.10. Integrated Assessment of Safety

Safety assessments were performed in one phase 2b (METO-IN-002) and two phase 3 (METO-IN-003 and METO-IN-004) studies. Additional supportive safety assessment from study 25,512-302R, conducted by the previous sponsor using a different formulation was also reviewed. Since different doses were used and none of those doses were the proposed 15-mg dose, a pooled safety analysis across studies does not provide meaningful or useful information, and therefore, we did not perform an integrated analysis.

8.3. Conclusions and Recommendations

There were no deaths in any of the clinical trials. The proportion of patients that developed SAEs were generally similar between the treatment groups. Most of the AEs were observed in the CNS category and were considered probably and possibly related to the administration of Gimoti; a more females discontinued the study drug than males did in the Gimoti treatment groups.

AEs suggestive of EPS, a labeled side effect of metoclopramide (listed drug), were noted in the Gimoti IN clinical trials:

- In study METO-IN-002, AEs suggestive of EPS included tremor in two patients, myoclonus, nystagmus, and tunnel vision in one patient, and jitteriness, restlessness, anxiety, and inability to focus/concentrate in one patient. All four patients were in the Gimoti groups.

- In study METO-IN-003 (conducted in only female patients), EPS-like symptoms including dystonia (n=2), dysarthria (n=1), tremor (n=1), and restlessness (n=1) were noted in the Gimoti group.

- TD was not observed in any trial; however, the risk of developing TD is typically associated with longer use (i.e., >12 weeks). It appears that EPS-related symptoms occurred infrequently; however, the number of subjects assessed was small, and the relationship of the reported events to the drug, dose, duration, or route of administration could not be readily discerned from the available data.

AEs suggestive of cardiovascular and GI system were numerically higher in the Gimoti group than in the placebo group. However, the QT study revealed no problems with prolongation of the QT-interval. The nasal AEs were observed more often in the placebo group than in the Gimoti group, and more often in male patients than female patients.

The most common TEAE not related to the special interest group was diarrhea. The incidence of diarrhea was similar among male and female patients treated with Gimoti but lower than the placebo group in study METO-IN-002. However, in studies METO-IN-003 and METO-IN-004, diarrhea was reported in a higher proportion of patients in the Gimoti group than in the placebo group. Other TEAEs as per PT were observed in only one or two patients in different treatment groups, and no trend or causality could be ascertained based on the temporal or plausibility basis due to a small number of events.

While most of the AEs observed during the clinical trials for IN Gimoti are listed in the labeling information of Reglan tablets, there are several limitations that preclude applying the safety profile from the clinical trials to the currently proposed labeling:

- The clinical studies were conducted using the lower doses of Gimoti (10 and 14 mg QD) compared to the proposed dose of 15 mg QD.

- Both the risk of developing TD and the likelihood that TD becomes irreversible increase with duration of treatment and total cumulative dose. Since Gimoti is likely to be used off label for longer than the duration of conducted clinical trials (4 weeks), clinical trials with longer duration are needed to address the incidence/occurrence of potential neurological AEs including TD.

- The incidence rates of AEs with Gimoti compared to Reglan cannot be compared as the supportive clinical trials did not include Reglan as an active comparator. The safety data

based on oral administration of metoclopramide could have addressed the concern regarding potentially higher CNS toxicity due to the drug characteristics and nasal mode of administration. The concern is based on the theoretical possibility of drug reaching the brain directly at higher concentration through the venous drainage of nasal portion to the cavernous sinus, olfactory nerve, and through cribriform plate.

9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held for this application.

10 Pediatrics

The agreed initial pediatric study plan, dated July 24, 2015, submitted under IND 25512 includes a request for a full waiver based on studies being impossible or highly impracticable because the number of pediatric patients with DG is very small (section 505B(a)(4)(A)(i) of the Act).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The substantial review issues identified during the review precluded finalization of the label.

12 Risk Evaluation and Mitigation Strategies

No recommendations can be made at this time because of the CR recommendation.

13 Postmarketing Requirements and Commitment

No recommendations can be made at this time because of the CR recommendation

14 Deputy Division Director (DGIEP) Comments (Designated Signatory Authority)

I concur with the reviewers' recommendation for a Complete Response action for this 505(b)(2) new drug application. The Study METO-IN-006 failed to establish a pharmaco-kinetic bridge

between the Gimoti 15 mg dose and the Reglan tablet 10 mg dose and is not sufficient to justify reliance on the finding of efficacy for Reglan to assure comparable safety and efficacy between Gimoti and Reglan. The clinical trials do not support effectiveness of Gimoti at the propose dose. Additional deficiencies were identified regarding the quality information submitted. Refer to the letter for listing of deficiencies and recommendations to address the deficiencies.

15 Appendices

15.1. References

See footnotes in Section 2 and Section 8.

15.2. Financial Disclosure

The Applicant provided the list of clinical investigators who conducted the clinical trials METO-IN-002, METO-IN-003, METO-IN-004 and METO-IN-006 and Form FDA 3454. Financial disclosure documents were obtained from all the investigators and subinvestigators.

It was stated that the Applicant, Evoke Pharma, did not enter into any financial arrangements with the listed clinical investigators or subinvestigators whereby the value of compensation to the investigator would be affected by the outcome of the study, as defined in 21 CFR 54.2(a). No clinical investigator or subinvestigator disclosed any proprietary interest in the aforementioned studies or significant equity in Evoke Pharma as defined in 21 CFT 54.2(b). In addition, no listed investigator was the recipient of significant payments of other sorts, as defined in 21 CFR 54.2(f), for these clinical studies. The Applicant also stated that none of the clinical investigators were employees (full-time or part-time) of Applicant.

Covered Clinical Study (Name and/or Number): METO-IN-002, METO-IN-003, METO-IN-004 and METO-IN-006.

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 111		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: None Significant payments of other sorts: None Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in S Sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Not Applicable	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Not Applicable	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Not Applicable	No ☐ (Request explanation from Applicant)

15.3. Additional Clinical Outcome Assessment Analyses

Refer to consult review by the clinical outcome assessment team, dated March 25, 2019.
This submission included a patient reported outcome (PRO) evidence dossier and study synopsis. We consulted the clinical outcome assessment (COA) staff for input on the appropriateness of the GSA used in the phase 3 trial METO-IN-003. In summary, the consult review concludes that the evidence submitted by the applicant is sufficient to demonstrate that the GSA is fit-for-purpose to measure severity of gastroparesis symptoms in the context of use. However, it is unknown what is the threshold of clinical meaningful within patient change in GSA scores due to the limitations of the anchor scales included by the sponsor and it is unknown whether the improvement shown in the post hoc analysis of a subgroup of patients with GSA score >2.7 is clinically meaningful.

Previous COA Reviews:

- AT 2011-070_Miskala dated November 15, 2011 (DARRTS Reference ID: 3042751)
- AT 2016-237_IND 025512_Daniels (DARRTS Reference ID: 4034017)

15.4. Clinical Safety Assessment

15.4.1. Summary of Supportive Safety Information

The Applicant has also submitted safety data from a phase 2 study (25,512-302R) and AE datasets and tables from legacy studies:

- The study 25.512-302R was conducted by the previous holder of the current IND and used a different metoclopramide nasal spray formulation (b) (4) The primary aim of this phase 2 study was to evaluate the PK parameters of IN doses of 10- and 20-mg of metoclopramide compared to 10-mg oral metoclopramide administered for 6 weeks. The Applicant intends to support the proposed to-be-marked 15-mg dose of Gimoti by the safety data for a 20-mg dose as well as provide comparative safety data versus 10-mg Reglan tablets administered QD for 6 weeks. The safety data from this study was evaluated and is presented separately due to the differences in the study design as well as separate formulation used in this study.

- Safety data from the legacy studies that evaluated other nasal formulations of metoclopramide used for indications other than DG were reviewed and summarized briefly.

The safety analysis includes all patients who were randomized and received at least one dose of study drug. There were 89 patients (48 females; 41 males) enrolled into the clinical study and 82 completed the study. The drug exposure based on the duration of treatment in days was comparable between the three treatment groups (Table 36).

Table 36: Drug Exposure

Duration of Treatment Days	Oral 10 mg (n 18) %	Nasal 10 mg (n 35) %	Nasal 20 mg (n 36) %
14	94	94	94
28	94	94	94
42	89	88	89

Source: Table 2 of Clinical Study Report 25,512-302R

Serious Adverse Events: No SAEs were observed during this trial.

Discontinuation Due to AEs

Of the 89 patients, three female patients and zero male patients, discontinued the study treatment due to AEs. Two patients discontinued due to AEs related to severe restlessness, drowsiness, and headache in the 10- and 20-mg group each and one patient in the 10-mg group due to development of rash on hands, chest, and arms. All the AEs appear to be related to the study drug. Brief narrative of the three patients is provided:

- Patient (b) (6) (IN 20 mg): A 54-year-old female developed sleepiness 3 days into the trial, rash on hands, chest, and arms and nasal soreness and tenderness 4 days prior to the termination of study drug.

- Patient (b) (6): (IN 20 mg): A 31-year-old female developed severe restlessness and drowsiness and headache 1 day after initiation of the study. Study drug was withdrawn, and her symptoms resolved within 1 day.

- Patient (b) (6) (10-mg tablet): A 61-year-old female patient developed severe restlessness and drowsiness and headache 3 days after the initiation of study drug. Study

drug was discontinued 2 days after the symptoms started and symptoms resolved within 3 days.

The overall TEAEs in the three treatment groups (Oral 10 mg, IN 10 mg , and IN 20 mg), TEAEs as per sex, and comparison of TEAEs between females and males are shown in Table 37 and Table 38, respectively.

Table 37: Overview of TEAEs by Sex

	Females			Males		
TEAEs	**Oral 10 mg (N=9)**	**IN MCP 10 mg (N=16)**	**IN MCP 20 mg (N=23)**	**Oral 10 mg (N=9)**	**IN MCP 10 mg (N=19)**	**IN MCP 20 mg (N=13)**
Subjects with TEAE(s) %	67	69	56	55	58	77
TEAEs (n)	18	35	43	16	30	29
Subjects with treatment-related TEAE(s)[1]	33	62	48	44	42	46
Subjects with SAEs	0	0	0	0	0	0
Discontinuation due to TEAEs	11 (1 patient)	0	9 (2 patients)	0	0	0
TEAE of special interest						
Central nervous system disorders	33	12	22	33	11	30
Psychiatric disorders	11	0	4	11	0	7.5
Cardiovascular disorders	11	6	4	11	0	0
Nasal events	11	62	48	11	57	45

Abbreviations: IN=intranasal; TEAE=treatment emergent adverse event; SAE serious adverse event; MCP=metoclopramide
Source: Compiled from the ADAE data sets of CSR 25.512-302

Table 38: TEAEs Related to the Special Interest

	Oral MCP 10 mg		IN MCP 10 mg		IN MCP 20 mg	
System Organ Class/ Preferred Term	**Males (N=9) %**	**Females (N=9) %**	**Males (N=19) %**	**Females (N=16) %**	**Males (N=13) %**	**Females (N=23) %**
Subjects reporting at least one adverse event/events	55	66	58	69	77	56
Nervous system disorders	33	33	11	12	30	22
Dizziness (b) (6)	11 (1 pt)	11 (1 pt)	5	0	0	4
Headache	22	0	5	6 (1 pt)	0	9
Drowsiness headache	0	11 (1 pt)	0	0	7.5 (1 pt)	9 (2 pts)
Tired, fatigue	0	11 (1 pt)	0	6 (1 pt)	15	0
Increased energy	0	0	0	0	7.5	0
Psychiatry	0	11	0	0	7.5	4
Restlessness, irritability	0	11	0	0	7.5	4
Nasal	0	11	57	62	45	48
Nasal irritation, runny nose, bloody nose, sinus pain	0	11	47	50	38	39
URI, bronchitis, allergic symptoms	0	0	10	12	7.5	9
Cardiovascular	0	11	0	6	0	4
High BP	0	11	0	0	0	4
Palpitation	0	0	0	6	0	0
Gastrointestinal	22	44	16	12	15	9

System Organ Class/ Preferred Term	Oral MCP 10 mg		IN MCP 10 mg		IN MCP 20 mg	
	Males (N=9) %	Females (N=9) %	Males (N=19) %	Females (N=16) %	Males (N=13) %	Females (N=23) %
Nausea, vomiting, worsening, bloating, diarrhea, flatulence	22	33 (3 pt)	11	12	7.5	9
Sour taste mouth	0	11 (1 pt)	5	0	7.5	0
Kidney	0	22	0	6	0	0
Infection, hematuria	0	22	0	6	0	0
Skin	0	0	0	0	0	0
Rash hands, chest and arms	0	0	0	0	0	4
Others	22	22	22	18	21	17
Weight gain	11	0	5	0	0	0
Sprain ankle, knee pain, toe, cold, influenza, etc.	11	11	0	12	21	0
Blood sugar low and or increased and infection: gum infection and pneumonia.	0	11	5	0	0	4
Low WBC count ((b) (6))	0	0	5	6	0	0
Elevated liver enzymes and hypoglycemia ((b) (6))	0	0	5	0	0	0
Influenza, fever, body aches	0	0	0	0	0	13

Abbreviations: WBC white blood cell; IN=intranasal; MCP=metoclopramide, URI=upper respiratory infection, BP blood pressure
* One patient could have more than 1 AE
Source: Compiled from the ADAE data sets of CSR 25.512-302

Summary

Nearly half of the patients developed nasal events in this study. It is important to note that the formulation used in this trial, conducted by another sponsor, was slightly different from the formulation used in studies conducted by the Applicant. The overall TEAEs observed during this study were similar to the TEAEs observed in studies METO-IN-002, METO-IN-003, and METO-IN-004.

Overall, the proportion of patients with TEAEs were comparable in the three treatment groups: 61%, 63%, and 64% in oral 10-mg, IN 10-mg, and IN 20-mg groups, respectively. Patients who discontinued due to TEAEs were similar in the IN 20-mg (5%) and oral 10-mg groups (5%), compared to no discontinuation in IN 10-mg group (Table 37).

The overall TEAEs in the female patients were numerically higher than in males in the oral 10 mg (67% and 55%) and IN 10-mg groups (69% and 58%). The TEAEs were numerically higher in males than in females in the IN 20-mg group (77% and 56%) (Table 37).

The special interest TEAEs included AEs related to the CNS, nasal events, psychiatry and cardiovascular system:

- TEAEs related to the CNS in females were lower in 10-mg and 20-mg groups (12% and 22%) than in the oral Reglan 10-mg group (33%). The TEAEs related to the CNS in males were lower at 10 mg IN dose (11%) but comparable to oral 10-mg dose at 20-mg IN dose (30% and 33%). The CNS events included headache, drowsiness, fatigue, and dizziness (Table 38). The proportion of female patients who experienced CNS-related

TEAEs was comparable to that in males at the IN 10-mg dose (11% and 12%) but lower at 20-mg dose (22% vs. 30%).

- In this study, the TEAEs related to the nasal events in females and males were higher and comparable at the 10-mg dose (47% and 50%) and lower and comparable at 20-mg dose (38% and 39%).

- The TEAEs related to the psychiatry and cardiovascular system were lower compared to the oral 10-mg group.

The GI AEs including but not limited to nausea, vomiting and diarrhea were lower compared to the oral 10-mg group but comparable between the IN 10- and 20-mg doses. The other AEs related to the other SOC as per PT were too small to notice any trend or signal for safety related to the IN formulation.

Legacy Studies Safety

The Applicant has included study summary reports of 25 legacy studies conducted by the previous sponsors between 1984 and 1995, to support the safety of nasal formulation of metoclopramide (Appendix 15.4). The 25 legacy studies were reviewed for the basic study design, target population, nasal formulations, and duration of metoclopramide administration:

- PK/BE/BA studies: Thirteen studies were conducted in healthy 258 volunteers; mostly single doses of nasal gel/spray ranging from 10 mg to 80 mg were administered.

- Cancer patients: Ten studies, conducted in 420 cancer patients, evaluated efficacy and safety of the metoclopramide nasal spray alone or in combination with dexamethasone for the treatment of nausea/vomiting associated with administration of chemotherapy. The dosing ranged from 20 mg to 80 mg, multiple doses for up to maximum of 16 hours.

- Postoperative nausea or vomiting and functional dyspepsia:
  - One dose finding study evaluated safety and efficacy of nasal metoclopramide compared to placebo in 215 patients for the treatment of postoperative nausea or vomiting. The doses used were 5, 10, 20, and 40 mg for the maximum of 3 doses over 2 hours.
  - One study evaluated efficacy and safety of 10 mg nasal spray compared to oral 10 mg Reglan in 24 patients for the symptomatic treatment of functional dyspepsia. The duration of treatment was for 4 weeks.

The safety information from the legacy studies is very limited and includes usage of different formulations than the current formulation, different patient population (healthy volunteers and cancer patients), and lower drug dosing and limited duration of treatment (Table 39). The safety data from the legacy studies are not adequate to support the safety of proposed dosing and duration of the Gimoti; therefore, further review of the safety data was not conducted.

Table 39: Summary of Legacy Studies

Study No. Year CSR Completed	Study Design	Dose of Nasal Metoclopramide	No. of Subjects Exposed [1] No. of Females Exposed [1]	Age Range [2] Males/Females [2] Predominant Race [2]
Studies evaluating metoclopramide nasal gel [3] in healthy volunteers				
26169 1985	Open-label, single-dose, randomized, 2-way crossover study followed by single- and multiple-dose, randomized, 3-way crossover study to evaluate the BA of metoclopramide nasal gel (10 mg; Nastech), oral metoclopramide tablets (10 mg; Reglan® [A.H. Robins]), and IV metoclopramide (10 mg)	10 mg	19 0	18 to 43 years 20 males/0 females White (17 subjects)
86103-B 1986	Open-label, multiple-dose, randomized, 3-way crossover study comparing rate and extent of absorption of nasal metoclopramide hydrochloride formulations	10 mg, 20 mg, and 40 mg	12 0	21 to 43 years 12 males/0 females Black and white (6 subjects each)
8251-A 1987	Controlled, multiple-dose, 3-way crossover study comparing BA of different modes of administration of nasal metoclopramide hydrochloride	40 mg	15 0	NR (ages 18 to 45 years eligible) 15 males/0 females NR
87030 1987	Randomized, 2-way crossover BE evaluation of metoclopramide hydrochloride 20 mg via nasal spray (200 mg/1.3 mL) and nasal gel (200 mg/mL)	20 mg	12 0	18 to 44 years 12 males/0 females NR
28-02-8924-88 (8924) 1988	Two-way crossover BA study of metoclopramide nasal gel 40 mg (400 mg/mL) and metoclopramide nasal spray 40 mg (400 mg/mL)	40 mg	28 0	19 to 45 years 28 males/0 females Black (18 subjects)
28-03-9256-88 (9256) 1988	Single-dose, randomized, 3-way crossover study of the BA of metoclopramide nasal gel 40 mg (400 mg/mL) in 1 nostril vs. metoclopramide nasal spray 40 mg (400 mg/mL) in 1 nostril vs. metoclopramide nasal spray 20 mg (200 mg/mL) in each nostril	40 mg	6 0	20 to 31 years 6 males/0 females Black (6 subjects)
28-04-9360-88 (9360) 1989	Single-dose, 3-way crossover study of relative BA of metoclopramide nasal gel 40 mg (400 mg/mL) in 1 nostril vs. metoclopramide nasal spray 40 mg (400 mg/mL) in 1 nostril vs. metoclopramide nasal spray 20 mg (200 mg/mL) in each nostril	40 mg	33 0	19 to 41 years 33 males/ 0 females Black (18 subjects)
Studies evaluating metoclopramide nasal spray in healthy volunteers				
920210 1992	Open-label, randomized, 2-way crossover study of the BE of metoclopramide solution (400 mg/mL; Rugby-Darby) in healthy adult males following a 40 mg dose (0.1 mL in 1 nostril vs. 0.05 mL in both nostrils)	40 mg	28 0	18 to 32 years 28 males/0 females NR
901697 (original and amendment) 1993; amendment 1995	Open-label, randomized, 3-way crossover study of the BA of metoclopramide hydrochloride 80 mg following IV (5 mg/mL), nasal (400 mg/mL), and oral (10 mg tablets; Reglan) administration in healthy adult males	80 mg	27 0	18 to 44 years 29 males/0 females White (23 subjects)
MCP 01/91-PK 1991	Single-dose, 2-way crossover PK and BA study of metoclopramide nasal spray 20 mg vs. metoclopramide 20 mg IV in healthy subjects	20 mg	10 7	19 to 35 years 3 males/7 females NR
90762 1991	Single-dose, 4-way crossover study evaluating the PK/BA of metoclopramide 40 mg from 4 metoclopramide preparations (200 mg/mL nasal spray; 400 mg/mL nasal spray; 10 mg tablet [Reglan]; 5 mg/mL IV solution) in healthy volunteers	40 mg	32 0	19 to 30 years 35 males/0 females NR
901709 (clinical summary and PK report) 1992	Open-label, multiple-dose, single-period study of metoclopramide nasal solution (800 mg/mL; Rugby-Darby)	40 mg	12 0	21 to 26 years 12 males/0 females White (12 subjects)
901707 (clinical summary and PK report) 1992	Open-label, single-dose, randomized, 3-way crossover study of single doses of dose-proportionality of metoclopramide nasal solution (200 and 400 mg/mL; Rugby-Darby) in healthy adult males	20 mg, 40 mg, and 80 mg	24 0	18 to 27 years 24 males/0 females NR

Study No. Year CSR Completed	Study Design	Dose of Nasal Metoclopramide	No. of Subjects Exposed [1] No. of Females Exposed [1]	Age Range [2] Males/Females [2] Predominant Race [2]
Studies evaluating metoclopramide nasal spray in patients with cancer				
U-90-02/A 1991	Double-blind, multiple-dose, randomized, parallel-arm (3 arms) study comparing antiemetic and antinausea efficacy and safety of nasal metoclopramide with placebo in cancer patients treated with emetogenic cancer chemotherapeutic agents	20 mg and 40 mg (multidose, 8 doses over 16 hours)	60 18	17 to 79 years 65 males/25 females White (90 subjects)
U-91-02BH (volume 1 and volume 2) 1992	Randomized, double-blind, multiple-dose, parallel-arm study evaluating the antiemetic and antinausea efficacy and safety of nasal metoclopramide versus placebo in cancer patients treated with emetogenic chemotherapeutic agents	20 mg and 40 mg (multidose, 8 doses over 16 hours)	13 0	18 to 40 years 19 males/0 females White (19 subjects)
U-90-09 1992	Open-label, multiple-dose, phase 2 pilot study to estimate side effects, patient acceptance, and efficacy of nasal metoclopramide as an antiemetic in patients receiving chemotherapy	40 mg and 80 mg (multidose, 8 doses over 16 hours)	13 6	47 to 84 years 7 males/6 females NR
U-90-01 1993	Randomized, double-blind, multiple-dose, parallel-arm (4 arms) multicenter study evaluating the efficacy and safety of nasal metoclopramide versus placebo in cancer patients treated with emetogenic chemotherapeutic agents	20 mg, 40 mg, and 80 mg (multidose, 8 doses over 16 hours)	125 44	20 to 84 years 112 males/51 females NR
U-90-03 1993	Randomized, double-blind, multiple-dose, parallel-arm (3 arms) study evaluating antiemetic and antinausea efficacy and safety of nasal metoclopramide versus placebo in cancer patients treated with emetogenic chemotherapy agents	40 mg and 80 mg	81 30	17 to 84 years 76 males/42 females White (86 subjects)
DP-011D-D-92 1993	Randomized, double-blind, multiple-dose, parallel-arm (2 arms), multicenter study evaluating efficacy and safety of nasal metoclopramide versus placebo in patients treated with emetogenic chemotherapeutic agents	80 mg (multidose, 8 doses over 16 hours)	53 0	18 to 71 years 99 males/7 females NR
MCP 02/90 NR	Single-dose, 2-way crossover study evaluating PK and BA of metoclopramide nasal spray 20 mg vs. 20 mg IV dose in cancer patients	20 mg	11 5	45 to 68 years 6 males/5 females NR
MCP 02/91 NR	Multiple-dose, parallel-group, 3-phase, balanced-block-design study evaluating efficacy and tolerability of metoclopramide nasal spray vs. metoclopramide IV as symptomatic therapy for vomiting induced by antiblastic chemotherapy in cancer outpatients	40 mg (multidose, 3 doses over 8 hours)	12 3	44 to 76 years 9 males/3 females NR
MCP 01/92 1994	Pilot open-label study of metoclopramide nasal spray for prevention of delayed hyperemesis in cancer patients under cisplatin treatment	20 mg (3 times per day for 6 days)	12 11	23 to 64 years 1 males/11 females NR
MCP 02/92 1994	Randomized, multiple-dose study evaluating control of delayed emesis with metoclopramide nasal spray plus dexamethasone versus metoclopramide tablets (Reglan) and dexamethasone in patients receiving low emetogenic chemotherapy	40 mg (4 times per day on Days 2/3 and 22/23)	40 33	33 to 70 years 8 males/37 females NR
Studies evaluating metoclopramide nasal spray in patients with postoperative nausea and vomiting				
U-90-04A 1992	Randomized, double-blind, dose-finding study assessing safety and efficacy of nasal metoclopramide vs. placebo in the treatment of postoperative nausea or vomiting	5 mg, 10 mg, 20 mg, and 40 mg (maximum of up to 3 doses over 2 hours)	110 105	18 to 79 years 8 males/128 females White (114 subjects)
Studies evaluating metoclopramide nasal spray in patients with dyspepsia				
MCP 01/91-FD 1993	Randomized, parallel-arm (including Reglan comparator), efficacy and tolerability study of metoclopramide nasal spray in the symptomatic treatment of functional dyspepsia	10 mg (twice daily for 4 weeks)	15 9	18 to 65 years 11 males/20 females NR

BA = bioavailability; BE = bioequivalence; CSR = clinical study report; DC = discontinuation; IV = intravenous; NR = not reported; PK = pharmacokinetic or pharmacokinetics

[1] Number of subjects exposed to a nasal formulation of metoclopramide.

[2] Includes subjects who received placebo and non-nasal formulations of metoclopramide.

[3] The nasal gel formulation of metoclopramide was discontinued by the sponsor, Nastech, in favor of the nasal spray formulation.

Source: CSRs in Modules 5.3.1.1, 5.3.1.2, 5.3.3.1, and 5.3.5.4; and Legacy Studies Datasets (Adverse Events and Medical History)

15.4.2. Summary of SAEs: Supportive Information

Brief narratives for the SAEs are provided including start dates of the treatment, occurrence of the SAEs and whether the drug was withdrawn.

15.4.2.1. Study METO-IN-002

Gimoti:

- **Patient (b) (6) (14 mg):** A 65-year-old female was started on Gimoti (14-mg group) on (b) (6). In addition to the DG, she had coronary artery disease status post stent placement, hyperlipidemia, HTN, diverticulosis, anxiety and depression and was taking the following medications: aspirin, Coreg, Klonopin, Plavix, ferrous sulfate, insulin, Nitroglycerin, Zantac, Zoloft and Zocor. She was admitted to the hospital on (b) (6) with complaints of (c/o) chest pain/burning. Her cardiac workup was negative, and endoscopy showed retained residue suggestive of GP and her symptoms were assessed to be due to GP and not related to the study drug (Gimoti). Dosing was not changed.

  The Applicant's assessment seems reasonable as this patient had many medical conditions and was also receiving several concomitant medications. However, Gimoti may have had some contribution to the AE given that Gimoti is administered intranasally and could have contributed to the feeling of chest pain/burning in either the trachea or esophagus.

- **Patient (b) (6) (14 mg):** A 41-year-old female was started on 14-mg Gimoti on (b) (6) (b) (6). In addition to the DG, the patient had hyperlipidemia, HTN, gastritis, GERD, recurrent UTIs neurogenic bladder, gall stones, and depression and was taking the following medications: Lisinopril, insulin, pravastatin, Prozac, and Lasix. Patient was admitted to the hospital on (b) (6) with c/o intractable nausea, vomiting and abdominal pain for the past 1 week. At admission, she was dehydrated, hypotensive (77/62) and labs showed leukocytosis, uncontrolled blood sugars, and a hepatobiliary iminodiacetic acid scan consistent with cystic duct obstruction. Patient had laparoscopic cholecystectomy on (b) (6) and discharged the next day.

  The Applicant's assessment that AE of cholecystitis is unlikely to be due to the study drug (Gimoti) appears reasonable.

Placebo:

- **Patient (b) (6):** A 43-year-old female patient was started on the study drug on (b) (6) (b) (6) In addition to the DG, she had bipolar disorder, h/o attempted suicide, anxiety, depression, HTN, hypothyroidism, hypercholesterolemia, asthma, Crohn's disease, GERD, Munchausen's syndrome, May-Thurner Syndrome (iliac vein compression syndrome) with h/o deep vein thrombosis of the left leg and was taking the following medications: Synthroid, Asacol, Ambien, Seroquel, Niferex (iron), Zanaflex, Toprol XL, insulin, metformin, lovastatin, Ativan, Cytotec, Lyrica, and valsartan. She had an h/o multiple admission for DKA up to 3 months before the start of the study. Patient was

admitted to the hospital on (b) (6) with nausea, vomiting, abdominal pain, and high blood sugars (902) and positive ketones and was diagnosed as DKA and pneumonia. Study drug was withdrawn on (b) (6)

Her past medical history was significant for recurrent episodes of hypoglycemia after self-injecting insulin due to Munchausen's syndrome and depression. During this episode, she adamantly denied self-injecting insulin and despite lowering of the insulin dosing she continued to have hypoglycemic episodes. She was transferred to Indiana University where further investigation showed very low c-peptide (0.1) and cortisol stimulation test showed low pre-level of 0.9, 30 minutes post level was 15.3, and 60 minutes level was 17.7. Her condition stabilized on (b) (6) and was discharged.

The Applicant's assessment that the AE of DKA is unlikely related to the study drug is reasonable.

- **Patient** (b) (6)**:** A 33-year-old female was started on the study drug on (b) (6) In addition to the DG, patient had other medical conditions that include anemia, HTN, depression, asthma, and GERD; also, her medication history was not known. Patient was admitted to the hospital on (b) (6), with c/o nausea and pain. Her labs showed positive ketones and glucose 375 (DKA) and she was also diagnosed with pyelonephritis. She was treated with IV fluids, antibiotics, and insulin; was discharged on (b) (6) .

  The Applicant's assessment that AE of DKA and pyelonephritis were not related to the study drug is reasonable.

- **Subject** (b) (6)**:** A 60-year-old female patient was started on study drug on (b) (6) (b) (6). In addition to the DG she had significant medical history for asthma, COPD, sleep apnea, irregular heartbeat, HTN, coronary artery disease, congestive heart failure, anemia, hypothyroidism, myelodysplasia, GERD, scoliosis, anxiety, depression, and allergies to penicillin, sulfa, mycin, and latex and was taking the following medications: Singulair (montelukast sodium), glipizide, omeprazole, Klonopin, trazodone, and Synthroid. Patient was admitted to the hospital on (b) (6), due to COPD exacerbation.

  Her sputum culture was positive for gram-positive cocci and gram-negative rods, white blood cells, and epithelial cells. She was started with broad-spectrum IV antibiotics and steroids. While in the hospital she received Cardizem for tachycardia following COPD treatment and bronchodilators were changed to Xopenex, levosalbutamol and ipratropium. A cardiologist was consulted for substernal discomfort, and subject received morphine and Lasix for volume overload. The patient felt better. Her cardiology workup was negative. Study drug was not discontinued due to the event, and the subject continued in the study. Her symptoms resolved on (b) (6), she recovered from the bronchitis, and was discharged with instructions to follow-up in the clinic in 1 week.

Patient was admitted again to the hospital with c/o chest pain (b) (6). Cardiac workup including a Myocardial Perfusion SPECT and echocardiogram were normal, diagnosis of NCCP was made and was discharged.

The Applicant's assessment of the COPD exacerbation and NCCP as not related to the study drug is appropriate.

15.4.2.2. Study METO-IN-003

Brief narratives of the patients with SAEs are provided including start dates of the treatment, occurrence of the SAEs and whether the drug was withdrawn.

Gimoti:

- **Subject (b) (6):** A 47-year-old female with DG started study drug on (b) (6) and was hospitalized on (b) (6), with c/o increased weakness, postural dizziness and occipital headache and was found to have orthostatic hypotension. She denied nausea, vomiting, diarrhea, fever, chills, shortness of breath and chest pain. The patient had several significant concomitant medical conditions such as ongoing dizziness, neuropathy, diabetic retinopathy, stage 3 chronic kidney disease due to diabetes with GFR of 30–59 mL/min, diabetic foot status post amputation of great, 3rd and 4th toes, HTN, sickle cell trait (b) (6), iron deficiency anemia as well as anemia due to chronic disease, previous deep vein thrombosis lower extremity, and anxiety-depression. Concomitant medications included insulin, Xanax, trazodone, Percocet (as needed for neuropathy and osteoarthritis since (b) (6)), Topamax, amlodipine, Benicar, torsemide, Cymbalta, and other supportive treatments. The patient was diagnosed with orthostatic hypotension likely due to dehydration, volume depletion, and autonomic neuropathy. She was managed conservatively and discharged from the hospital on (b) (6). Her discharge diagnosis was orthostatic hypotension and outpatient follow-up was recommended with primary care, endocrinology, nephrology, hematology, and cardiology. The study drug was withdrawn by the Applicant.

  Although hypotension, observed in this patient, is listed in the Reglan labeling information, it is difficult to ascribe the AE of hypotension to the investigational drug due to several preexisting medical conditions and since the patient was receiving several concomitant medications that can cause hypotension. However, the possibility of Gimoti contributing to the SAE of hypotension cannot be definitively excluded.

- **Subjects (b) (6):** A 55-year-old female with DG started study drug on (b) (6), and was hospitalized on (b) (6), for worsening of preexisting cellulitis of the right index finger. The patient also had significant preexisting neuropathy, HTN, migraine headaches, depression elevated blood calcium level, and hyperlipidemia; was receiving duloxetine, lisinopril, lovastatin, trazodone, insulin, metformin, and fenofibrate. The finger lesion was incised and drained in the ER and treated with antibiotics as per wound and blood cultures reports. The study drug was not withdrawn by the Applicant.

- **Subject (b) (6):** A50-year-old female with DG started study drug on (b) (6) (b) (6), and was hospitalized on (b) (6), with a chalazion in the right eye. The

patient also had other significant medical conditions that include peripheral neuropathy, fibromyalgia, restless leg syndrome, fatty liver, rheumatoid arthritis, osteoarthritis, COPD, dyslipidemia, hypothyroidism, HTN, Hepatitis C, and esophageal stricture. Concomitant medications included insulin, AccuNeb, Atrovent, hydroxychloroquine, levothyroxine, Lyrica and Wellbutrin. The patient was treated with appropriate antibiotics. The study drug was not withdrawn by the Applicant.

Subjects (b) (6) and (b) (6) developed worsening of preexisting infective conditions that are common in diabetic patients. Therefore, we agree that these SAEs are unlikely to be associated with administration of Gimoti.

Placebo:

- **Subject (b) (6):** A 54-year-old female with DG started study drug on (b) (6) and was admitted for worsening of anxiety disorder, panic attack, on (b) (6). The patient had other significant medical conditions: fibromyalgia, IBS, anxiety disorder, panic attack, hyperlipidemia, osteoarthritis, Barrett's esophagus and NCCP. Concomitant medications included: verapamil, benazepril, pantoprazole, tramadol, alprazolam and atorvastatin. Patient was out of Xanax for 1 week prior to her panic attack. The patient was treated with Xanax 1 mg as needed and recovered. The investigator assessed the episode as possibly related to the study drug. The blind was not broken and study drug (placebo) was discontinued due to this SAE. However, the Applicant disagreed with the investigator as there were alternative explanations for the worsening of anxiety of her anxiety disorder.
- **Subject (b) (6):** A 48-year-old female with DG was started on study drug on (b) (6), (b) (6), and hospitalized on (b) (6), with symptoms of chest pain. The patient also had other significant medical conditions such as morbid obesity, HTN, asthma, fibromyalgia, interstitial cystitis, migraine, attention deficit disorder, insomnia, GERD, depression, hypercholesterolemia. Important concomitant medications included: insulin, metformin, metoprolol, losartan, Lipitor, Cymbalta, Lyrica, Ritalin, Topamax, trazodone, and Klonopin. An ECG showed no significant change from a previous study, serial troponin levels were normal, and a myocardial perfusion imaging study was reported within normal limits. A diagnosis of NCCP was made and was considered not related to study drug. The study blind was not broken, and the subject completed study participation.

  Subject (b) (6) developed worsening of preexisting anxiety disorder due to discontinuation of Xanax, however the investigator discontinued the study drug. Subject (b) (6), with several coexisting medical conditions and concomitant medications, developed NCCP and study drug was continued. Both the conditions were later found (on study completion) to be appropriately not related to the study drug administration by the Applicant.

In addition, two patients developed severe AE, as described. Both were in the Gimoti group:

- **Subject (b) (6):** A 32-year-old female patient was started on study drug on (b) (6). Patient developed increased sleepiness on (b) (6). The AE was considered possibly related to the study drug administration and drug was withdrawn.

- **Subject** (b) (6)**:** A 75-year-old female patient was started on study drug on (b) (6). Patient reported multiple symptoms of headache, nausea, heart burn during the study. The AEs were considered unlikely or not related to the study drug administration. The study drug was not discontinued.

15.4.2.3. Study METO-IN-004

Brief narratives of the SAEs are provided:

- **Patient** (b) (6)**:** A 50-year-old male patient was started on study drug on (b) (6). Patient was admitted to the hospital with uncontrolled DM and worsening GP symptoms on (b) (6). In addition to the DG, patient had h/o CAD, status post stent placement, CCF, HTN, cardiomyopathy, cardioverter defibrillator placement, peripheral neuropathy, hyperlipidemia, and GERD. Concomitant medications included: gabapentin, furosemide, Coreg, simvastatin, Plavix, lisinopril, Flomax, hydralazine, amlodipine, insulin and digoxin. Patient also developed depression and the study drug was withdrawn. His symptoms improved with medical treatment and was discharged in 2 days.

- **Patient** (b) (6)**:** A 27-year-old male patient stated on study drug on (b) (6). In addition to DG, patient had medical h/o HTN, GERD, colitis and he was taking the following concomitant medications: Accupril, Protonix, insulin, and lisinopril/hydrochlorothiazide. He was admitted to the hospital with shin abscess due to MRSA on (b) (6). He was managed with IV antibiotics (vancomycin, Zosyn, and clindamycin) and control of diabetes. Patient was discharged in 2 days.

The Applicant's assessment that these SAEs are unrelated to the study drug, since patients were receiving placebo, appears appropriate.

15.4.3. Discontinuations: Narratives of Patients for Study METO-IN-003

Brief summaries of the patients that discontinued are presented:

Gimoti:

- **Subject** (b) (6)**:** A 32-years-old female patient with significant medical h/o DM, GP, migraine headache, Graves' disease, anxiety and bilateral edema legs taking insulin, Bentyl, Phenergan, Topamax, Linzess, Zyrtec, Xanax, and Lasix. The study drug was started on (b) (6) and patient developed sleepiness 1 day after starting the study drug. The AE of sleepiness was considered possible and the drug was withdrawn.

  As the patient was already taking other drugs which have sleepiness included as AEs in the labeling, the administration of study drug with similar effect potentiated the AE of sleepiness. The reason for withdrawal was reported as AE.

- **Subject** (b) (6)**:** Discussed under the SAE summaries.

- **Subject** (b) (6)**:** A 58-year-old female patient with significant medical h/o DM, GP, anxiety-depression, GERD, HTN, duodenal ulcer, and iron deficiency anemia was taking

the following concomitant medications: aspirin, Arthrotec, sertraline, gabapentin, metformin, metoprolol, triamterene, and Xanax. Patient was started on study drug on (b) (6) and developed worsening of anxiety and joint pain on (b) (6), that lasted for 2 days. The drug was withdrawn. The reason for withdrawal in CRF is stated as withdrawal of consent (Feels study too demanding imposing on her job responsibilities).

- **Subject (b) (6):** A 50-year-old female patient with medical h/o DM, DG, diabetic neuropathy, carpal tunnel syndrome, insomnia, anxiety-depression was taking the following concomitant medications: Insulin, altace, Lyrica, Cymbalta, alprazolam, Ambien CR, Niferex, and Bactrim for UTI for 5 days. Patient was started on study drug on (b) (6) and developed right leg tremor on (b) (6), drug was withdrawn on (b) (6) and tremor recovered on (b) (6). The patient had pre-existing UTI from (b) (6) to (b) (6) and high potassium was reported on labs on (b) (6) The reason for withdrawal was reported as AE.

- **Subject (b) (6):** A 31-year-old female patient with medical h/o DM. GP, hypothyroidism, hyperlipidemia and Phenergan allergy was taking the following concomitant medications: Synthroid and atorvastatin. Patient was started on study drug on (b) (6) and developed generalized muscle cramps and numbness on (b) (6), (b) (6) the drug was withdrawn. The reason for withdrawal was reported as AE.

- **Subject (b) (6):** A 58-year-old female patients with medical h/o DM, GP, hypothyroidism, and migraine was taking the following concomitant medications: insulin, midodrine, Armour Thyroid, metoclopramide, JUBLIA, Lamisil, Toujeo, and topiramate. Patient was started on the study drug on (b) (6) and developed palpitations on (b) (6); the drug was withdrawn on (b) (6) and palpitations recovered (b) (6) The reason for withdrawal was reported as AE.

Placebo:

- **Subject (b) (6):** Discussed under SAE summaries.

- **Subject (b) (6):** A 72-year-old female patient with significant medical h/o DM, GP, COPD, anxiety-depression, hyperlipidemia, HTN, and vitamin D deficiency was taking the following concomitant medications: amlodipine, citalopram, valsartan, atorvastatin, metformin, cholecalciferol, and inhalers (fluticasone/salmeterol). Patient was started on the study drug on (b) (6) and developed numbness of fingers on (b) (6) (b) (6) (lasted for 2 days), auditory hallucinations (b) (6) (lasted until (b) (6) left nostril bleed on (b) (6) and right nostril soreness on (b) (6). The study drug was stopped on (b) (6). All AEs recovered in following discontinuation of the study drug.

Study drug administration was interrupted temporarily in the following four patients. These patients were identified to be in the placebo group on completion of the study.

- **Subject** [redacted]: Patient with c/o numbness of mouth (mild) on the first day of the study, [redacted], improved on the same day. The drug was interrupted but continued for rest of the study duration and last day of study drug intake was [redacted].

- **Subject** [redacted]: Patient with c/o severe headache (moderate), started on first day of the study, [redacted] and improved on the 3rd day. The drug was interrupted but continued and last day of study drug intake was [redacted]

- **Subject** [redacted]: Patient with c/o NCCP (severe), started on first day of the study, [redacted], improved in 2 days. The study drug was interrupted but continued and last day of study drug intake was [redacted]

- **Subject** [redacted]: Patient with c/o itching of the body (moderate), started on 2nd day of the study, [redacted], and improved after 2 days. The drug was interrupted and last day of study drug intake was [redacted].

15.4.4. Adverse Events Other Than Special Interest Group

The AEs related to the other than special interest SOC/PT are summarized below.

15.4.4.1. Study METO-IN-002

Table 40: Study METO-IN-002 - Common AEs as per SOC and PT, Proportion of Patients With at Least One Event and Higher Than Placebo

	Placebo		Meto 10 mg		Meto 14 mg	
System Organ Class/ Preferred Term	Males (N=27) %	Females (N=68) %	Males (N=31) %	Females (N=64) %	Males (N=25) %	Females (N=70) %
Subjects reporting at least one adverse event/events	41	62	65	52	68	57
Gastrointestinal disorders	22	25	26	14	20	13
Abdominal pain/lower/upper, bloating, distension, stomach pain, worsening of GP, suprapubic tenderness	4	10	16	1.5	8	6
Nausea, and or vomiting	4	6	0	3	4	4.5
Heartburn, increased acid reflux, worsening GERD	0	3	6	6		1.5
Constipation	0	3	0	1.5	0	0
Pyrosis	0	0	0	0	4	0
Abdominal mass	0	0	0	0	0	1.5
GI sounds abnormal	0	0	3	0	0	0
Leukoplakia oral	0	0	3	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1.5	0	6	0	1.5
Dyspnea	0	0	0	1.5	0	1.5
Bronchitis, chest cold	0	0	0	3	0	0

System Organ Class/ Preferred Term	Placebo		Meto 10 mg		Meto 14 mg	
	Males (N=27) %	Females (N=68) %	Males (N=31) %	Females (N=64) %	Males (N=25) %	Females (N=70) %
Infections and infestations	7	11	10	12	0	7
Infusion site infection	0	0	0	1.5	0	0
UTI, kidney infection	0	1.5	0	3	0	0
Flu like symptoms, common cold, head cold	4	1.5	6	6	0	1.5
Vulvovaginal mycotic infection	0	0	0	0	0	1.5
General disorders and administration site conditions	7	3	3	5	8	4.5
Edema peripheral	0	0	3	3	0	0
Chest pain/NCCP	0	1.5	0	0	4	0
Hunger	0	0	0	1.5	0	0
Pyrexia	0	0	0	0	0	1.5
Decrease appetite	0	0	0	0	4	1.5
Fever	0	0	0	0	0	1.5
Investigational	12	9	10	5	8	16
Hyperglycemia, increased A1C	4	4.5	0	1.5	4	6
Hypoglycemia	0	1.5	3	0	0	4.5
Leukocytosis	0	0	0	0	0	1.5
Hyperkalemia	0	0	6	0	0	0
AST increase (027-10)				1.5		
ALT, AST, and creatinine increased (all in one pt: 072-02)					4 (Only ALT- 039-05)	
Metabolic and nutrition	0	3	3	0	0	0
Worsening gout pain			3	0	0	0
Musculoskeletal and connective tissue disorders	4	7	10	3	4	4.5
Hip pain, wrist pain, worsening joint pain, RA, low back pain, lower extremity pain, shoulder pain, pulled muscle pain	4	7	10	3	4	4.5
Skin and subcutaneous tissue disorders	7	1.5	6	3	4	4.5
Dermatitis	0	0	0	0	4	0
Dry skin	0	0	3	0	0	0
Hypoesthesia facial	0	0	0	0	0	1.5
Onychomalacia	0	0	0	0	0	1.5
Pruritus of arm, mouth and nose	0	0	0	1.5	0	0
Hot flashes	0	0	0	0	0	1.5
Blood and lymphatic system disorders	0	1.5	3	1.5	0	1.5
Lymphadenopathy	0	1.5	3	1.5	0	0
Lymph node pain	0	0	0	0	0	1.5
Eye disorders	4	1.5	3	1.5	0	3
Eye pain/discomfort	0	1.5	0	1.5	0	0
Vision blurred, cataract	0	0	0	0	0	3
Renal and urinary disorders	0	0	0	0	4	3
Polyiuria	0	0	0	0	0	3
Renal pain	0	0	0	0	4	0

System Organ Class/ Preferred Term	Placebo		Meto 10 mg		Meto 14 mg	
	Males (N=27) %	Females (N=68) %	Males (N=31) %	Females (N=64) %	Males (N=25) %	Females (N=70) %
Ear and labyrinth disorders	0	0	0	0	0	1.5
Ear pain	0	0	0	0	0	0
Tympanic membrane hyperemia	0	0	0	0	0	1.5
Hepatobiliary disorders	0	0	0	0	0	1.5
Acute cholelithiasis	0	0	0	0	0	1.5

Abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; B/L=bilateral; DKA diabetic ketoacidosis; GP gastroparesis; Hb=hemoglobin; NCCP=non-cardiac chest pain; RBC red blood cell; RA rheumatoid arthritis; GERD=gastroesophageal reflux disease; GI=gastrointestinal; COPD=chronic obstructive pulmonary disease; UTI urinary tract infection; MVA=motor vehicle accident
Source: Compiled from the ADAE datasets of the CSR METO-IN-002

15.4.4.2. Study METO-IN-003

Table 41: Study METO-IN-003 - Common AEs by SOC and PT, Proportion of Patients With at Least One Event and Higher Than Placebo

System Organ Class/ Preferred Term	All Patients	
	Placebo IN (N=103) %	Gimoti 10 mg IN (N=102) %
Subjects reporting at least one adverse event	35	36
Gastrointestinal disorders	10	10
Abdominal pain, tenderness, cramping, epigastric tenderness, worsening of GERD, intermittent abdominal pain, stomach burning, lower abdominal pain	6	4
Diarrhea, viral GE	0	4
Nausea, heart burn, belching and bloating	0	1
Decreased appetite	0	1
Infections and infestations	7	7
Cellulitis right index finger	0	1
Mycoplasma pneumonia	0	1
Vulvo-vaginal mycotic infection	0	1
Acne related skin infection	0	1
Investigations	1	6
Elevated creatinine	0	1
Increased blood glucose	0	1
Elevated potassium level, mild hyperkalemia	0	2
Hypoglycemia	1	1
Magnesium deficiency	0	1
Metabolic and nutrition	1	1
Diabetic ketoacidosis	1	0
Dehydration	0	1
Musculoskeletal and connective tissue disorders	2	2
Back pain	0	1
Arthralgia	0	1
Torn right rotator cuff	0	0
Skin and subcutaneous tissue disorders	4	1
Contact dermatitis	0	1
Blood and lymphatic system disorders	0	1
Worsening anemia	0	1
Eye disorders	2	2
Chalazion	0	1

System Organ Class/ Preferred Term	All Patients	
	Placebo IN (N=103) %	Gimoti 10 mg IN (N=102) %
Renal and urinary disorders	0	1
Dysuria	0	1
Immune system disorders	0	1
Allergic reaction	0	1

Abbreviations: NCCP non-cardiac chest pain; UTI=urinary tract infections; IN intranasal; GERD=gastroesophageal reflux disease; GE=gastric emptying; AE=adverse event
Note: Some patients had ≥1 AEs
Source: Compiled from ADAE data sets of CSR METO-IN-003

15.4.4.3. Study METO-IN-004

Table 42: Study METO-IN-004 - Common AEs by SOC and PT, Proportion of Patients Reporting at Least One AE and Higher Than Placebo

System Organ Class/ Preferred Term	All Patients	
	Placebo IN (N=27) %	Gimoti 10 mg IN (N=26) %
Gastrointestinal disorders	11	11
Constipation	0	0
Diarrhea, viral GE	0	3.5
Nausea, heart burn, belching and bloating	0	3.5
Stomach flu symptoms	0	0
Infections and infestations	3.5	3.5
Hay fever, head cold	0	3.5
Shortness of breath	0	0
Investigations	11.5	7
Elevated potassium level, mild hyperkalemia	0	0
Low platelets	0	3.5
Musculoskeletal and connective tissue disorders	0	3.5
Arthralgia, left wrist sprain	0	3.5
Skin and subcutaneous tissue disorders	0	3.5
Contact dermatitis, poison oak rash left elbow	0	3.5

Abbreviations: IN=intranasal; GERD=gastroesophageal reflux disease; GE=gastric emptying
Source: Compiled from the ADAE datasets of CSR METO-IN-004

Signatures

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Statistical Reviewer	Paul Imbriano, Ph.D.	OTS/OB/DBIII	Sections: 7, 8.1	**Select one:** __X_ Authored ___ Approved
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Statistical Team Leader	George Kordzakhia, Ph.D.	OTS/OB/DBIII	Sections: 7, 8.1 (made changes and edits)	**Select one:** ___ Authored ___X Approved
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Acting Deputy Division Director (OB/DBIII)	Gregory Levin, Ph.D.	OTS/OB/DBIII	Sections: 1, 7, 8	**Select one:** ___ Authored __X_ Approved
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Clinical Reviewer	Anil Nayyar, M.D.	DGIEP/ODE III	Sections:2, 3, 8, 9, 16	**Select one:** ___X Authored ___ Approved
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Clinical Team Leader	Juli Tomaino, M.D.	DGIEP/ODE III	Sections: 1, 4, 6, 10, 11, 12, 13 (authored and/or added information based on separate review memos)	**Select one:** ___ Authored _X__ Approved (all sections)
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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
OPQ Branch Chief and Technical Lead	Hitesh Shroff, Ph.D.	OPQ/ONDP/DNDPII/NDPBV	Section: 4	**Select one:** __X_ Authored __X Approved
	Signature: Hitesh N. Shroff -S Digitally signed by Hitesh N. Shroff -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S Date: 2019.03.22 17:03:08 -04'00'			
Nonclinical Reviewer	Kenrick Semple, Ph.D.	ODE III/DGIEP	Sections: 5 (5.1, 5.2)	**Select one:** __X_ Authored ___ Approved
	Signature: Kenrick M. Semple -S Digitally signed by Kenrick M. Semple -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001652874, cn=Kenrick M. Semple -S Date: 2019.03.25 12:16:40 -04'00'			
Nonclinical Supervisor	Sushanta Chakder, Ph.D.	ODE III/DGIEP	Sections: 5 (5.1, 5.2)	**Select one:** ___ Authored __X_ Approved
	Signature: Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144003, cn=Sushanta K. Chakder -S Date: 2019.03.25 12:27:47 -04'00'			

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Addendum to Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 209388
Link to EDR	\\CDSESUB1\evsprod\NDA209388\0001
Submission Date	June 1, 2018
Submission Type	Original Submission/ 505(b)(2), Standard Review
Brand Name	Gimoti
Generic Name	Metoclopramide
Dosage Form and Strength	Nasal spray, 15 mg
Proposed Dosing Regimen	15 mg four times daily
Proposed Indication	The relief of symptoms in adult females with acute and recurrent diabetic gastroparesis
Applicant	Evoke
Associated IND	IND 025512
OCP Review Team	Sojeong Yi, PhD Lian Ma, PhD (DPM TL) Insook Kim, PhD (DCP III TL)
OCP Final Signatory	Shirley Seo, PhD

This addendum is the review on the additional information that the Applicant provided on March 19, 2019 via email to project manager, Maureen Dewey; this information was formally submitted to the NDA on March 25, 2019 (SDN 23).

We requested the case report forms and available documentation to better understand the reason why some subjects demonstrated little to no absorption or substantially high exposure while the Applicant claimed that those were caused by "user error" or "user variability". In most cases, there was no documentation that indicate an incomplete dosing, while the observers documented full dosing. In a few the case report forms indicated the subject moved his/her head or sneezed immediately (immediately defined as the 2 minutes following dose administration); however, the such cases did not result in low systemic exposure to metoclopramide and could not explain the PK variability observed. As such the review of this additional information does not address the OCP review deficiencies and does not change the OCP review conclusion.

The Applicant submitted case report forms for the following 17 subjects.

- Nine subjects who had little to no absorption (C_{max} < 5 ng/mL): subjects (b) (6) and (b) (6) at Gimoti 15 mg; subjects (b) (6) and (b) (6) at Gimoti 16 mg; subjects (b) (6) and (b) (6) at Gimoti 17 mg; subject (b) (6) at Gimoti 15, 16, and 17 mg

- Three subjects who had little to no absorption, but the PK profile was excluded from the PK dataset because its pre-dose concentration was > 5% of C_{max}: subjects [(b) (6)] and [(b) (6)] at Gimoti 15 mg; subjects [(b) (6)] at Gimoti 16 mg
- Five subjects who showed substantially high exposure (AUC_{inf} > 1000 h*ng/mL): subjects [(b) (6)] and [(b) (6)] at Gimoti 15 mg; subjects [(b) (6)] at Gimoti 16 mg; subject [(b) (6)] at Gimoti 15 and 17 mg; subject [(b) (6)] at 15 mg and 16 mg

The case report forms included specific questions on whether the subject moved his/her head or sneezed immediately (immediately defined as the 2 minutes following dose administration). The following issues were documented; however, the information provided did not explain the PK variability observed:

- Subject [(b) (6)] moved her head after Gimoti 17 mg and another subject (ID [(b) (6)]) sneezed after Gimoti 17 mg; however, the drug absorption was adequate for both subjects at the 17 mg dose. Subject [(b) (6)] demonstrated little to no absorption after the 16 mg dose (no head movements or sneezing documented after the 16 mg dose).
- A note was made for Subject [(b) (6)] after Gimoti 17 mg that stated "When Subject # [(b) (6)] (17 mg) was dosed, I noticed that the vial plunger dropped quickly. After Chad completed the dosing for this subject, I said to him, 'I did not hear a spray when you dosed this subject.' He said that it did not feel like much of a spray came out…not much pressure in the vial." However, her PK profile at the 17 mg was not deemed little to no absorption (C_{max}= 16.8 ng/mL).
- In the study monitor "dosing debrief summary" notes provided, one note described that "all vials were primed with 10 pumps and demonstrated full spray patterns except for one 16 mg vial. This vial showed no spray after 10 pumps. A full spray pattern was seen at pumps #12-20. This vial will be used for tomorrow's dosing." This note corresponded to a total 4 cases (i.e., subject ID [(b) (6)] (17 mg), [(b) (6)] (16 mg), [(b) (6)] (16 mg), and [(b) (6)] (16 mg)). Out of 4 cases, only subject [(b) (6)] (16 mg) showed low C_{max} <= 5 ng/mL. However, given that the documentation suggests that the vial required additional priming but was fully primed before dosing and only one out of the 4 cases showed little to no absorption, it is unclear whether the vials requiring additional priming was related to incomplete drug delivery. Of note, PK profile for 16 mg from subject [(b) (6)] was exclude from PK analysis due to its pre-dose concentration => 5% of its C_{max}. Refer to the page 18 of the Clinical Pharmacology Review dated Mar 7, 2019 for more details.

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Addendum to Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 209388
Link to EDR	\\CDSESUB1\evsprod\NDA209388\0001
Submission Date	June 1, 2018
Submission Type	Original Submission/ 505(b)(2), Standard Review
Brand Name	Gimoti
Generic Name	Metoclopramide
Dosage Form and Strength	Nasal spray, 15 mg
Proposed Dosing Regimen	15 mg four times daily
Proposed Indication	The relief of symptoms in adult females with acute and recurrent diabetic gastroparesis
Applicant	Evoke
Associated IND	IND 025512
OCP Review Team	Sojeong Yi, PhD Lian Ma, PhD (DPM TL) Insook Kim, PhD (DCP III TL)
OCP Final Signatory	Shirley Seo, PhD

This addendum is to correct the following errors in the Clinical Pharmacology Review dated Mar 7, 2019. Incorrect values are in strikethrough and corrections are in red. Of note, these corrections do not affect the OCP review conclusion.

(1) 3. Comprehensive Clinical Pharmacology Review, Section 3.2.1, Page 12, Table 8

Table 1. Bioequivalence Analysis Excluding 11 PK Profiles with Concentrations < 5 ng/mL at All Time Points in Comparison to the Original BE analysis in METO-IN-006

	Original Result[a] Geometri Mean Ratio to Reglan (90% CI)			Sensitivity Analysis excluding 11 PK profiles[b] Geometri Mean Ratio to Reglan (90% CI)		
	Gimoti 15 mg (N=97)	Gimoti 16 mg (N=98)	Gimoti 17 mg (N=98)	Gimoti 15 mg (N=94)	Gimoti 16 mg (N=96)	Gimoti 17 mg (N=93)
C_{max}	80.32 (69.29-93.11)	80.37 (69.36-93.12)	84.27 (72.74-97.64)	**90.18 (81.50-99.80)**	**90.05 (81.43-99.58)**	**99.75** (b) (4) **(90.11-110.4)**
AUC_{t}	90.25 (79.48-104.1)	91.76 (80.84-104.1)	97.01 (85.48-110.1)	99.62 (91.11-108.9)	100.7 (92.19-110.0)	111.7 (102.1-122.2)
AUC_{inf}	94.96 (85.43-105.5)	96.75 (87.09-107.5)	111.7 (100.4-124.3)	100.1 (91.70-109.3)	102.8 (94.17-112.1)	112.1 (102.7-122.4)

a.= Source: METO-IN-006 Clinical Study Report Table 11-3.=
b.= Reviewer's analysis using the dataset under Section 5.3.1.2. METO-IN-006, pp.xpt (SDN 4), N=3, 2, and 5= cases were excluded from Gimoti 15, 16, and 17 mg, respectively.=

(2) 4. Appendices, Section 4.1.1, Page 19, Table 14.

Table 2. Bioequivalence Analyses Excluding 11 PK Profiles with Extremely Low Concentrations (< 5 ng/mL at all time points) (Sensitivity Analysis II)

Group=	Par=	Geometric mean ratio (%) for Gimoti/Reglan (90% CI)=		
		Gimoti 15 mg=	Gimoti 16 mg=	Gimoti 17 mg=
Overall=	N	~~94~~	= 96	= 93 =
	$C_{max=}$	**90.18 (81.50-99.80)**	**90.05 (81.43-99.58)**	**99.75** (b) (4) **(90.11-110.4)**
	$AUC_{t=}$	99.62 (91.11-108.9)=	100.7 (92.19-110.0)=	111.7 (102.1-122.2)=
	$AUC_{inf=}$	100.1 (91.70-109.3)=	102.8 (94.17-112.1)=	112.1 (102.7-122.4)=
Female=	N	~~42~~	= 43	= 43 =
	$C_{max=}$	94.58 (81.10-110.3)=	92.92 (79.74-108.3)=	108.6 (93.06-126.6)=
	$AUC_{t=}$	104.9 (91.24-120.6)=	108.1 (94.14-124.2)=	122.3 (106.4-140.7)=
	$AUC_{inf=}$	104.7 (91.12-120.4)=	107.9 (93.90-123.9)=	122.5 (106.5-140.8)=
Male=	N	~~57~~	= 57	= 55 =
	$C_{max=}$	86.81 (75.66-99.60)=	87.84 (76.63-100.7)=	93.90 (81.78-107.8)=
	$AUC_{t=}$	95.89 (85.18-107.9)=	95.48 (84.88-107.4)=	104.5 (92.76-117.7)=
	$AUC_{inf=}$	96.95 (86.44-108.7)=	99.09 (88.36-111.1)=	105.1 (93.68-118.0)=

Source: Reviewer's analysis using the dataset under Section 5.3.1.2. METO-IN-006, pp.xpt (SDN 4)

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03/21/2019 04:00:25 PM

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 209388
Link to EDR	\\CDSESUB1\evsprod\NDA209388\0001
Submission Date	June 1, 2018
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Applicant	Evoke
Associated IND	IND 025512
OCP Review Team	Sojeong Yi, PhD Lian Ma, PhD (DPM TL) Insook Kim, PhD (DCP III TL)
OCP Final Signatory	Shirley Seo, PhD

Table of Contents

1. EXECUTIVE SUMMARY

In this original NDA, the Applicant is seeking approval of the metoclopramide nasal spray, Gimoti, for the relief of symptoms in adult women with acute and recurrent diabetic gastroparesis via 505(b)(2) pathway with Reglan oral tablet as the listed drug. The proposed dosage regimen of Gimoti is 15 mg four times daily, 30 minutes before each meal and at bedtime for 2 to (b)(4) weeks. Reglan was approved for acute and recurrent diabetic gastroparesis on Dec 30, 1980 (NDA 17584) with a regimen of one 10 mg oral tablet four times daily.

Notably, the Applicant proposed to indicate only for female patients while the listed drug, Reglan, is indicated for both male and females claiming that benefit in male patients with acute and recurrent diabetic gastroparesis has not been demonstrated in phase 2 and phase 3 clinical studies. However, per the clinical review team, the female only indication was not adequately justified in this submission as the clinical data is insufficient to conclude that male patients would not receive benefit at the proposed dose (See the clinical review for more details).

To establish a bridge between Gimoti and Reglan, the Applicant conducted a relative bioavailability (BA) study (METO-IN-006) as a pivotal study. In METO-IN-006, systemic exposure to metoclopramide was compared between single nasal administration of Gimoti at 15 mg, 16 mg, or 17 mg and single oral administration of Reglan tablet 10 mg in 98 healthy male and female subjects. Gimoti for all three doses showed comparable AUC but 16 to 20% lower C_{max} than Reglan. The Applicant proposed Gimoti 15 mg dose for female patients only based on a post-hoc subgroup analysis of relative BA by sex claiming that Gimoti 15 mg showed the most closely matched systemic exposure to Reglan in the subgroup of female subjects. However, the female only indication is not adequately supported and the bridge between Gimoti and Reglan needs to be established regardless of sex. The post-hoc subgroup analysis of relative BA by sex conducted by the Applicant is not acceptable to establish a bridge between Gimoti and Reglan.

The OCP review focused on the analyses of relative bioavailability without regard sex to support the reliance of the efficacy and safety of Reglan. Gimoti, at all tested doses (15 mg, 16 mg, and 17 mg), demonstrated lower metoclopramide C_{max} than Reglan, but the potential effects of the lower C_{max} on efficacy have not been adequately addressed. Therefore, OCP has concluded that the potential for suboptimal efficacy due to the lower C_{max} cannot be ruled out and the results of METO-IN-006 do not adequately support the bridging of efficacy between Gimoti and Reglan. In addition, substantially higher variability in systemic metoclopramide exposure after Gimoti administration was noted. Several subjects demonstrated little to no absorption of metoclopramide only when Gimoti was administered (but not with Reglan), which may indicate incomplete dosing from the Gimoti nasal spray.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the submission and concluded that the submitted data is inadequate to support the approval of the proposed product, Gimoti 15 mg, from a clinical pharmacology standpoint. We recommend a complete response for this NDA.

To address the clinical pharmacology deficiency, we recommend that the Applicant identify the reasons for the variability of PK for Gimoti. Subsequently, the Applicant may need to reformulate the product to ensure consistent and complete drug delivery and then conduct another relative BA

study with a new formulation in both male and female subjects. A human factor study may be warranted to assure consistent and complete drug delivery.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Metoclopramide is a dopamine-receptor antagonist, an antiemetic, and a stimulant of upper gastrointestinal motility. Oral and injectable formulations of metoclopramide have been approved for the relief of symptoms associated with acute and recurrent diabetic gastroparesis.

The Applicant has developed Gimoti as a nasal spray formulation of metoclopramide, to provide systemic delivery through nasal mucosa bypassing the gastrointestinal (GI) system. Even though intranasal administration is typically expected to avoid GI and hepatic first-pass effect, some extent of intranasally administered dose is known to be absorbed in the GI[1].

Per the approved label of Reglan, metoclopramide undergoes enzymatic metabolism via oxidation as well as glucuronide and sulfate conjugation reactions in the liver. A major oxidative metabolite, is formed primarily by CYP2D6, an enzyme subject to genetic variability. Metoclopramide and its metabolites are primarily excreted in urine. The mean elimination half-life in subjects with normal renal function was 5 to 6 hours following oral administration. Metoclopramide is not extensively bound to plasma proteins (about 30%).

Pharmacokinetic parameters of Gimoti across studies

Following single dose nasal administration of Gimoti in healthy male and female subjects, systemic exposure increased proportionally with dose between 10 to 80 mg. **Table 1** shows the summary of pharmacokinetic (PK) parameters from METO-IN-001 and METO-IN-006. Of note, the median T_{max} of Gimoti was similar to that of Reglan but a greater variability in T_{max} was noted for Gimoti. Following nasal administration, half-life ranged from 7 to 8 hours.

Table 1. Summary of Key PK parameters for Metoclopramide following Single Dose in Healthy Subjects

Study	Formulation	N	Mean (CV%)		Median (Range)
			C_{max} (ng/mL)	$AUC_{0\text{-}36h}$ (ng*h/mL)	T_{max} (h)
METO-IN-001	Reglan Tablet 10 mg	39	43.9 (36.0)	376 (54.8)	1.25 (0.5-3.5)
	Reglan IV 5 mg	39	35.8 (42.2)	224 (36.1)	0.25 (0.25-1.25)
	Gimoti 10 mg	38	22.8 (55.5)	232 (63.0)	1.5 (0.5-3.5)
	Gimoti 20 mg	39	54.2 (45.9)	510 (52.2)	1.5 (0.75-3.5)
METO-IN-006	Reglan Tablet 10 mg	102	39.4 (36.9)	305 (35.2)	1.0 (0.5-3.5)
	Gimoti 15 mg	97	31.6 (112)	274 (96.9)	1.25(0.5-10.0)
	Gimoti 16 mg	98	31.7 (102)	280 (92.2)	1.25 (0.25-8.0)
	Gimoti 17 mg	98	33.5 (126)	298 (109)	1.25 (0.25-16.0)

Source: METO-IN-001, Clinical Study Report In-text Table 11-2 and Table 15.2.5; METO-IN-006 Clinical Study Report Table 14.2.2

[1] Grassin-Delyle et al, Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. Pharmacol Ther. 2012 Jun;134(3):366-79.

Relative bioavailability of Gimoti 15, 16, and 17 mg compared to Reglan 10 mg

In METO-IN-006, a pivotal relative BA study, Gimoti 15 mg showed similar AUC but approximately 20% lower C_{max} compared to Reglan. Likewise, despite having comparable AUC to Reglan, both Gimoti 16 mg and 17 mg showed consistently lower C_{max} than that of Reglan by 20% and 16%, respectively (**Table 2**).

Table 2. Relative Bioavailability of Gimoti to Reglan 10 mg from METO-IN-006

	Geometric mean ratio (%) for Gimoti/Reglan 10 mg (90% CI)		
	Gimoti 15 mg (N=97)	Gimoti 16 mg (N=98)	Gimoti 17 mg (N=98)
C_{max}	80.32 (69.29-93.11)	80.37 (69.36-93.12)	84.27 (72.74-97.64)
AUC_t	90.25 (79.48-102.5)	91.76 (80.84-104.1)	97.01 (85.48-110.1)
AUC_{inf}	94.96 (85.44-105.5)*	96.75 (87.09-107.5)*	111.7 (100.4-124.3)*

* N=95, N=96, and N=93 for Gimoti 15 mg, 16 mg, and 17 mg, respectively.
Source: METO-IN-006 Clinical Study Report Table 11-3.

One hypothesis is that the approximately 20% lower C_{max} was caused by inconsistent and incomplete drug delivery of Gimoti. There were 11 PK profiles from 9 subjects (6 males and 3 females) across doses demonstrated virtually no drug absorption (plasma concentrations < 5 ng/ml at all time points) when administered Gimoti while those same subjects demonstrated expected metoclopramide absorption when given oral Reglan.

As a sensitivity analysis by the reviewer, when the 11 PK profiles (3 from 15 mg, 3 from 16 mg, 5 from 17 mg) from 9 subjects with virtually no drug absorption were excluded from the PK dataset, both C_{max} and AUC of Gimoti for all three different doses compared to Reglan fell within the standard "no-effect" criteria (i.e., 90% CI: 80-125%).

Effects of Sex on PK of metoclopramide

The Applicant found that females had higher systemic exposure to metoclopramide than males for both Gimoti and Reglan across PK studies. The effects of sex on metoclopramide PK is stated neither in Reglan label nor in published literature. The magnitude of sex difference varied substantially depending on formulation and study, e.g., mostly 22-56% higher AUC_{inf} with one case of 3% higher AUC_{inf} in females than in males (**Table 3**).

The potential reason for the sex difference in PK was not clearly explained in this submission. When normalized to body weight, the geometric mean AUC and C_{max} were still higher than females than in males (i.e., 33-97% for AUC_{inf} per kg; 62% for C_{max} per kg). On the other hand, the Applicant's population PK analysis suggested that the PK difference between sexes is attributed to difference in lean body mass. Females (who tend to have lower lean body mass than males) are likely to have lower clearance, subsequently resulting in higher exposure compared to males.

Still, provided that intrinsic factors (such as sex) are controlled in a crossover study design, sex effect is not expected to affect comparison of bioavailability between formulations. Therefore, regardless of sex differences in PK, METO-IN-006 was designed such that Gimoti could have demonstrated comparable bioavailability to Reglan in both male and female subjects.

Table 3. Sex Difference (%) in AUC_{inf} by Treatment and Sex Across Studies

Study	Treatment	Geometric mean [geometric CV%] (N)		Sex Difference (%) [(Female-Male)/Male*100]
		Male	Female	
METO-IN-006	Reglan 10 mg	287 [35.1] (58)	360 [34.8] (43)	25.70
	Gimoti 15 mg	261 [85.9] (57)	391 [57.5] (43)	49.59
	Gimoti 16 mg	229 [92.4] (56)	385 [80.2] (44)	48.60
	Gimoti 17 mg	282 [89.2] (56)	415 [94.8] (42)	46.88
METO-IN-001	Reglan 5 mg IV	188 [27.8] (24)	280 [35.9] (14)	49.23
	Reglan 10 mg	296 [42.9] (25)	463 [54.7] (14)	56.39
	Gimoti 10 mg	214 [74.2] (22)	220 [82.3] (13)	2.83
	Gimoti 20 mg	434 [45.1] (24)	532 [93.7] (12)	22.44
METO-IN-005 (Reviewer's analysis)	Gimoti 20 mg	181 [112] (24)	252 [91.1] (24)	39.54
	Gimoti 80 mg	534 [177] (24)	733 [111] (24)	37.16

Source: Other than METO-IN-005, data from Clinical Pharmacology Summary, Table 17; Reviewer's analysis for METO-IN-005 used the dataset under Section 5.3.4.1. METO-IN-005B, pp.xpt (SDN 1)

Relative bioavailability of Gimoti to Reglan by sex

The Applicant conducted a post-hoc subgroup analysis by sex for the relative BA data in METO-IN-006; the relative BA of Gimoti to Reglan in female subjects was higher than that of male subjects and was closer to Reglan (**Table 4**). The Applicant claimed that nearly comparable AUC and C_{max} of Gimoti 15 mg to Reglan in female subgroup supports approval of Gimoti 15 mg dose for female patients while the Applicant did not propose a dose for male patients because they did not seek an indication for male patients.

However, the post-hoc subgroup analysis for the relative BA data cannot be considered confirmatory to support the establishment of a bridge between Gimoti 15 mg and Reglan in the female population only, even though that the relative BA nearly met the standard "no-effect" criteria in the subgroup. The results from the post-hoc subgroup analysis should be interpreted in an exploratory manner.

Table 4. Relative Bioavailability of Gimoti to Reglan 10 mg by Sex from METO-IN-006

Group	Par	Geometric mean ratio (%) for Gimoti/Reglan (90% CI)		
		Gimoti 15 mg	Gimoti 16 mg	Gimoti 17 mg
Female	N	41	42	43
	C_{max}	**93.08 (76.60-113.1)**	87.44 (72.02-106.2)	92.79 (76.56-112.5)
	AUC_t	**102.9 (86.07-123.1)**	101.9 (85.28-121.8)	105.6 (88.55-126.0)
	AUC_{inf}	**102.8 (88.73-119.0)**	101.5 (87.70-117.5)	120.3 (103.9-139.4)[a]
Male	N	56	56	55
	C_{max}	72.04 (58.11-89.32)	75.85 (61.19-94.03)	78.60 (63.33-97.56)
	AUC_t	81.91 (68.46-98.02)	85.10 (71.13-101.8)	91.22 (76.16-109.2)
	AUC_{inf}	89.45 (76.85-104.1)[b]	93.15 (80.05-108.4)[b]	105.7 (90.64-123.2)[b]

a. N=41

b. N=54, N=54, and N=52 for Gimoti 15 mg, 16 mg, and 17 mg, respectively.

Source: METO-IN-006 Clinical Study Report, Table 11-5, Table 11-6

In METO-IN-006, the lower relative BA of Gimoti to Reglan in males (but not in females) appeared to suggest that the sex difference in PK is specifically correlated to formulations or route of administration (i.e., sex-by-formulation effect). However, from additional analysis of METO-IN-001 (the subgroup analysis of relative BA by sex), the review team found that the sex difference on relative BA of Gimoti to Reglan is inconsistent between METO-IN-006 and METO-IN-001 suggesting that the sex difference in PK may NOT be specifically correlated to formulations (see Section 3.2.2 for further details).

Potential for QT prolongation

In the tQT study, METO-IN-005, no significant effects on QTc prolongation was detected at single dose Gimoti 20 mg and 80 mg (**Table 5**). Refer to the IRT-QT review (dated Jun 23, 2016 under IND 25512 in DARRTS) for further details.

Table 5. The Point Estimates for ddQTcF and the 90% CIs Corresponding to the Largest Upper Bounds for Metoclopramide Nasal Spray (Single Dose of 20 mg and 80 mg) and the Largest Lower Bound for Moxifloxacin (IRT-QT review)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Metoclopramide 20 mg	3	3.5	(1.0, 6.0)
Metoclopramide 80 mg	2	4.1	(1.6, 6.6)
Moxifloxacin 400 mg*	4	13.4	(10.0, 16.8)

* Multiple endpoint adjustment of 4 time points was applied.

Source: IRT-QT review Jun 23, 2016 under IND 25512 in DARRTS

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosage regimen for Gimoti is 15 mg (single pump) QID, 30 minutes before each meal and at bedtime, in adult women with acute and recurrent diabetic gastroparesis.

2.2.2 Therapeutic individualization

Per the approved label of Reglan, dose regimens between 5 mg BID and 10 mg QID are recommended for specific populations such as geriatric patients, patients with moderate or severe renal or hepatic impairment, and CYP2D6 poor metabolizers/CYP2D6 inhibitor users (**Table 6**). Unlike Reglan, the proposed nasal spray formulation cannot adjust the dose delivered per pump. (b) (4) (b) (4)

The Applicant provided (b) (4) (b) (4) (b) (4) should not be considered unless further information is made available.

Table 6. Proposed Dose Adjustment for Gimoti compared to Reglan

Population	Gimoti Proposed dosage regimen	Reglan Approved dosage regimen
Adult patients	15 mg QID (maximum 60 mg/day)	10 mg QID (maximum 40 mg/day)
Mild hepatic impairment (Child-Pugh A)		
Elderly patients	(b) (4)	5 mg QID with titration to 10 mg QID based upon response and tolerability (maximum 40 mg/day)
Moderate or severe hepatic impairment (Child-Pugh B or C)		5 mg QID (maximum 20 mg/day)
CYP2D6 poor metabolizers		
Concomitant use with strong CYP2D6 inhibitors (e.g., quinidine, bupropion, fluoxetine, and paroxetine)		
Moderate or severe renal impairment (creatinine clearance ≤60 mL/minute)		
Patients with End-Stage Renal Disease (ESRD) including those treated with hemodialysis and continuous ambulatory peritoneal dialysis		5 mg BID (maximum 10 mg/day)

Source: Section 1.14.1.3. Draft Labeling Text and Section 1.14.3.3. Labeling Text for Listed Drug

2.3 Outstanding Issues

(1) Gimoti, at all tested doses (15 mg, 16 mg, and 17 mg), failed to demonstrate comparable bioavailability to the listed drug (Reglan 10 mg). As C_{max} of Gimoti is on average 16 to 20% lower than that of Reglan and no adequate justification for the potential suboptimal efficacy due to the lower C_{max} was provided. As such, the results of METO-IN-006 cannot support the establishment of an adequate pharmacokinetic bridge between Gimoti and Reglan. In addition, the following were noted:

- Inconsistent and incomplete drug delivery of Gimoti suggested by virtually no drug absorption in a few cases seems to have significantly contributed to the lower C_{max} of Gimoti to Reglan across studied doses. It could potentially lead to suboptimal and inconsistent effect of the drug.
- There was higher overall inter- and intra-subject variability in drug exposure for Gimoti as compared to that of Reglan. It raises a potential safety concern for cases with substantially higher exposure than that of Reglan.

(2) (b) (4)

2.4 Summary of Labeling Recommendations

Not applicable.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Each nasal spray of Gimoti delivers a pre-determined volume (70 µL) containing metoclopramide 15 mg. To establish a bridge between Gimoti 15 mg and Reglan 10 mg, the Applicant conducted a pivotal relative BA study (METO-IN-006). In addition, 5 clinical trials including a tQT study using different metoclopramide dose levels and 1 supportive clinical study with different nasal sprays from the final formulation of Gimoti were submitted (**Table 7**).

Table 7. Clinical Studies Included in the Submissions

Study Number	Design	Subjects	Regimen/Treatment
METO-IN-006 (Pivotal Relative BA study)	4-way crossover, comparative bioavailability	Healthy male and female (N=108)	Single dose/ Gimoti 15 mg Gimoti 16 mg Gimoti 17 mg Reglan oral 10 mg
METO-IN-001 (Phase 1)	4-way crossover, comparative bioavailability	Healthy male and female (N=40)	Single dose/ Gimoti 10 mg Gimoti 20 mg Reglan oral 10 mg Reglan IV 5 mg
METO-IN-002 (Phase 2)	Randomized, double-blind, placebo-controlled, dose-ranging	Male and female patients with diabetic gastroparesis (N=287)	QID for 4 weeks/ Gimoti 10 mg Gimoti 14 mg Placebo
METO-IN-003 (Phase 3)	randomized, double-blind, placebo-controlled study	**Female** patients with diabetic gastroparesis (N=205)	QID for 4 weeks Gimoti 10 mg (N=102) Placebo (N=103)
METO-IN-004 (Phase 3)	randomized, double-blind, placebo-controlled study	**Male** patients with diabetic gastroparesis (N=53)	QID for 4 weeks/ Gimoti 10 mg Placebo
METO-IN-005 (tQT study)	Randomized, double-blind, placebo-controlled, 4-way crossover study	Healthy male and female (N=48)	Single dose/ Gimoti 20 mg Gimoti 80 mg Placebo Moxifloxacin 400 mg
25,512-302R (supportive PK-PD study)	randomized, open-label, active-controlled study	Male and female patients with diabetic gastroparesis (N=89)	Nasal spray 10 mg* Nasal spray 20 mg* Reglan oral 10 mg

*a different nasal spray formulation from Gimoti

The Applicant proposes the indication in female patients with diabetic gastroparesis based on clinical efficacy data from METO-IN-002, METO-IN-003, and METO-IN-004, claiming that male patients would not benefit from Gimoti. Refer to the clinical review for comments on the efficacy trials.

However, given that the phase 2 and phase 3 clinical studies were conducted at lower doses than the proposed dose and failed to demonstrate clinical efficacy with the primary endpoint, the phase 2 and phase 3 studies are not considered relevant to support the proposed dose or the clinical pharmacology information. Therefore, this review is focused on the pivotal relative BA study (METO-IN-006 with Gimoti 15, 16, and 17 mg), and the supportive relative BA study (METO-IN-001 with Gimoti 10 and 20 mg).

Of note, the Office of Study Integrity and Surveillance (OSIS) reviewed the inspectional findings of the clinical site and concluded that the clinical data from Study METO-IN-006 are reliable (the bioanalytical site inspection was waived). Refer to the Bioequivalence Establishment Inspection Report Review by OSIS dated Jan 14, 2019 in DARRTS.

It should also be noted that the following points had been discussed with the Applicant before this NDA submission:

- On Mar 28, 2017, the Applicant updated that the phase 2 and phase 3 clinical studies at Gimoti 10 mg and 14 mg had failed to show significant efficacy compared to placebo. The Applicant and the FDA discussed taking 505(b)(2) pathway with Reglan oral tablet as the listed product. Regarding the design of a relative BA study, the Applicant proposed a relative BA study only in female subjects. FDA recommended not limiting the enrollment to females unless female only indication is adequately justified even if an indication for females only was being considered.
- On Jan 25, 2018, in the Pre-NDA meeting with the data from the completed METO-IN-006, the Applicant was advised to address the clinical implication of a 20% lower C_{max} for the proposed Gimoti 15 mg compared to the listed product (b) (4) (b) (4) Also, the FDA stated that the proposed restriction to the target population of only adult females might be acceptable provided that submitted justification could adequately support the reason why the proposed Gimoti 15 mg would not be effective in males.

3.2 Clinical Pharmacology Questions

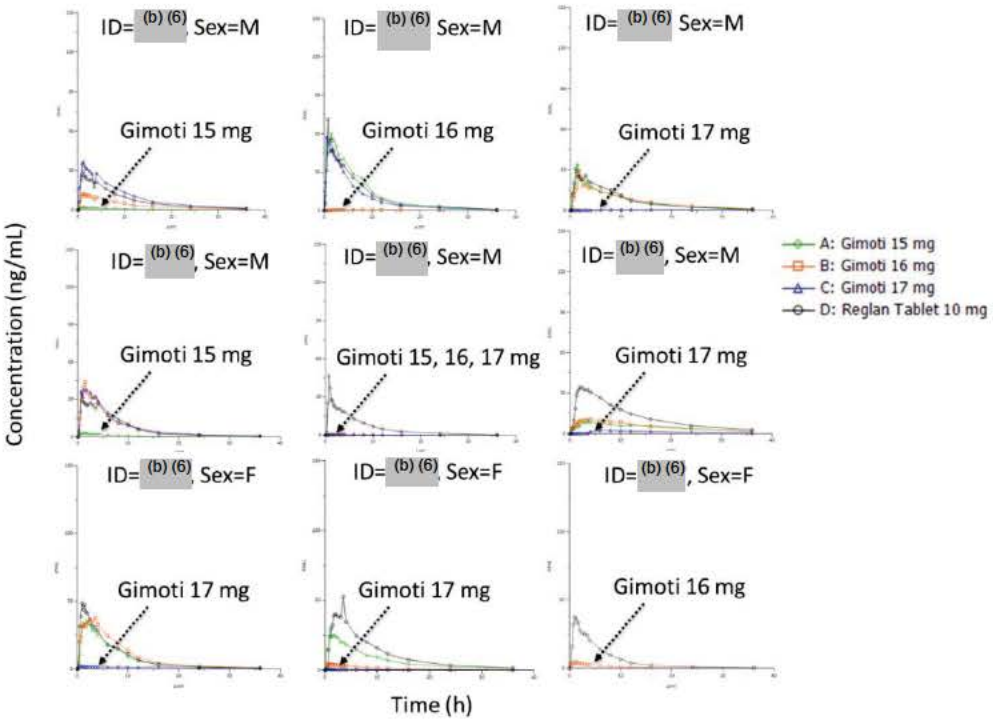
3.2.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

No. Gimoti at the proposed dose of 15 mg showed 20% lower C_{max} compared to Reglan 10 mg in METO-IN-006. Potential effects of lower C_{max} on the efficacy was not adequately addressed and potentially suboptimal efficacy of Gimoti due to lower C_{max} cannot be ruled out. Thus, comparable efficacy between Gimoti 15 mg and Reglan 10 mg cannot be supported by PK based bridging.

METO-IN-006 was an open-label, 4-way crossover, single-dose study to compare bioavailability between nasal administration of Gimoti 15, 16, and 17 mg and oral administration of Reglan 10 mg in 98 healthy male and female subjects. Gimoti 15 mg showed comparable AUC but approximately 20% lower C_{max} than that of Reglan. Likewise, despite having comparable AUC to Reglan, both Gimoti 16 mg and 17 mg showed consistently lower C_{max} than that of Reglan by 20% and 16%, respectively (**Table 2. Relative Bioavailability of Gimoti to Reglan 10 mg from METO-IN-006**, Section 2.1).

One hypothesis is that the approximately 20% lower C_{max} was caused by inconsistent and incomplete drug delivery of Gimoti. Virtually no drug absorption was observed in several subjects when administered Gimoti while expected metoclopramide absorption was observed when given oral Reglan. Specifically, there were 11 PK profiles from 9 subjects showing plasma concentrations < 5 ng/ml at all time points in comparison to the mean C_{max} around 30 ng/mL, which accounted for 3.7% of total 293 PK profiles following Gimoti administration (**Figure 1**).

Figure 1. Individual Plasma Concentration-Time Profiles of Subjects Whose Concentrations Were < 5 ng/mL at All Time Points Following Nasal Administration of Gimoti



Source: Reviewer's plots using the dataset under Section 5.3.1.2. METO-IN-006, pc.xpt (SDN 4)

As a sensitivity analysis, when the aforementioned 11 PK profiles were excluded, all three doses of Gimoti fell within the standard "no-effect" criteria for both C_{max} and AUC (**Table 8**). The lower C_{max} was driven by the handful of subjects with virtually no drug absorption following Gimoti administration. A near-complete lack of systemic exposure to metoclopramide following nasal spray, i.e., plasma concentrations < 5 ng/ml at all time points, may indicate either subject error in administering the dose and/or a faulty spray device.

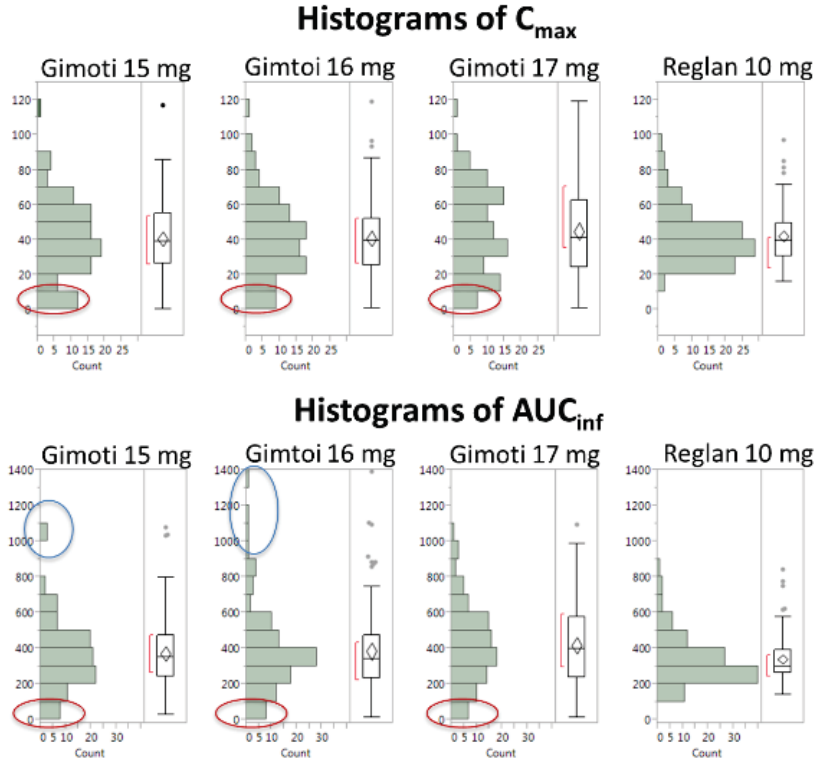
Table 8. Bioequivalence Analysis Excluding 11 PK Profiles with Concentrations < 5 ng/mL at All Time Points in Comparison to the Original BE analysis in METO-IN-006

	Original Result[a] Geometri Mean Ratio to Reglan (90% CI)			Sensitivity Analysis excluding 11 PK profiles[b] Geometri Mean Ratio to Reglan (90% CI)		
	Gimoti 15 mg (N=97)	Gimoti 16 mg (N=98)	Gimoti 17 mg (N=98)	Gimoti 15 mg (N=94)	Gimoti 16 mg (N=96)	Gimoti 17 mg (N=93)
C_{max}	80.32 (69.29-93.11)	80.37 (69.36-93.12)	84.27 (72.74-97.64)	**90.18 (81.50-99.80)**	**90.05 (81.43-99.58)**	**99.75 (81.43-99.58)**
AUC_t	90.25 (79.48-104.1)	91.76 (80.84-104.1)	97.01 (85.48-110.1)	99.62 (91.11-108.9)	100.7 (92.19-110.0)	111.7 (102.1-122.2)
AUC_{inf}	94.96 (85.43-105.5)	96.75 (87.09-107.5)	111.7 (100.4-124.3)	100.1 (91.70-109.3)	102.8 (94.17-112.1)	112.1 (102.7-122.4)

a. Source: METO-IN-006 Clinical Study Report Table 11-3.
b. Reviewer's analysis using the dataset under Section 5.3.1.2. METO-IN-006, pp.xpt (SDN 4), N=3, 2, and 5 cases were excluded from Gimoti 15, 16, and 17 mg, respectively.

Furthermore, from not only individual PK profiles but also histograms of C_{max} and AUC, we found higher inter- and intra-subject variability in drug exposure for Gimoti as compared to that of Reglan. Due to the greater variability, some subjects showed substantially higher drug exposure than that of the listed product (**Figure 2**, blue circle) whereas other subjects showed extremely low exposure (**Figure 2**, red circle), consistent with the aforementioned PK profiles showing virtually no drug absorption.

Figure 2. Distribution of C_{max} and AUC_{inf} by treatment in METO-IN-006



Source: Reviewer's plot using the dataset under Section 5.3.1.2. METO-IN-006, pp.xpt (SDN 4)

This inconsistent drug absorption with higher variability than the listed drug is deemed clinically significant because it raises a potential safety concern for cases with substantially higher exposure than that of the listed product while an efficacy concern also exists for cases with virtually no drug absorption. Since a human factor study was not conducted for Gimoti, a human factor study may be warranted to assure consistent and complete drug delivery.

3.2.2 Is the proposed general dosing regimen appropriate for the female patient population for which the indication is being sought?

No. The proposed dose, Gimoti 15 mg, for female patients only is not appropriate given that in METO-IN-006 Gimoti 15 mg could not demonstrate comparable bioavailability to Reglan as discussed in Section 3.2.1 and the proposed female only indication was not adequately justified, per the clinical review team.

The Applicant claimed that Gimoti 15 mg dose for female patients can be supported by a post-hoc subgroup analysis of the relative BA data in METO-IN-006 which showed nearly comparable AUC and C_{max} at Gimoti 15 mg in female subgroup (**Table 4. Relative Bioavailability of Gimoti to Reglan 10 mg by Sex from METO-IN-006**, Section 2.1.). However, the subgroup analysis which was not originally planned cannot be confirmatory to support the establishment of a bridge between Gimoti and Reglan. Of note, while there were 41 female subjects for Gimoti 15 mg in METO-IN-006, if the subgroup analysis by sex had been pre-specified as a primary objective in the protocol, approximately 75-100 subjects per sex would have been needed to have 80-90% power assuming an intra-subject variability of 43% obtained from METO-IN-001.

In the Applicant's supplemental PK analysis, females consistently showed higher exposure to metoclopramide than males in both Gimoti and Reglan across PK studies (see Appendix 4.1.4. for details of the Applicant's supplemental sex-based PK analysis). However, it is noted that Reglan is approved for use in both females and males at the same dose. Since sex effect as an intrinsic factor that is controlled in a crossover study design, sex difference in PK does not affect comparison of bioavailability between formulations. Therefore, regardless of sex differences in PK, the study was designed such that Gimoti could have demonstrated comparable bioavailability to Reglan, in both male and female subjects.

Furthermore, in a subgroup analysis of METO-IN-006, the relative BA (Gimoti vs. Reglan) in males was lower than that in females at all three doses. It appeared to suggest that the sex difference in PK is specifically correlated to formulation or route of administration (i.e., sex-by-formulation effect); in other words, only male subjects tended to have lower absorption when they received Gimoti compared to when they received Reglan. However, the review team found that the sex difference in relative BA of Gimoti to Reglan is inconsistent between studies which would suggest that the sex difference in PK may NOT be specifically correlated to formulation. In METO-IN-006, the relative BA of Gimoti to Reglan in males was lower than females whereas in METO-IN-001, it was higher than females (**Table 9**).

Table 9. Relative Bioavailability of Gimoti to Reglan 10 mg by Sex Across Studies

Study	Treatment	Parameter	GMR (Gimoti/Reglan) (90% CI)	
			Female	Male
METO-IN-006[a] (Male, N = 57; Female, N= 42)	Gimoti 15 mg	C_{max}	93.08 (76.60-113.1)	72.04 (58.11-89.32)
		AUC_{inf}	102.8 (88.73-119.0)	89.45 (76.85-104.1)
	Gimoti 16 mg	C_{max}	87.44 (72.02-106.2)	75.85 (61.19-94.03)
		AUC_{inf}	101.5 (87.70-117.5)	93.15 (80.05-108.4)
	Gimoti 17 mg	C_{max}	92.79 (76.56-112.5)	78.60 (63.33-97.56)
		AUC_{inf}	120.3 (103.9-139.4)	105.7 (90.64-123.2)
METO-IN-001[b] (Male, N = 25; Female, N= 14)	Gimoti 10 mg	C_{max}	38.09 (28.39-51.10)	51.29 (40.89-64.33)
		AUC_{inf}	44.30 (33.18-59.14)	72.97 (61.49-86.60)
	Gimoti 20 mg	C_{max}	98.18 (73.75-130.7)	135.0 (107.6-169.5)
		AUC_{inf}	109.4 (81.04-147.7)	151.3 (128.1-178.8)

a. Source: METO-IN-006 Clinical Study Report Table 11-3.
b. Reviewer's analysis using the dataset under Section 5.3.1.2. METO-IN-001, pp.xpt (SDN 4)

In addition, when three PK profiles of 15 mg in males with concentrations < 5 ng/ml at all time points were excluded from the analysis, the "no-effect" criteria were met for C_{max} and AUC (see Section 3.2.1 above) indicating that incomplete drug delivery at least in part contributed to the lower mean C_{max} for Gimoti in male subjects. Of note, PK profiles of virtually no absorption was observed in both male and female subjects across doses.

3.2.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors or extrinsic factors?

Yes. Per the labeling of Reglan, dose adjustment is recommended for specific populations such as geriatric patients, patients with moderate or severe renal or hepatic impairment, and CYP2D6 poor metabolizers/CYP2D6 inhibitor users. However, unlike Reglan, the dose in the proposed Gimoti nasal spray cannot be adjusted to deliver a different amount per pump and a lower strength formulation, e.g., 7.5 mg, is not available. Therefore, no recommendations can be made for use in specific populations until a lower strength formulation becomes available.

Originally, the Applicant proposed (b) (4)

(b) (4)

4. APPENDICES

4.1 Individual Study Review

4.1.1 METO-IN-006: Pivotal Relative BA Study

Title: A Four-Period, Four-Treatment, Four-Sequence Randomized Crossover Study of the Comparative Bioavailability of Metoclopramide After Nasal and Oral Administration to Healthy Volunteers Under Fasted Conditions

Design: This study was an open-label, randomized, 4-treatment, 4-period, 4-sequence crossover study at a single study center designed to identify the Gimoti dose that provided equivalent systemic exposure to the listed drug, Reglan Tablets 10 mg. The study enrolled 108 healthy subjects to achieve 100 subjects for the PK population.
The sequence of the treatments was randomly assigned using a Williams Latin square, so all subjects received a single dose of metoclopramide per sequence assignment, i.e., 3 Gimoti doses or the Reglan Tablets as follows:

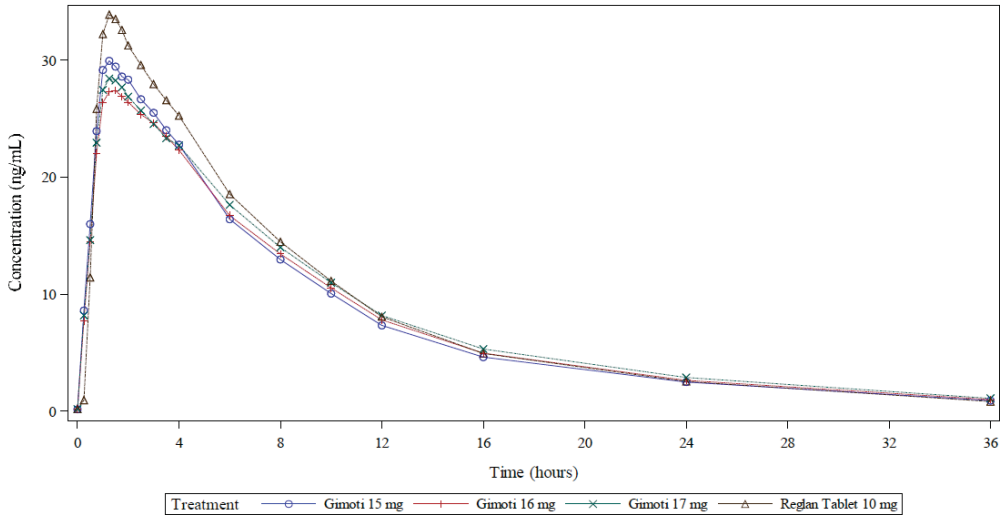
	Period 1	Period 2	Period 3	Period 4
Sequence 1 (ABCD)	A: Gimoti 15 mg	B: Gimoti 16 mg	C: Gimoti 16 mg	D: Reglan 10 mg
Sequence 2 (BDAC)	B: Gimoti 16 mg	D: Reglan 10 mg	A: Gimoti 15 mg	C: Gimoti 16 mg
Sequence 3 (CADB)	C: Gimoti 16 mg	A: Gimoti 15 mg	D: Reglan 10 mg	B: Gimoti 16 mg
Sequence 4 (DCBA)	D: Reglan 10 mg	C: Gimoti 16 mg	B: Gimoti 16 mg	A: Gimoti 15 mg

Subjects remained confined to the CRU until after the final PK samples were collected at 36 hours after each dose. Subjects returned to the CRU after a minimum 5-day washout period for subsequent doses until the 4-period crossover was completed. Although it was not specified how nasal spray dosing was instructed in the protocol, the directions for nasal administration of Gimoti was included in the Appendix of the protocol.

Standard meals were provided at such times as to allow for a fasted state of at least 10 hours at the time of study drug administration. Blood draws for PK sampling were collected before dosing (Time 0), and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, and 36 hours post-dose.

Result: The PK population included 102 subjects who received at least 2 doses of study drug, one of which was the listed product (Reglan Tablet) and provided an adequate number of blood samples for the determination of plasma PK parameters. The results of PK analysis are shown in **Figure 3** and **Table 10.**

Figure 3. Geometric Mean Plasma Concentrations of Metoclopramide after Single Doses of Gimoti and Reglan in Healthy Subjects



Source: METO-IN-006 Clinical Study Report, Figure 11-1

Table 10. Summary of Geometric Mean (CV%) of Metoclopramide PK

Parameter	Gimoti 15 mg	Gimoti 16 mg	Gimoti 17 mg	Reglan Tablets 10 mg
N	97 [2]	98 [2]	98 [2]	102 [2]
AUC_t (h*ng/mL)	274 (96.9)	280 (92.2)	298 (109)	305 (35.2)
AUC_∞ (h*ng/mL)	302 (76.8) (N = 95)	308 (79.5) (N = 96)	360 (68.1) (N = 93)	316 (36.8) (N = 101)
C_{max} (ng/mL)	31.6 (112)	31.7 (102)	33.5 (126)	39.4 (36.9)
t_{max} [1] (h)	1.25 (0.50-10.00)	1.25 (0.25-8.00)	1.25 (0.25-16.00)	1.00 (0.50-3.50)
λ_z (/h)	0.0868 (22.0) (N = 96)	0.0858 (24.1) (N = 97)	0.0869 (19.5) (N = 96)	0.0949 (16.1) (N = 101)
$t_{½}$ (h)	7.99 (22.0) (N = 96)	8.08 (24.1) (N = 97)	7.98 (19.5) (N = 96)	7.30 (16.1) (N = 101)

Source: METO-IN-006 Clinical Study Report Table 11-2

The results of the bioequivalence analyses for the overall population, and subgroups by sex are presented in **Table 11**.

Table 11. Bioequivalence Analyses for Metoclopramide

Population	Parameter	Geometric mean ratio (%) for Gimoti/Reglan (90% CI)		
		Gimoti 15 mg	Gimoti 16 mg	Gimoti 17 mg
Overall	N	97	98	98
	C_{max}	**80.32 (69.29-93.11)**	80.37 (69.36-93.12)	84.27 (72.74-97.64)
	AUC_t	**90.25 (79.48-102.5)**	91.76 (80.84-104.1)	97.01 (85.48-110.1)
	AUC_{inf}	**94.96 (85.44-105.5)**[a]	96.75 (87.09-107.5)[a]	111.7 (100.4-124.3)[a]
Female	N	41	42	43
	C_{max}	**93.08 (76.60-113.1)**	87.44 (72.02-106.2)	92.79 (76.56-112.5)
	AUC_t	**102.9 (86.07-123.1)**	101.9 (85.28-121.8)	105.6 (88.55-126.0)
	AUC_{inf}	**102.8 (88.73-119.0)**	101.5 (87.70-117.5)	120.3 (103.9-139.4)[b]
Male	N	56	56	55
	C_{max}	72.04 (58.11-89.32)	75.85 (61.19-94.03)	78.60 (63.33-97.56)
	AUC_t	81.91 (68.46-98.02)	85.10 (71.13-101.8)	91.22 (76.16-109.2)
	AUC_{inf}	89.45 (76.85-104.1)[c]	93.15 (80.05-108.4)[c]	105.7 (90.64-123.2)[c]

a. N=95, N=96, and N=93 for Gimoti 15 mg, 16 mg, and 17 mg, respectively.
b. N 41
c. N=54, N=54, and N=52 for Gimoti 15 mg, 16 mg, and 17 mg, respectively.
Source: METO-IN-006 Clinical Study Report Table 11-3, Table 11-5, and Table 11-6

Reviewer's comment:
*(1) When the reviewer repeated noncompartmental PK analysis and the bioequivalence test using WinNonlin, overall results (**Table 12**) were consistent with the Applicant's analysis indicating that AUCs of Gimoti 15, 16, and 17 mg are similar but C_{max} is 16-20% lower compared to Reglan. There were discrepancies in values for AUC_{inf} between the reviewer's and the Applicant's analyses because the Applicant excluded a few AUC_{inf} parameters (see **Table 11**'s footnotes) if the percentage of extrapolated AUC was >20% whereas the reviewer did not. Nonetheless, such difference did not affect the overall conclusion.*

Table 12. Reviewer's Bioequivalence Analyses for Metoclopramide

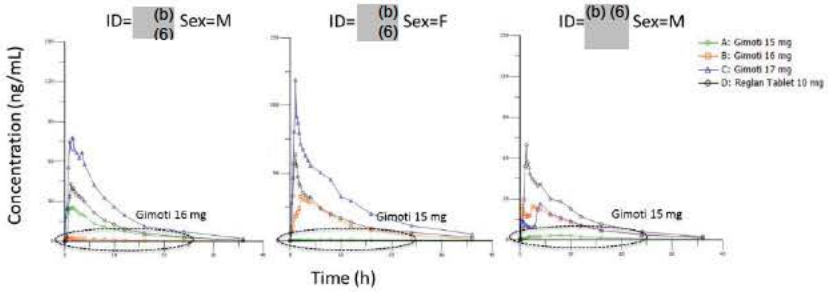
Population	Parameter	Geometric mean ratio (%) for Gimoti/Reglan (90% CI)		
		Gimoti 15 mg	Gimoti 16 mg	Gimoti 17 mg
Overall	N	97	98	98
	C_{max}	80.32 (69.29-93.11)	80.37 (69.36-93.12)	84.27 (72.73-97.64)
	AUC_t	90.25 (79.48-102.5)	91.76 (80.84-104.2)	97.01 (85.41-110.1)
	AUC_{inf}	93.42 (83.18-104.9)	94.02 (83.75-105.6)	102.6 (91.39-115.3)
Female	N	41	42	43
	C_{max}	93.08 (76.60-113.1)	87.44 (72.02-106.2)	92.79 (76.56-112.5)
	AUC_t	102.9 (86.07-123.1)	101.9 (85.28-121.8)	105.6 (88.55-126.0)
	AUC_{inf}	102.6 (86.86-121.2)	101.8 (86.22-120.1)	111.8 (94.76-132.0)
Male	N	56	56	55
	C_{max}	72.04 (58.10-89.32)	75.85 (61.19-94.03)	78.60 (63.33-97.56)
	AUC_t	81.91 (68.45-98.00)	85.10 (71.13-101.8)	91.22 (76.16-109.3)
	AUC_{inf}	87.55 (74.38-103.1)	88.92 (75.56-104.6)	96.66 (82.06-113.9)

Source: Reviewer's analysis of bioequivalence test with PK parameters estimated by reviewer's analysis of NCA using the dataset under Section 5.3.1.2. METO-IN-006, pc.xpt (SDN 4)

(2) Given the average half-life was about 8 hours, the 5-day washout period was reasonably planned; however, in 40 of 399 PK profiles (10.0%), pre-dose concentrations were greater than LLOQ (0.1 ng/mL) ranging from 0.1-8.98 ng/mL. Out of 40 PK profiles, the Applicant excluded the PK profiles of the following 4 subjects were excluded from the PK dataset based on criterion, i.e., pre-dose concentration was ≥5% of the C_{max}, for the respective dose levels: Subjects (b) (6) for Period 3, 16 mg, (b) (6) for Period 3, 15mg, (b) (6) for Period 2, 16 mg and (b) (6) for Period 4, 15mg.

*However, it should be noted that aside from the PK profile with pre-dose level of 8.98 ng/mL, although the pre-dose levels of the other 3 PK profiles were almost negligible (i.e., 0.1-0.5 ng/mL with LLOQ at 0.1 ng/ml) the 3 PK profiles were excluded as a result that the C_{max} of those profiles were extremely low (i.e., 0.962, 2.19, and 3.21 ng/mL)(**Figure 4**). The exclusion of data with pre-dose level > 5% of C_{max} is generally recommended per FDA's BA/BE guidance; however, in these three subjects, the pre-dose levels were at or close to the LLOQ. As these data should be included in the analysis, a sensitivity analysis was conducted; when the 4 PK profiles with pre-dose levels >5% of C_{max} were added to the PK dataset, the relative BA results for overall population became further deviated from the "no-effect" criteria for all three doses (**Table 13**).*

Figure 4. Plasma Concentration-Time Profiles of Subjects (b) (6), and (b) (6) Whose One PK profile was excluded from PK dataset



Source: Reviewer's plot using the dataset under Section 5.3.1.2. METO-IN-006, pc.xpt (SDN 4)

Table 13. Bioequivalence Analyses Including 4 PK Profiles with Pre-dose concentrations > 5% of C_{max} (Sensitivity Analysis I)

Group	Par	Geometric mean ratio (%) for Gimoti/Reglan (90% CI)		
		Gimoti 15 mg	Gimoti 16 mg	Gimoti 17 mg
Overall	N	99	100	98
	C_{max}	**75.42 (64.31-88.45)**	**78.68 (67.13-92.22)**	**84.19 (71.75-98.77)**
	AUC_t	86.00 (75.05-98.54)	90.01 (78.60-103.09)	96.94 (84.57-111.11)
	AUC_{inf}	91.90 (81.44-103.70)	92.29 (81.86-104.05)	102.66 (90.95-115.89)
Female	N	42	43	43
	C_{max}	84.81 (67.96-105.83)	87.87 (70.49-109.54)	92.42 (74.16-115.19)
	AUC_t	95.55 (78.44-116.40)	102.50 (84.23-124.74)	105.27 (86.52-128.09)
	AUC_{inf}	95.26 (79.33-114.40)	100.92 (84.12-121.08)	105.30 (87.78-126.30)
Male	N	57	57	55
	C_{max}	69.17 (55.14-86.77)	72.39 (57.71-90.79)	78.63 (62.54-98.86)
	AUC_t	79.37 (65.65-95.97)	81.43 (67.36-98.44)	91.18 (75.27-110.45)
	AUC_{inf}	86.91 (72.86-103.67)	84.66 (70.98-100.97)	96.36 (80.56-115.25)

Source: Reviewer's analysis using the dataset under Section 5.3.1.2. METO-IN-006, pp.xpt (SDN 4)

*(3) Additionally, there were 11 PK profiles from 9 subjects showing extremely low concentrations (< 5 ng/mL at all time points) compared to the average C_{max} values around 30 ng/mL while the same subjects did not show such profiles following Reglan administration. The 11 PK profiles accounted for 3.7% out of 298 PK profiles following Gimoti administration across three different doses (N=3 for Gimoti 15 mg and 16 mg, respectively; N=5 for Gimoti 17 mg). These were probably caused by inconsistent and incomplete drug delivery of nasal administration. As a sensitivity analysis, when the 11 PK profiles were excluded from the PK dataset, the relative BA results for overall population fell within the standard "no-effect" criteria for all three doses (**Table 14**). Of note, out of the 9 subjects, male subjects were more than female subjects, i.e., N=6 vs. N=3, which may have contributed to the lower relative BA of Gimoti to Reglan in males compared to that of females from subgroup analysis by sex in METO-IN-006.*

Table 14. Bioequivalence Analyses Excluding 11 PK Profiles with Extremely Low Concentrations (< 5 ng/mL at all time points) (Sensitivity Analysis II)

Group	Par	Geometric mean ratio (%) for Gimoti/Reglan (90% CI)		
		Gimoti 15 mg	Gimoti 16 mg	Gimoti 17 mg
Overall	N	94	96	93
	C_{max}	**90.18 (81.50-99.80)**	**90.05 (81.43-99.58)**	**99.75 (81.43-99.58)**
	AUC_t	99.62 (91.11-108.9)	100.7 (92.19-110.0)	111.7 (102.1-122.2)
	AUC_{inf}	100.1 (91.70-109.3)	102.8 (94.17-112.1)	112.1 (102.7-122.4)
Female	N	42	43	43
	C_{max}	94.58 (81.10-110.3)	92.92 (79.74-108.3)	108.6 (93.06-126.6)
	AUC_t	104.9 (91.24-120.6)	108.1 (94.14-124.2)	122.3 (106.4-140.7)
	AUC_{inf}	104.7 (91.12-120.4)	107.9 (93.90-123.9)	122.5 (106.5-140.8)
Male	N	57	57	55
	C_{max}	86.81 (75.66-99.60)	87.84 (76.63-100.7)	93.90 (81.78-107.8)
	AUC_t	95.89 (85.18-107.9)	95.48 (84.88-107.4)	104.5 (92.76-117.7)
	AUC_{inf}	96.95 (86.44-108.7)	99.09 (88.36-111.1)	105.1 (93.68-118.0)

Source: Reviewer's analysis using the dataset under Section 5.3.1.2. METO-IN-006, pp.xpt (SDN 4)

*(4) In the statistical consultation (dated Feb 20, 2019 in DARRTS), Meiyu Shen, PhD, the statistical reviewer, pointed out that the statistical model of the Applicant's analysis was misspecified because the Applicant appeared to have ignored the period effect and put the sequence-by-group interaction and the period effect nested in group as fixed effects. The Applicant defined 'groups' using the date of dose administration within the same period, which is not typically considered in bioequivalence tests. Nonetheless, judging by the fact that the Applicant's analysis results was generally consistent with the reviewer's analysis incorporating the period effect (**Table 12**), the influence of model misspecification on the results seems negligible.*
*Also, she criticized that the Applicant included subjects who did not fully complete the study per protocol if they received at least 2 doses of study drug, one of which was the listed product. Since this is Latin square design, the complete cases are recommended for analyses. Of note, this definition of PK population had been defined in the original protocol. Dr. Shen's bioequivalence analysis only including complete cases per protocol resulted in further decreased relative BA below the standard "no-effect" criteria compared to the Applicant's original analysis (**Table 15**).*

Table 15. Bioequivalence Analyses Using Complete Cases for Metoclopramide

PK Parameter	Comparison	Ratio	90% CI	
			Lower	Upper
C_{max}	Gimoti 15 mg vs Reglan	0.772	0.657	0.908
	Gimoti 16 mg vs Reglan	0.805	0.685	0.947
	Gimoti 17 mg vs Reglan	0.865	0.736	1.017
AUC_t	Gimoti 15 mg vs Reglan	0.874	0.762	1.003
	Gimoti 16 mg vs Reglan	0.914	0.796	1.048
	Gimoti 17 mg vs Reglan	0.992	0.864	1.138
AUC_{inf}	Gimoti 15 mg vs Reglan	0.936	0.829	1.057
	Gimoti 16 mg vs Reglan	0.938	0.831	1.058
	Gimoti 17 mg vs Reglan	1.052	0.932	1.188

Source: Statistical consultation dated Feb 20, 2019 in DARRTS

Of note, the Office of Study Integrity and Surveillance (OSIS) reviewed the inspectional findings of the clinical site and subsequently concluded that the clinical data from Study METO-IN-006 are reliable. Refer to the Bioequivalence Establishment Inspection Report Review by OSIS dated Jan 14, 2019 in DARRTS.

4.1.2 METO-IN-001: Supportive Relative BA Study

Title: A 4-Period, 4-Treatment, 4-Sequence Randomized Crossover Study of the Bioavailability and Pharmacokinetics of Metoclopramide after Nasal, Oral, and IV Administration to Healthy Volunteers Under Fasted Conditions

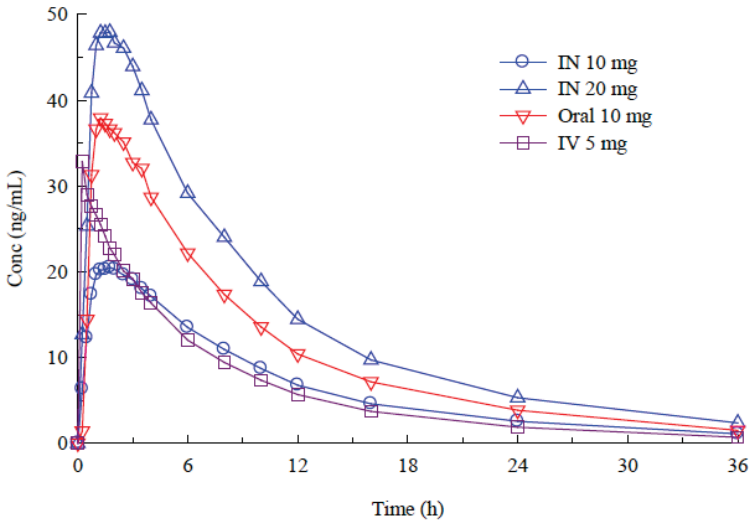
Design: This study was an open-label, 4-treatment, 4-period, 4-sequence crossover study conducted at a single study center. The sequence of the treatments was randomly assigned to 40 eligible subjects. After an overnight fast, all subjects received a single dose of metoclopramide, i.e., Gimoti 10 mg, Gimoti 20 mg, oral Reglan 10 mg, or Reglan IV, according to their sequence group assignment as follows:

	Period 1	Period 2	Period 3	Period 4
Sequence 1 (ABCD)	A: Gimoti 10 mg	B: Gimoti 20 mg	C: Reglan PO 10 mg	D: Reglan IV 5 mg
Sequence 2 (BDAC)	B: Gimoti 20 mg	D: Reglan IV 5 mg	A: Gimoti 10 mg	C: Reglan PO 10 mg
Sequence 3 (CADB)	C: Reglan PO 10 mg	A: Gimoti 10 mg	D: Reglan IV 5 mg	B: Gimoti 20 mg
Sequence 4 (DCBA)	D: Reglan IV 5 mg	C: Reglan PO 10 mg	B: Gimoti 20 mg	A: Gimoti 10 mg

Standard meals were provided at such times to allow for a fasted state of at least 10 hours at the time of study drug administration. Blood draws for PK sampling were collected prior to dosing, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, and 36 hours post-dose.

Results: Out of total 40 subjects randomized, the PK analysis population therefore consisted of 37 subjects who received all 4 treatments and 2 subjects who received 3 of the 4 treatments. The results of PK analysis are shown in **Figure 5** and **Table 16**.

Figure 5. Mean Plasma Concentrations of Metoclopramide after Single Dose of Gimoti 10 mg and 20 mg, Reglan Tablets 10 mg, and Reglan IV 5 mg in Healthy Subjects



conc = concentration; IN = intranasal; IV = intravenous; PO = oral

Source: METO-IN-001 Clinical Study Report In-text Figure 11-1

Table 16. Summary of PK Parameters for Metoclopramide after Single Dose of Gimoti 10 mg and 20 mg, Reglan Tablets 10 mg, and Reglan IV 5 mg in Healthy Subjects

Parameter	Gimoti 10 mg	Gimoti 20 mg	Reglan Tablets 10 mg	Reglan 5 mg IV
N [1]	38	39	39	39
C_{max} (ng/mL)				
Mean	22.8	54.2	43.9	35.8
±SD; CV	12.7; 55.5	24.9; 45.9	15.8; 36.0	15.1; 42.2
Range	2.1 – 49.1	11.1 – 102.9	15.7 – 90.1	19.9 – 87.4
t_{max} (h) [2]				
Median	1.50	1.50	1.25	0.25
Range	0.50-3.50	0.75 – 3.50	0.50 – 3.50	0.25 – 1.25
AUC_t (h*ng/mL)				
Mean	232	510	376	224
±SD; CV	146; 63.0	266; 52.2	206; 54.8	80.9; 36.1
AUC_∞ (h*ng/mL)				
Mean	263	540	397	232
±SD; CV	164; 62.4	308; 57.0	246; 62.0	92.9; 40.0
$t_{½}$ (h)				
Mean	8.03	8.11	7.12	6.80
±SD; CV	2.17; 27.1	2.44; 30.1	2.00; 28.1	1.77; 26.1

Source: METO-IN-001 Clinical Study Report In-text Table 11-2

Relative bioavailability was estimated compared to Reglan PO 10 mg (**Table 17**).

Table 17. Comparison of Bioavailability of Metoclopramide

	Least Squares Geometric Mean Ratio (%)[a,b]	
Parameter	Estimate	90% Confidence Interval
IN 10 mg vs. Oral 10 mg		
Cmax	45.29	38.08 → 53.87
AUC(0-t)	55.26	47.49 → 64.30
AUC(inf)	60.11	51.86 → 69.66
IN 20 mg vs. Oral 10 mg		
Cmax	117.82	99.20 → 139.93
AUC(0-t)	133.15	114.57 → 154.75
AUC(inf)	132.99	114.90 → 153.92
IN 10 mg vs. IV 5 mg		
Cmax	55.69	46.75 → 66.34
AUC(0-t)	86.82	74.51 → 101.17
AUC(inf)	94.89	81.76 → 110.12
IN 20 mg vs. IV 5 mg		
Cmax	144.87	121.79 → 172.33
AUC(0-t)	209.21	179.77 → 243.47
AUC(inf)	209.94	181.17 → 243.27

IN=Intranasal metoclopramide (metoclopramide nasal spray).
a: Based on analysis of natural log-transformed data.
b: Data were not corrected for dose before comparison.

Source: METO-IN-001 Clinical Study Report In-text Table 11-3

Reviewer's comment: *In order to check whether METO-IN-006 also showed higher relative BA in females than those of males, subgroup analysis by sex for relative BA of METO-IN-001 was performed by the reviewer. It indicated a contradictory sex-by-formulation effect from METO-IN-006; relative BA in males were higher than those of females (**Table 18**).*

Table 18. Relative Bioavailability of Gimoti to Reglan 10 mg by Sex from METO-IN-001

Group	Par	Geometric mean ratio (%) for Gimoti/Reglan PO 10 mg (90% CI)	
		Gimoti 10 mg	Gimoti 20 mg
Female	N	13	14
	C_{max}	38.09 (28.39-51.10)	98.18 (73.75-130.7)
	AUC_t	45.00 (33.68-60.13)	119.1 (89.92-157.8)
	AUC_{inf}	44.30 (33.18-59.14)[a]	109.4 (81.04-147.7)[a]
Male	N	25	25
	C_{max}	51.29 (40.89-64.33)	135.0 (107.6-169.5)
	AUC_t	63.26 (52.54-76.17)	147.5 (122.4-177.7)
	AUC_{inf}	72.97 (61.49-86.60)[b]	151.3 (128.1-178.8)[b]

a. N= 12
b. N= 22 for Gimoti 10 mg; N=24 for Gimoti 20 mg

Source: Reviewer's Analysis using the dataset under Section 5.3.1.2. METO-IN-001, pp.xpt (SDN 4)

4.1.3 25,512-302R: Supportive PK-PD Study

Title: Comparison of the Pharmacokinetics and Safety of (b) (4) Metoclopramide, Nasal Spray) Versus Orally Administered Reglan® (Metoclopramide Tablets, USP) in Patients with Diabetic Gastroparesis

- The (b) (4) metoclopramide nasal spray formulation which is different from the final formulation of Gimoti.

Design: This was a phase 2a, controlled, randomized, open-label, parallel-design study in patients with diabetic gastroparesis conducted in multiple centers in the United States.
Efficacy was also evaluated by comparing the total symptom score (TSS) at baseline and at the end of the study following 6-week treatment as a primary endpoint.
Subjects meeting all eligibility criteria were randomized to 1 of 3 metoclopramide dose groups in a 2:2:1 ratio: metoclopramide nasal spray 10 mg, metoclopramide nasal spray 20 mg, or Reglan Tablets 10 mg. Study drug was to be administered 4 times daily, before meals and at bedtime, for 6 weeks.
Blood samples for the measurement of plasma concentrations of metoclopramide were collected at the following time points relative to dosing: pre-dose, 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8, 10, 12, 14 and 24 hours postdose on Day 1 and Day 42.

Result:
Efficacy
Efficacy results for this study are presented in **Table 19**. For the ITT analysis of the primary efficacy endpoint, all treatment groups showed an improvement in TSS. However, both the metoclopramide nasal spray 10 mg and 20 mg groups showed greater improvement than the Reglan Tablets group at the end of study assessment (Week 6). Mean change from baseline was -16.8 for metoclopramide nasal spray 10 mg, -18.0 for metoclopramide nasal spray 20 mg, and -14.3 for Reglan Tablets 10 mg, with a significant difference noted between the metoclopramide nasal spray 20 mg group and Reglan Tablets group (p 0.026).

Table 19. Primary endpoint Adjusted Mean Change from Baseline to the End of Study for Total Symptom Score (ITT Population)

Treatment	Number of subjects	Mean Baseline	Mean Change from Baseline	Difference from Oral 10mg Mean (95% CI)	p-value
Reglan Tablets 10 mg	18	22.9	-14.3		
MCP nasal spray 10 mg	34	23.4	-16.8	-2.5 (-5.8, 0.8)	0.132
MCP nasal spray 20 mg	35	21.3	-18.0	-3.8 (-7.1,-0.5)	0.026

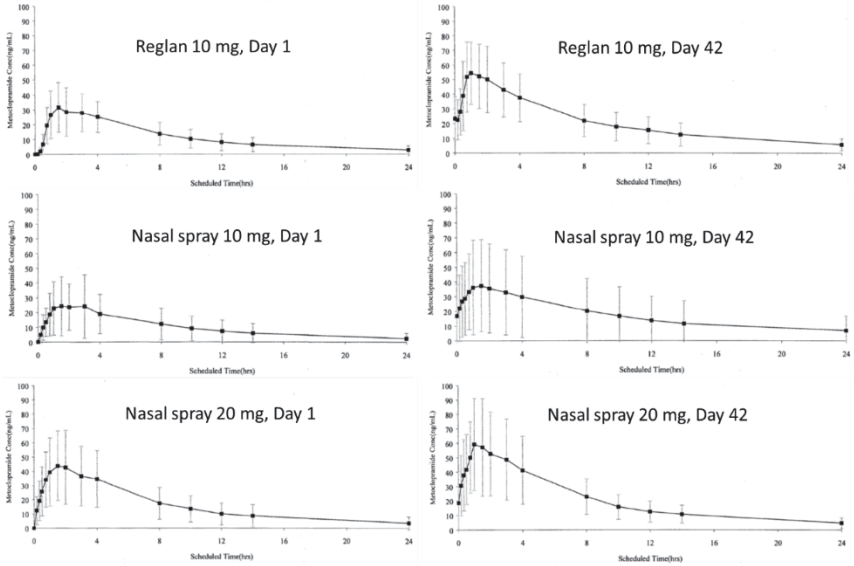
CI = confidence interval; ITT = intent to treat; MCP = metoclopramide
Source: 25,512-302R Clinical Study Report Table 15.1.1.4

Reviewer's comment: *Given the open-labelled design, the efficacy results should be only supportive data. Interpretation of the efficacy data is deferred to clinical reviewers.*

Pharmacokinetics
A summary of the PK results for the 10 mg and 20 mg metoclopramide spray group and Reglan

Tablets 10 mg group is provided in **Figure 6** and **Table 20**.

Figure 6. Mean Metoclopramide Plasma Concentration-Time Profiles Following Single (Day 1) and Multiple (Day 42) Administrations



Source: 25,512-302R Clinical Study Report, Figure 15.2.2.1, Figure 15.2.2.14

Table 20. Summary of PK Parameters for Two Doses Metoclopramide Nasal Spray versus Reglan Tablets in Subjects with Diabetic Gastroparesis

Parameters	Nasal Spray		Reglan Tablets 10 mg
	10 mg	20 mg	
Day 1			
N [1]	34	35	18
C_{max} (ng/mL)			
Mean	29.13	48.78	36.41
±SD; CV	23.72; 81.40	25.35; 52.00	13.64; 37.50
Range	2.21 – 103.00	12.10 – 107.00	12.50 – 61.10
t_{max} (h)			
Mean	1.76	1.81	1.72
±SD; CV	1.38; 78.50	0.93; 51.40	0.83; 48.00
Range	0.50 – 8.00	0.50 – 4.00	1.00 – 4.00
AUC_∞ (h*ng/mL)			
Mean	268.97	412.12	304.09
±SD; CV	242.45; 90.10	271.30; 65.80	173.50; 57.10
$t_{½}$ (h)			
Mean	6.90	7.63	6.89
±SD; CV	2.93; 42.40	3.41; 44.70	2.38; 34.50
Day 42			
N [1]	31	33	17
C_{max} (ng/mL)			
Mean	41.11	67.23	61.21
±SD; CV	32.77; 79.70	35.04; 52.10	24.86; 40.60
Range	11.10-146.00	2.96 – 152.00	22.60 – 106.00
t_{max} (h)			
Mean	1.48	1.18	1.19
±SD; CV	0.83; 56.4	0.70; 59.20	0.56; 47.20
Range	0.33 – 3.00	0.00 – 3.00	0.00 – 2.00
AUC_{0-24} (h*ng/mL)			
Mean	515.79	573.16	564.44
±SD; CV	678.39; 131.5	301.79; 52.70	280.43; 49.70
$t_{½}$ (h)			
Mean	8.86	8.03	8.44
±SD; CV	3.09; 34.9	2.70; 33.6	2.59; 30.7

AUC = area under the concentration-time curve; AUC_∞ = AUC from time 0 to infinity; AUC_{0-24} = AUC from time 0 to 24 hours; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; PK = pharmacokinetic; SD = standard deviation; $t_{½}$ = elimination half-life; t_{max} = time to C_{max}

[1] For AUC and $t_{½}$, Day 1 N = 33 for 10 mg Nasal Spray, Day 42 N = 27 for 10 mg Nasal Spray, and Day 42 N = 31 for 20 mg Nasal Spray.

Source: 25,512-302R Clinical Study Report Table 15.1.3.1 and Table 15.1.3.2

Reviewer's comment: *The observed PK parameters in patients with gastroparesis at Reglan 10 mg generally in line with those of healthy volunteers observed in METO-IN-001 and METO-IN-006. This conflicts with the Applicant's presumption that patients with gastroparesis tend to present delayed or unpredictable drug absorption such as dose dumping due to delayed or erratic gastric emptying following oral administration of metoclopramide.*
Additionally, the Applicant's claim that nasal administration of metoclopramide would lead to consistent and faster absorption than oral administration by bypassing the GI tract especially in patients with gastroparesis whose oral absorption is impaired, the overall concentration-time profiles and the PK parameters in this trial did not evidently reveal faster and consistent absorption following nasal administration compared to those of oral administration.

Based on the 90% CI for the mean test/reference ratios for AUC and $C_{max,}$, dosing with metoclopramide nasal spray 10 mg resulted in lower exposure than with Reglan Tablets 10 mg on both Day 1 and Day 42, and dosing with metoclopramide nasal spray 20 mg resulted in higher exposure levels than with Reglan Tablets 10 mg on Day 1 and similar levels on Day 42 (**Table 21**).

Table 21. Statistical Comparison of PK Parameters for Metoclopramide

	Summary of PK Parameters [1]	
Parameter	**Ratio**	**90% Confidence Interval**
Metoclopramide Nasal Spray 10 mg vs. Oral 10 mg		
Day 1		
C_{max}	64.76	47.22 → 88.81
AUC_t	70.02	50.83 → 96.46
AUC_∞	76.61	56.26 → 104.33
Day 42		
C_{max}	67.17	40.65 → 93.68
AUC_t	85.44	50.47 → 120.41
AUC_∞	91.38	48.34 → 134.42
Metoclopramide Nasal Spray 20 mg vs. Oral 10 mg		
Day 1		
C_{max}	124.50	90.93 → 170.47
AUC_t	128.51	93.43 → 176.76
AUC_∞	130.55	96.17 → 177.22
Day 42		
C_{max}	109.84	83.60 → 136.07
AUC_t	100.48	65.89 → 135.08
AUC_∞	101.54	59.59 → 143.50

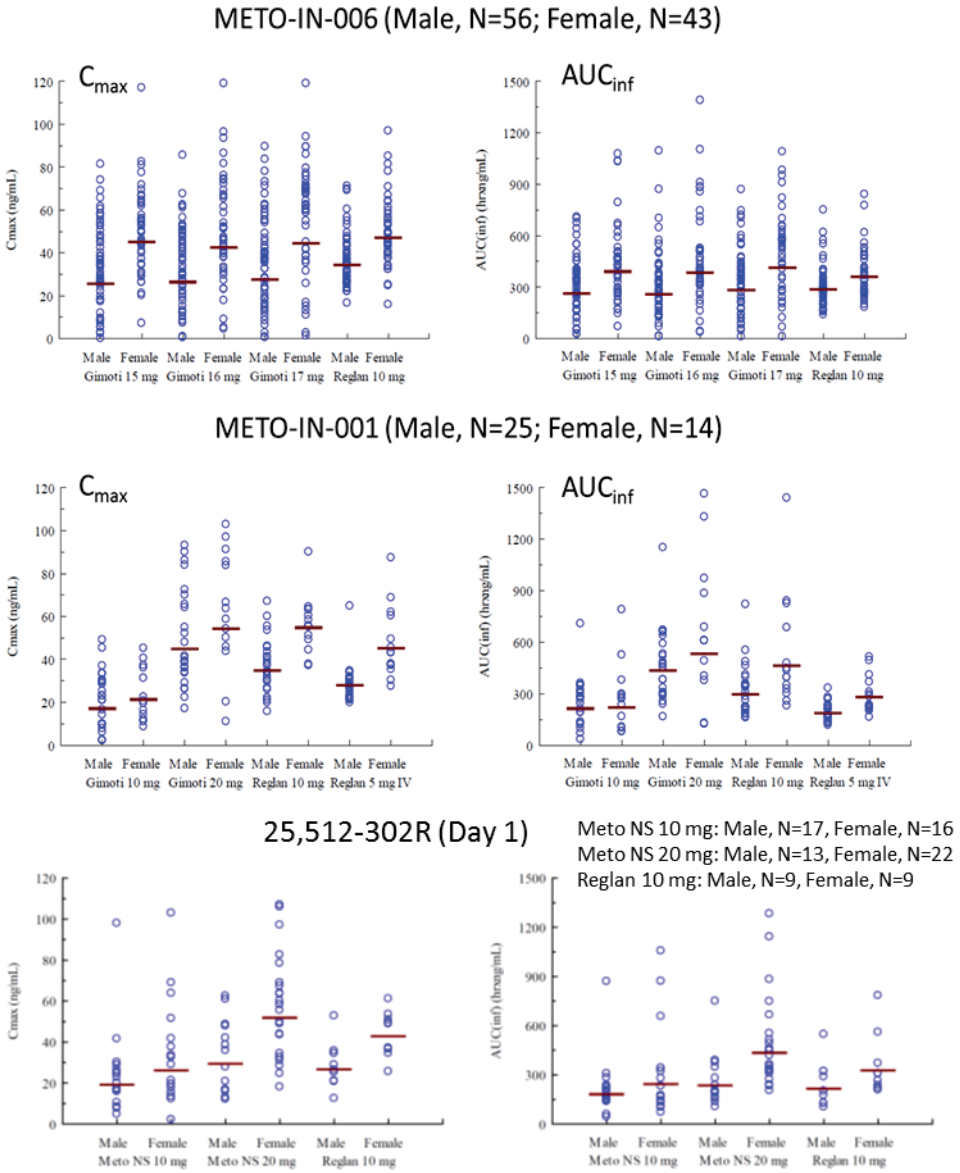
AUC = area under the concentration-time curve; AUC_∞ = AUC from time 0 to infinity; AUC_t = AUC from 0 to the final sample with a concentration ≥ limit of quantitation; C_{max} = maximum observed plasma concentration
[1] Data were not corrected for dose before comparison.

Source: 25,512-302R Clinical Study Report Table 15.1.3.6 and Table 15.1.3.9

4.1.4 Supplemental Sex-based PK Analyses

The Applicant's data inspection of the METO-IN-006 data revealed unexpectedly large differences in exposure by sex. Retrospective analysis of the data revealed there were higher levels of exposure in females than males across metoclopramide formulations and multiple studies (METO-IN-001, 25,512-302R as well as METO-IN-006) that had not previously been recognized.
Comparing PK parameters between sex showed the geometric means for C_{max} and AUC in females were consistently greater than those in males in both Gimoti and Reglan across studies (**Figure 7**).

Figure 7. Distribution of Individual Subject C_{max} and AUC_{inf} by Treatment and Sex



Solid line denotes geometric mean of C_{max} and AUC_{inf}
Meto NS, Metoclopramide nasal spray (different nasal spray formulation from Gimoti)

Source: METO-IN-006 Supplemental Report, Figure 1; METO-IN-001 Supplemental Report, Figure 1; 25,512-302R Supplemental Report, Figure 1

These sex difference in exposure was not disappeared when corrected with body weight; the Mean body weight normalized AUC_{inf} for Gimoti was still higher in females than males (**Table 22**).

Table 22. Percentage Difference [(Female-Male)/Male*100)] in Exposure (Females vs. Males) for PK Parameters by Treatment Across Studies

Study	Treatment	C_{max}	C_{max}/kg	AUC_{inf}	AUC_{inf}/kg
METO-IN-006	Reglan 10 mg	36.52	62.17	25.70	48.90
	Gimoti 15 mg	76.29	110.59	49.59	78.71
	Gimoti 16 mg	61.16	92/12	48.60	77.15
	Gimoti 17 mg	61.83	93.72	46.88	74.47
METO-IN-001	Reglan 5 mg IV	61.49	113.11	49.23	96.93
	Reglan 10 mg	56.94	105.85	56.39	105.13
	Gimoti 10 mg	24.16	59.74	2.83	32.96
	Gimoti 20 mg	21.09	58.82	22.44	56.27
255,12-302R (Day 1)	Reglan 10 mg	60.4	96.3	52.6	86.8
	Nasal Spray* 10 mg	36.1	36.9	33.9	36.4
	Nasal Spray* 20 mg	76.0	98.3	83.8	107
METO-IN-005 (Reviewer's analysis)	Gimoti 20 mg	55.9	-	39.54	-
	Gimoti 80 mg	57.3	-	37.16	-

*Nasal Spray 10 mg and 20 mg were different nasal spray formulations from Gimoti.
Source: METO-IN-006 Supplemental report, Appendix V; METO-IN-001 Supplemental report, Appendix V; 255,12-302R Supplemental report, Appendix V

Reviewer's comment: *Even though the higher mean AUC and C_{max} in females compared to males was consistently noted across formulations and studies, it should be noted that the magnitude of the difference significantly varied between studies and formulation. Also, the ranges of AUC and C_{max} are mostly overlapped between males and females.*

4.2 Population PK Analysis

The Applicant provided a population pharmacokinetic (popPK) analysis report entitled, "Population Pharmacokinetic Analysis of Three Studies with Metoclopramide Nasal Spray". Originally in the popPK report, the PK model of metoclopramide was established based on three clinical studies following nasal administration of metoclopramide, i.e., METO-IN-001, METO-IN-003, and 25512-302R. Since more extensive PK data at the proposed dose is available from METO-IN-006 and the sex difference in PK of metoclopramide should be explored in patient population if available, on Aug 13, 2018, we requested the Applicant to re-analyze popPK using all available PK data from clinical studies in patient population as well as healthy subjects. Subsequently, on Nov 13, 2018, the Applicant submitted the new popPK analysis report entitled, "Population Pharmacokinetic Analysis of Six Studies with Metoclopramide Nasal Spray" including PK data from six clinical studies briefly summarized in **Table 23**. Additionally, the Applicant supplemented the PK simulation results dated Dec 12, 2018 to demonstrate the proposed dose adjustment of Gimoti compared to the approved dose adjustment of Reglan in specific populations (e.g., hepatic/renal impairment, and CYP2D6 poor metabolizers).

Table 23. Summary of Clinical Studies Included in the Population PK Analysis of Nasal Spray of Metoclopramide

Study Number	Subjects	Regimen/ Treatment	Included PK data
METO-IN-001 (Phase 1, 4-way crossover study)	Healthy male and female (N 40)	Single dose, Gimoti 10 mg Gimoti 20 mg Reglan oral 10 mg Reglan IV 5 mg	Full-PK data obtained up to 36 h post-dose
METO-IN-006 (Pivotal relative BA, 4-way crossover study)	Healthy male and female (N=108)	Single dose, Gimoti 15 mg Gimoti 16 mg Gimoti 17 mg Reglan oral 10 mg	Full-PK data obtained up to 36 h post-dose
METO-IN-002 (Phase 2, randomized, double-blind, placebo-controlled study)	Male and female patients with diabetic pastroparesis (N=287)	QID for 4 weeks Gimoti 10 mg (N=95) Gimoti 14 mg (N=95) Placebo (N=95)	Sparse PK data obtained on Day 1
METO-IN-003 (Phase 3, randomized, double-blind, placebo-controlled study)	Female patients with diabetic gastroparesis (N=205)	QID for 4 weeks Gimoti 10 mg (N=102) Placebo (N=103)	Sparse PK data obtained on Day 7
METO-IN-004 (Phase 3, randomized, double-blind, placebo-controlled study)	Male patients with diabetic gastroparesis (N=53)	QID for 4 weeks Gimoti 10 mg (N=26) Placebo (N=27)	Sparse PK data obtained on Day 7
25,512-302R (Phase 2, randomized, open-label, active-controlled study)	Male and female patients with diabetic gastroparesis (N=89)	Nasal spray 10 mg* (N=35) Nasal spray 20 mg* (N=36) Reglan oral 10 mg (N=18)	Full PK data obtained Day 1 and Day 42

*different formulation from the final formulation of Gimoti

Source: Population Pharmacokinetic Analysis Report dated Nov 13, 2018, 3. Study Designs and 5. Method

The Applicant's PK modeling

The analysis was conducted using mixed-effects methods with NONMEM software. A linear two-compartment model with first-order absorption from a depot and an absorption lag was fit to the data. Different values for absorption rate, absorption lag, and relative BA to the intravenous dose in METO-IN-001 were permitted for each of the non-parenteral routes.

Table 24 summarize demographic information. Inclusion of covariates into the model was evaluated systematically. The model with allometric scaling of systemic parameters and a relationship between apparent clearance and renal function (MDRD) was finally adopted as the optimal model. The final PK model well described the observed data (**Figure 8**). The final PK model parameters are described in **Table 25.**

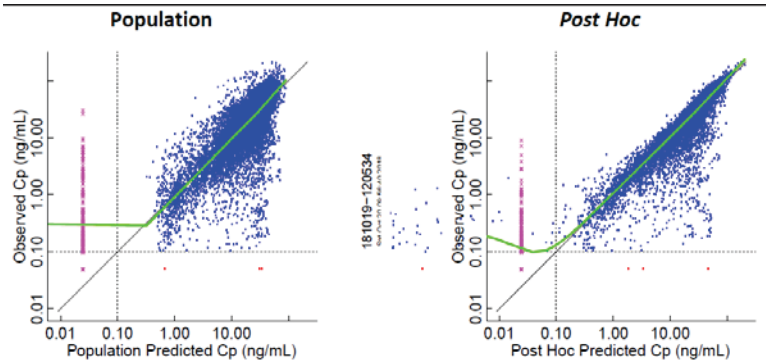
Table 24. Summary of Demographic Data

Descriptor	N	Mean	Standard Deviation	Median	Minimum	Maximum
Weight (kg)	509	86.9	22.0	83.3	46.8	186.0
Height (cm)	509	167.8	10.3	166.6	142.2	200.5
BMI (kg/m^2)	509	30.9	7.5	29.6	14.3	63.5
Body surface area (m^2)	509	2.00	0.27	1.97	1.40	3.07
Lean body mass (kg)	509	54.0	9.5	53.1	34.3	93.5
Age (years)	509	47.0	14.0	49	18	82
AST	508	22.6	10.8	20	8.0	107
ALT	509	25.8	15.8	21	4.0	143
Alkaline Phosphatase	241	89.7	27.9	85	31	201
Total Bilirubin	242	0.41	0.21	0.40	0.10	1.20
Serum Creatinine	509	0.871	0.238	0.83	0.36	1.90
Creatinine Clearance (Cockcroft-Gault; mL/min)	509	124.5	49.6	114.2	41.7	492.0
Creatinine Clearance (MDRD; mL/min/1.73m^2)	509	90.7	25.1	89.0	33.3	185.8

Covariate	Value	Descriptor	Count	Percentage
Race	1	White	303	59.53
	2	Black	146	28.68
	3	Asian	3	0.59
	4	Other	56	11.00
	9	White/Black	1	0.20
Gender	1	Male	200	39.29
	2	Female	309	60.71

Source: Population Pharmacokinetics Analysis Report dated Nov 13, 2018, Table 7 and Table 8.

Figure 8. Goodness-of-fit Plots for Observed vs. Predicted Concentrations.



The left panel shows the population analysis; the right, the individual *post hoc* analysis. Lines connect values for each subject. Solid black line at unity. Dotted lines mark the LOQ. Magenta points show observations < LOQ that were included in the analysis. Magenta X marks points for which the predicted Cp was < 0.01. The green line is a smoother.

Source: Population Pharmacokinetics Analysis Report dated Nov 13, 2018, Figure 24.

Table 25. Final PK model parameters of metoclopramide

Description	Estimate	Between-individual Variability*
RenalFactor†	1 + 0.00556 • (MDRD – 90)	—‡
Clearance (L / hour)	23.0399 • (LBM§ / 55)$^{0.75}$ • RenalFactor	0.4903
Central Volume (L)	179.005 • LBM§ / 55	0.3085
Distribution Clearance (L / hour)	6.50505 • (LBM§ / 55)$^{0.75}$	0.5068
Peripheral Volume (L)	48.9902 • LBM§ / 55	0.3974
Oral (Reglan) 10 mg		
Absorption Lag (minutes)	24.4288	0.3966
Absorption Rate (/ hour)	2.33421	0.6852
Bioavailability||	0.761988	—‡
Nasal (Gimoti) 10 mg		
Absorption Lag (minutes)	5.03246	0.6115
Absorption Rate (/ hour)	1.39398	0.9119
Bioavailability||	0.543692	—‡
Nasal (Gimoti) 20 mg in METO-IN-001 only		
Absorption Lag (minutes)	5.64119	0.4745
Absorption Rate (/ hour)	1.18784	0.6391
Bioavailability||	0.55122	—‡
Effect of Study and Treatment on Bioavailability¶		
METO-IN-002		
Nasal 10 mg	0.764354	—‡
Nasal 14 mg	1.05868	—‡
METO-IN-003 and METO-IN-004		—‡
Nasal 10 mg	1.25833	
METO-IN-006		
Nasal 15, 16 and 17 mg	0.938195	—‡
Oral 10 mg	0.972193	—‡
25512-302R		
Oral 10 mg	0.903928	—‡
Nasal 10 mg	0.884942	—‡
Nasal 20 mg	0.795798	—‡
Effect of Sampling Period (3 *vs.* 1) on Bioavailability in 25512-302R¶		
Oral 10 mg	1.02064	—‡
Nasal 10 mg	0.63441	—‡
Nasal 20 mg	0.824996	—‡
Effect of Study and Treatment on Absorption Rate¶		
METO-IN-003 Nasal 10 mg	0.669547	—‡
METO-IN-006 Nasal 10 mg	1.11799	—‡
Effect of Study and Treatment on Absorption Lag¶		
METO-IN-006 Nasal 15, 16 and 17 mg	1.08423	—‡
25512-302R Nasal 10 mg	0.530215	—‡

* Quantified as sqrt(OMEGA^2) where OMEGA^2 is the variance of inter-individual variability.

† MDRD is eGFR (in mL/min/1.73 m^2) calculated using the MDRD equation; 90 mL/min/1.73 m^2 is approximately the median value for subjects in the present analysis.

‡ Inter-individual variability was not permitted for this term.

§ LBM is lean body mass in kg; 55 was approximately the median value in this study.

|| Bioavailability relative to the intravenous dose in METO-IN-001

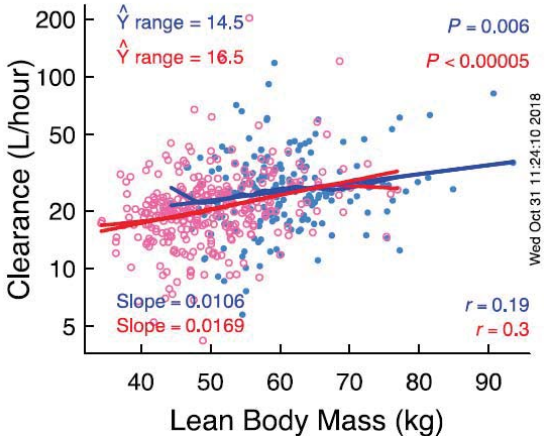
¶ Multiplicative factors for bioavailability, absorption rate and absorption lag relative to oral (Reglan) 10 mg or nasal (Gimoti) 10 mg, as appropriate

Source: Population Pharmacokinetics Analysis Report dated Nov 13, 2018, Table 1.

The Applicant's findings from popPK analysis included:

1) Metoclopramide clearance varied as a function of lean body mass (with allometric scaling [lean body mass raised to the 0.75 power] preferred over weight-normalization). Conversely, systemic exposure decreased with increasing lean body mass (LBM).
2) Systemic exposure to metoclopramide varied with renal function, with MDRD being a better predictor of drug elimination than Cockcroft-Gault.
3) Since women in general have lower lean body mass than men, women are expected to have lower metoclopramide clearance, and conversely a higher exposure, than men for a given height and weight. **Figure 9** shows that the post hoc-predicted clearance decreases LBM stratified by sex. It is apparent that gender did impact clearance, insomuch that females, with lower LBM in general, had lower clearance than males.

Figure 9. Post Hoc-Predicted Metoclopramide Clearance vs. LBM Stratified by Sex

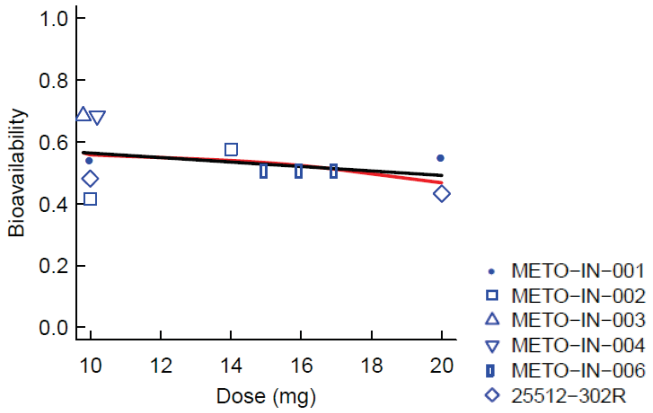


Blue indicates male; pink, female. Lines appear for linear regression (r and P values, range of fitted y values, and the slope of the linear relationships are shown) and smoother (Supersmoother) by sex.

Source: Population Pharmacokinetics Analysis Report dated Nov 13, 2018, Figure 26.

4) The bioavailability of metoclopramide nasal spray estimated ranging from 42% to 68% relative to intravenous administration and from 54% to 90% relative to oral administration. **Figure 10** plots bioavailability relative to METO-IN-001 for the 10 mg dose vs. dose. Bioavailability of metoclopramide nasal spray did not vary by dose over the range evaluated (10 mg to 20 mg). However, model-predicted exposure in METO-IN-003 and METO-IN-004 was 26% (90% CI 14% to 34%) higher than in the reference Study METO-IN-001. This difference remained after adjustment for body size and renal function. A key difference between studies is that METO-IN-003 and METO-IN-004 were conducted in patients with diabetic gastroparesis, whereas METO-IN-001 was conducted in healthy adults. However, the source of this difference in bioavailability could not be determined in the present analysis.

Figure 10. Estimated Bioavailability of Metoclopramide Nasal Spray Across Studies/ Doses



Bioavailability estimated relative to intravenous dose in METO−IN−001

Source: Population Pharmacokinetics Analysis Report dated Nov 13, 2018, Figure 2.

Reviewer's comment: *Overall, the Applicant's population PK analysis is acceptable to evaluate renal function and body size (LBM) as covariates on CL and for generally describing the PK of metoclopramide following nasal administration.*

It should be noted that after accounting for body weight, sex by itself was not a significant covariate on inter-individual variability of clearance. It conflicts with the Applicant statement that females showed higher C_{max} and AUC than males, even when C_{max} and AUC were normalized by body weight. This popPK analysis suggested that the sex difference in C_{max} and AUC may be attributed to body size and body composition effect on clearance.

This analysis estimated bioavailability of Gimoti all separately by studies and doses. Particularly, the estimated bioavailability in METO-IN-003 and METO-IN-004 was approximately 26% higher than METO-IN-001 even though the formulation used, i.e., Gimoti 10 mg, was identical. The Applicant pointed out that a key difference between studies was that METO-IN-003 and METO-IN-004 conducted in patients with diabetic gastroparesis, whereas METO-IN-001 was conducted in healthy adults. However, METO-IN-002 was also conducted in patients with diabetic gastroparesis and its estimated bioavailability was 24% lower at the same formulation (i.e., Gimoti 10 mg) in contrast to METO-IN-003/004. Thus, it is unclear whether the difference in estimated bioavailability between studies can be attributed to difference between healthy subjects and patient population.

The Applicant's PK simulation

(b) (4)

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(b) (4)

Reviewer's comment: *There are a few limitations with the Applicant's simulation for supporting the proposed dose adjustment for specific population.*

- *Instead of using actual patient demographics, hypothetical conditions (e.g., CrCL for elderly patients, 50% reduced clearance with moderate and severe HI patients, etc) for each specific population was assumed for simulations.*
- *The simulations were conducted in one virtual subject, not taking between-subject variability into account. The magnitude of difference in AUC and Cmin between Gimoti and Reglan could further increase if the variability were included in the simulation.*
- *Without adequate exposure-response data or any supporting data such as minimum effective concentrations, the clinical implication* (b) (4) *on efficacy is unknown.* (b) (4)

4.3 Bioanalytical Method Report

The Applicant submitted the bioanalytical validation reports ((b) (4) 42-0805 and (b) (4) 42-1702) and the bioanalytical analysis reports included in each 6 clinical study reports (METO-IN-001, METO-IN-002, METO-IN-003, METO-IN-004, METO-IN-005, and METO-IN-006).

A liquid chromatography tandem mass spectrometry (LC-MS/MS) method, (b) (4) 42-0805, was developed and validated for quantitation of metoclopramide in human plasma at a LLOQ of 0.1 ng/mL (**Table 27**). The analysis method included protein precipitation extraction and an internal standard ([$^2H_{10}$]-metoclopramide). (b) (4)S 42-0805 was used for the analyses of plasma samples in Studies METO-IN-001, METO-IN-002, METO-IN-003, METO-IN-004, and METO-IN-005.

A LC-MS/MS method, (b) (4) 42-1702, was developed and validated for detection of metoclopramide in human plasma at a LLOQ of 0.1 ng/mL (**Table 28**). The analytical method, (b) (4)-1702 for study METO-IN-006 was updated from the method, (b) (4) 42-0805 to implement an ultra-performance LC system to shorten the run time. For both methods, the accuracy and precision for plasma metoclopramide was all acceptable. The study samples were all analyzed within the established long-term storage stability.

In METO-IN-006, the pivotal relative BA study, in-study performance for measurement of metoclopramide was acceptable to support the study results (**Table 29**).

Of note, the OSIS recommended accepting the bioanalytical data of METO-IN-006 without an on-site inspection because the site had been recently inspected. Refer to the memorandum by OSIS dated Jul 16, 2018 in DARRTS.

Table 27. Bioanalytical Validation Summary for Plasma Metoclopramide ((b) (4) 42-0805)

Report Title	Validation of a Method for the Determination of Metoclopramide in Human Plasma by LC-MS/MS
Report Number	(b) (4)42-0805
Analyte Name	Metoclopramide
Internal Standard (IS)	[2H10]-Metoclopramide
Analytical Method Type	LC-MS/MS
Extraction Method	Protein precipitation
QC Concentrations	0.1, 0.3, 5, and 85 ng/mL
Standard Curve Concentrations	0.1, 0.25, 1, 2.5, 5, 25, 90, and 100 ng/mL
Lower Limit Of Quantitation	0.1 ng/mL
Upper Limit Of Quantitation	100 ng/mL
Average Recovery of Drug (%)	90.2
QC Intraday Precision Range (%CV)	0.5 to 16.0 (full validation) 0.8 to 2.8 (partial validation)[a]
QC Intraday Accuracy Range (%RE)	-4.0 to 8.0 (full validation) -2.4 to 6.0(partial validation)[a]
QC Interday Precision Range (%CV)	2.4 to 12.9 (full validation)
QC Interday Accuracy Range (%RE)	-1.4 to 6.3 (full validation)
Stock Solution Solvent	Methanol
Master Stock Solution Stability in Methanol	7 Hours at Room Temperature
Master Stock Solution Stability in Methanol	147 Days at -20°C
Reinjection Reproducibility in Processed Samples	157 Hours at 4°C
Benchtop Stability in Plasma	21 Hours at Room Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C
Long-term Storage Stability in Plasma	440 Days at -20°C (full validation) 369 Days at -70°C (partial validation)[a]
Dilution Integrity	500 ng/mL diluted 10-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS

Source: Bioanalytical Method Validation Report (Amendment 2) ((b) (4) 42-0805), Section 8

Table 28. Bioanalytical Validation Summary for Plasma Metoclopramide ((b) (4)S 42-1702)

Report Title	Validation of a Method for the Determination of Metoclopramide in Human Plasma by LC-MS/MS
Study Number	(b) (4)42-1702
Analyte Name	Metoclopramide
Internal Standard (IS)	[$^2H_{10}$]-Metoclopramide
Analytical Method Type	LC-MS/MS
Extraction Method	Protein Precipitation
Sample Volume	50 µL
QC Concentrations	0.1, 0.3, 5, 50, and 80 ng/mL
Standard Curve Concentrations	0.1, 0.2, 1, 2, 10, 40, 90, and 100 ng/mL
Lower Limit Of Quantitation	0.1 ng/mL
Upper Limit Of Quantitation	100 ng/mL
Mean Recovery of Analyte (%)	112.4
Mean Recovery of Internal Standard (%)	NA[a]
LLOQ QC Intraday Precision Range (%CV)	8.0 to 12.6
LLOQ QC Intraday Accuracy Range (%RE)	-7.2 to 0.0
Analytical QC Intraday Precision Range (%CV)	1.6 to 8.8
Analytical QC Intraday Accuracy Range (%RE)	-9.3 to 3.4
LLOQ QC Interday Precision (%CV)	9.9
LLOQ QC Interday Accuracy (%RE)	-4.4
Analytical QC Interday Precision Range (%CV)	2.1 to 7.5
Analytical QC Interday Accuracy Range (%RE)	-5.1 to -0.4
Stock Solution Stability in Methanol	97 Days at -20°C 20 Hours at Ambient Temperature
Processed Sample Stability	127 Hours at 4°C
Benchtop Stability in Plasma	24 Hours at Ambient Temperature
Freeze/Thaw Stability in Plasma	5 Cycles at -20°C 5 Cycles at -70°C
Benchtop Stability in Whole Blood	2 Hours in an Ice Bath centrifuged at 4°C 2 Hours in an Ice Bath centrifuged at Ambient Temperature
Long-term Storage Stability in Plasma	91 Days at -20°C and -70°C
Dilution Integrity	200 ng/mL diluted 20-fold
Selectivity	≤ 20.0% LLOQ for analyte; ≤ 5.0% for IS
2% Hemolyzed Plasma Test	No impact on assay performance
Lipemic Plasma Test	No impact on assay performance

[a] Not applicable since a stable isotope labeled internal standard was used. The results are expected to be similar to those of the unlabeled analyte.

Source: Bioanalytical Method Validation Report ((b) (4) 42-1702), Section 8.

Table 29. Summary of Analytical Runs for METO-IN-006

Validation parameter	Summary	Acceptability
Assay passing rate	• 60 out of 60 runs (including incurred sample reanalysis) (100%)	Yes
Standard curve performance	• Cumulative bias range: -1.5 to 2.0% • Cumulative precision: <5.7% CV	Yes
QC performance	• Cumulative bias range: -5.0 to 2.0% • Cumulative precision:< 9.3% CV	Yes
Method reproducibility	• Incurred sample reanalysis was performed in a total of 155 samples (2% of study samples) and 89% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Analyze within 53 days from collection (within established stability, 91 days)	

For Study 25,512-302R conducted with different formulations from the final formulation of Gimoti, plasma levels of metoclopramide were determined by high-performance liquid chromatography (HPLC). The analysis method included the extraction of metoclopramide and an internal standard (b) (4) from human plasma. Sample extracts were analyzed with fluorescence detection plasma at a LLOQ of 1.0 ng/mL. The HPLC method used was adequately validated for quantitation of metoclopramide as described in Method Validation LC4 Revision 1 under Section 5.3.1.4. The accuracy and precision for plasma metoclopramide was all acceptable. Cross-method validation between HPLC used for Study 25,512-302R and LC-MS/MS used for other studies was not performed.

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SOJEONG YI
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US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

New Drug Application

Biometrics Division: VI

NDA NO.:	209388
DATE RECEIVED BY OB:	1/23/2019
DRUG NAME:	Gimoti (metoclopramide nasal spray)
INDICATION:	Motility Modifier
SPONSOR:	EVOKE Pharma
REVIEW FINISHED:	02/20/2019
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D.
CONSULT REQUESTER:	Insook Kim, Ph.D.

Concur:
Yi Tsong, Ph.D., Division Director, DBVI, CDER/OTS/OB/DB VI
Distribution:

CDER/OTS/OB/DB VI/ Yi Tsong
CDER/OTS/OB/DB VI/ Meiyu Shen
CDER/OTS/OB/Lillian Patrician
CDER/OTS/OCP/DCPIII/ Insook Kim
CDER/OTS/OCP/DCPIII/Sojeong Yi

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1 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

1.1 Purpose of this review

On January 23, 2019, Office of Clinical Pharmacology (OCP-3) requests CMC statistics team in the Office of Biostatistics (OB) to evaluate Evoke Pharma's 4-period 4-tretament 4-sequence crossover bioequivalence trial for the relative bioavailability of a Gimoti (15 mg, 16 mg, 17 mg) vs. the approved Reglan Tablet 10 mg. Particularly, OCP requests OB to evaluate the followings:

- Please comment if the statistical approach of overall BE analyses is acceptable or if any critical statistical issues identified.
- Please comment on the statistical issues for subgroup analysis of BE by sex performed by the Applicant, that prevent the interpretation of the analysis results.
- Please comment on the sample size if a new prospective BE study in female subjects only may be conducted.

1.2 Sponsor's crossover design

In order to evaluate the relative bioavailability of a Gimoti (15 mg, 16 mg, 17 mg) vs. the approved Reglan Tablet 10 mg., a 4-sequence, 4-period, 4-treatment crossover study was conducted. The specific design is shown in **. The** primary objective of this study was to determine the bioequivalent dose of Gimoti™ compared with the listed drug, Reglan® tablet 10 mg, after administration to female and male volunteers under fasted conditions.

Table 1. The primary objective of this study was to determine the bioequivalent dose of Gimoti™ compared with the listed drug, Reglan® tablet 10 mg, after administration to female and male volunteers under fasted conditions.

Table 1 Study Design

Treatment Sequence	Period 1	Period 2	Period 3	Period 4
1	A	B	C	D
2	B	D	A	C
3	C	A	D	B
4	D	C	B	A

Treatments: A Gimoti 15 mg; B Gimoti 16 mg; C Gimoti 17 mg; D Reglan Tablet 10 mg

Multiple subjects were randomly assigned to each sequence.

Note that we denote the population mean of Gimoti 15 mg as μ_{T_A}, the population mean of Gimoti 16 mg as μ_{T_B}, the population mean of Gimoti 17 mg as μ_{T_C}, and the population mean of Reglan Tablet 10 mg as μ_R in the following sections.

1.3 Data

The sponsor calculated the following plasma PK parameters for metoclopramide using a noncompartmental approach.

- AUC0-t – AUC from time 0 to the last observed concentration (C_{last}) ≥limit of quantitation
- AUC0-inf – AUC from time 0 extrapolated to infinity
- AUCext – percentage of AUC0-inf obtained by extrapolation (a diagnostic parameter calculated and listed in a data listing, but not included in the descriptive statistics)
- Cmax – maximum observed plasma concentration
- Tmax – time to Cmax
- λ_z – elimination rate constant
- $t_{1/2}$ – elimination half-life

In total, 108 subjects were planned and enrolled. One hundred and two subjects were included in the PK population. Ninety-six subjects completed all periods. Note that AUCLST refers to AUC0-t. AUCIFO refers to AUC0-inf.

Figure 1 displays the distribution of AUCLST for all four treatments. Figure 2 displays the distribution of Cmax for all four treatments. Figure 3 displays the distribution of AUCIFO for all four treatments.

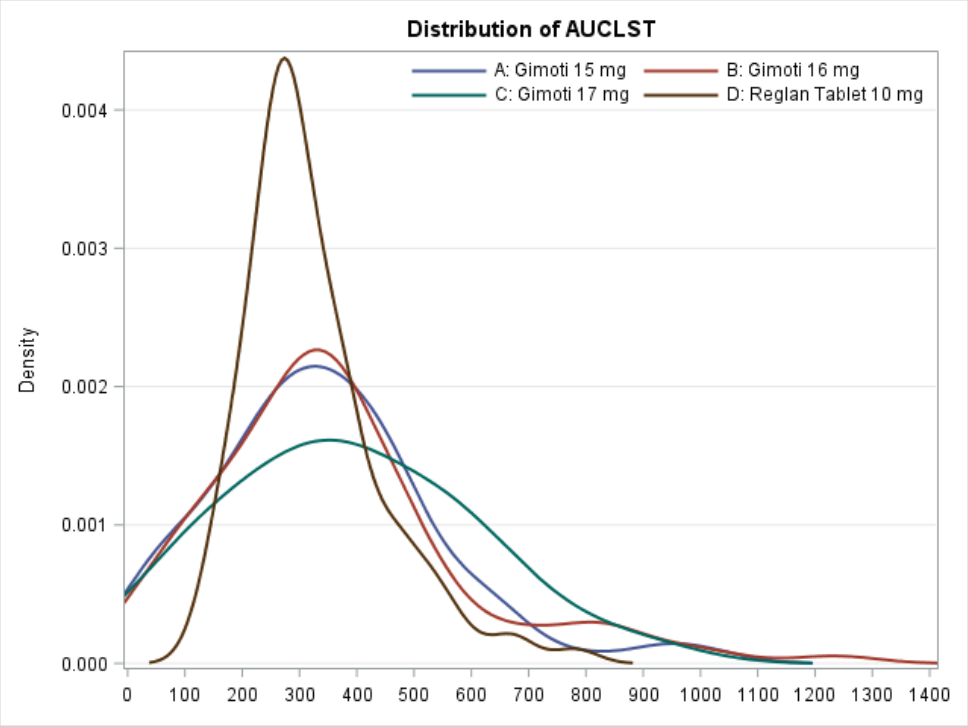

Figure 1 Comparison of distributions of AUCLST for four treatments

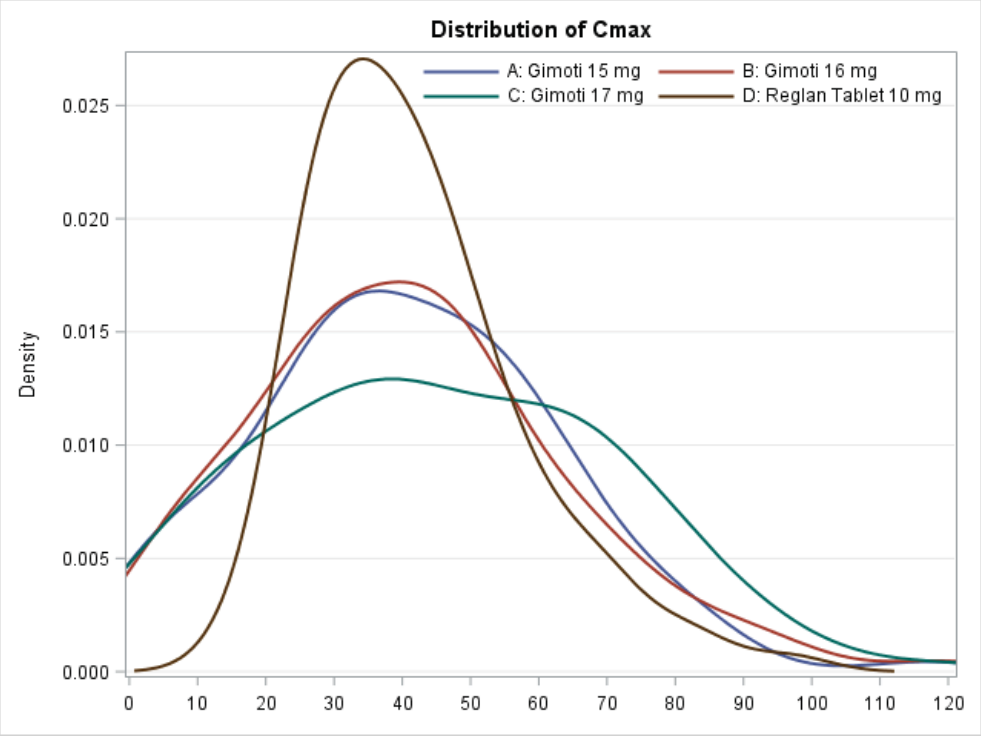

Figure 2 Comparison of distributions of Cmax for four treatments

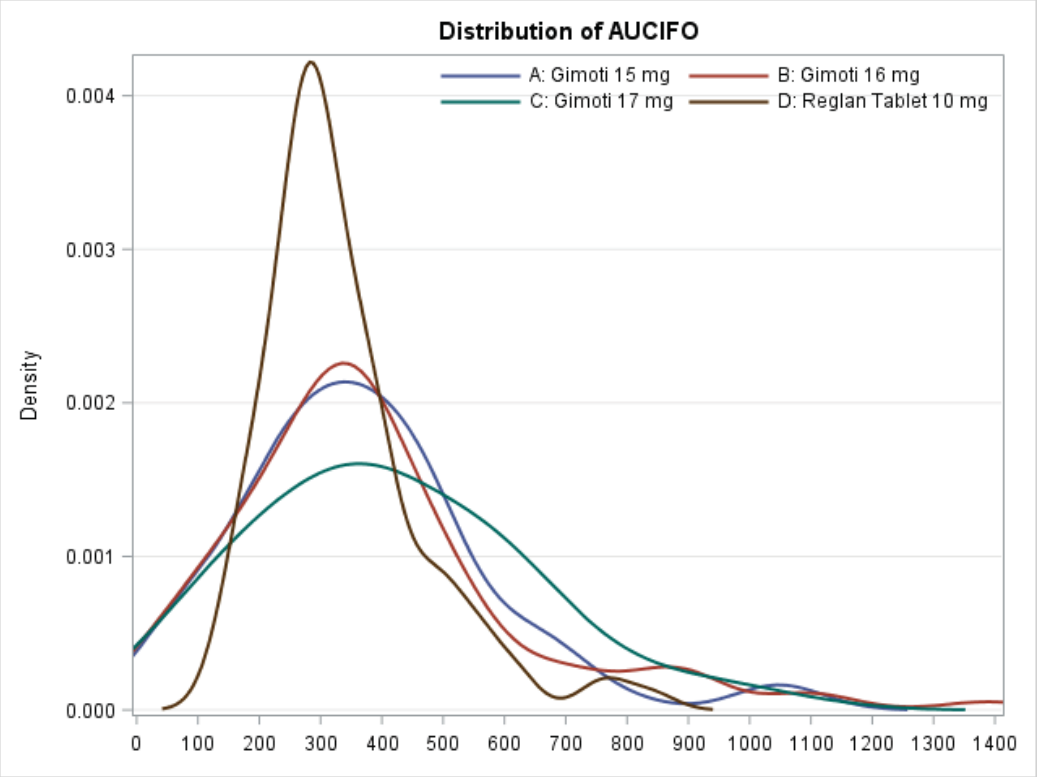

Figure 3 Comparison of distributions of AUCIFO for four treatments

Table 2 The summary statistics for the PK parameters: AUCLST, Cmax, and AUCIFO

TRTP	Number of subjects	PK Parameter	Min	Max	Mean	Percentile						
						5th	10th	25th	50th	75th	90th	95th
A: Gimoti 15 mg	104	AUCLST	3.6	1021.2	343.4	48.8	89.9	224.6	336.7	449.2	581.5	653.2
B: Gimoti 16 mg	103	AUCLST	10.3	1235.0	361.1	65.2	121.3	216.8	331.3	451.3	657.0	825.9
C: Gimoti 17 mg	100	AUCLST	9.1	934.5	388.0	46.4	110.4	220.1	375.7	544.1	676.4	761.2
D: Reglan Tablet 10 mg	102	AUCLST	138.2	781.3	323.4	172.4	196.3	251.4	290.9	374.8	471.6	548.1
A: Gimoti 15 mg	104	Cmax	0.1	117.0	40.6	5.2	8.8	26.5	39.1	54.9	67.0	77.5
B: Gimoti 16 mg	103	Cmax	0.5	119.0	40.7	7.4	11.9	25.2	39.6	52.2	69.2	81.7
C: Gimoti 17 mg	100	Cmax	0.6	119.0	44.8	4.5	12.7	24.9	41.0	62.5	76.5	87.7
D: Reglan Tablet 10 mg	102	Cmax	15.9	96.9	42.0	23.4	25.5	30.7	39.2	49.4	63.8	70.8
A: Gimoti 15 mg	101	AUCIFO	24.8	1076.8	369.3	67.8	145.9	245.6	349.2	469.2	620.0	699.4
B: Gimoti 16 mg	102	AUCIFO	11.8	1389.6	382.9	69.5	133.6	235.0	338.7	470.5	701.5	881.6
C: Gimoti 17 mg	98	AUCIFO	11.4	1090.5	414.2	67.5	122.2	240.6	396.1	572.0	705.3	869.9
D: Reglan Tablet 10 mg	101	AUCIFO	140.1	841.3	337.2	175.5	199.9	261.9	298.4	385.4	506.6	573.5

From Table 2, Minimum values of all three PK parameters in the Gimoti groups are much smaller than that in Reglan, and the 5th percentiles for all three PK parameters in the Gimoti groups than that in Regglan. Figures 1 to 3 clearly show that there are more smaller values in the Gimoti groups than those in Reglan and more larger values in the Gimoti groups than those in Reglan. Apparently, the distributions of all three PK parameters are very different between the Gimoti and Reglan.

Since this is Latin square design, the complete cases are recommended for analyses. However, the sponsor on purpose took away many observations or subjects by defining different exclusion criteria without following this general principle. These exclusions were not defined in the protocol dated August 17, 2017. These exclusions were added to the protocol dated February 2018 after the study was completed in September 20, 2017.

1.4 Sponsor's data handling

The sponsor excluded the profiles for the following subjects from their analyses based on the respective dose levels as their pre-dose concentrations were ≥5% of the Cmax: Subjects (b) (6) (Sequence 4: DCBA) for Period 3, (b) (6) (Sequence 2: BDAC) for Period 3, (b) (6) (Sequence 1: ABCD) for Period 2, and (b) (6) (Sequence 4: DCBA) for Period 4.

The sponsor also excluded some AUCinf data for the following subjects: Subjid= (b) (6) and Period =1 (AUCIFO=11.6 for Gimoti 17 mg) ; subjid= (b) (6) aperiod=3 (AUCIFO=15.3 for Gimoti 16 mg); subjid= (b) (6) aperiod=2 (AUCIFO=11.4 for Gimoti 17 mg) ;subjid= (b) (6) aperiod=3 (AUCIFO=171 for Gimoti 15 mg) ;subjid= (b) (6) aperiod=3 (AUCIFO=58.6 for Gimoti 17 mg). These values for AUCIFO are all very small.

The values for the PK parameters of these subjects are listed in Table 3. Comparing Table 2 and Table 3, we can see that almost all values except those subject (b) (6) in Period 2 are less than the 5th percentile of the corresponding treatment.

The sponsor also excluded the following 6 subjects from the PK population because they did not receive both the reference drug (Reglan Tablet) and at least 1 dose of Gimoti as follows: Subjects (b) (6) (Sequence 1: ABCD), (b) (6) (Sequence 1: ABCD), (b) (6) (Sequence 1: ABCD), (b) (6) (Sequence 1: ABCD), (b) (6) (Sequence 1: ABCD), and (b) (6) (Sequence 3: CADB). Also, Subject (b) (6) (Sequence 1: ABCD) had no drug concentrations reported for Period 1.

Statistical reviewer's comments: Apparently, some subjects with missing data in one or more periods are not excluded. Due to the nature of design, any cell missing would result in an incomplete case. The sponsor did not specify how to handle missing data.

Table 3 Values of PK parameters for excluded subjects in particular periods

SUBJID	Treatment	Period	PK parameter	Value	Sponsor's reason for data exclusion
(b) (6)	B: Gimoti 16 mg	3	AUCIFO	32.43	Pre-dose concentrations were ≥5% of the Cmax
	B: Gimoti 16 mg	3	AUCLST	26.69	
	B: Gimoti 16 mg	3	CMAX	2.19	
	A: Gimoti 15 mg	3	AUCLST	20.48	
	A: Gimoti 15 mg	3	CMAX	0.96	
	B: Gimoti 16 mg	2	AUCIFO	561.23	
	B: Gimoti 16 mg	2	AUCLST	546.25	
	B: Gimoti 16 mg	2	CMAX	62.30	
	A: Gimoti 15 mg	4	AUCIFO	67.78	
	A: Gimoti 15 mg	4	AUCLST	56.97	
	A: Gimoti 15 mg	4	CMAX	3.21	
	C: Gimoti 17 mg	1	AUCIFO	11.55	Percentage of AUCext was >20%.
	B: Gimoti 16 mg	2	AUCIFO	15.29	
	C: Gimoti 17 mg	3	AUCIFO	11.44	
	A: Gimoti 15 mg	3	AUCIFO	170.91	
	C: Gimoti 17 mg	3	AUCIFO	59.58	

1.5 Sponsor's model

In the sponsor's statistical analysis plan and statistical method of synopsis of clinical study report, the sponsor stated that model would include terms for treatment, sequence, group, sequence-by-group interaction, and period nested in group as fixed effects and subject nested within sequence-by-group as a random effect. Sequence, group, and sequence-by-group interaction will be tested using subject nested within sequence-by-group as the error term. The SAS Proc Mixed code is as follows:

proc mixed data=adpp;

by paramn paramcd param;

class usubjid trtseqp trtp aperiodc group;

model ln_aval=trtseqp group trtseqp*group trtp group*trtp aperiodc(group)/ddfm=kenwardroger;

random usubjid(trtseqp*group);

It appeared that the sponsor ignored the period effect and put the sequence-by-group interaction and period nested in group as fixed effects. Since any interaction term such as the sequence-by-group interaction and period nested in group is included in the model, the interpretation of BE is not feasible. However, in footnote of Sponsor's Table 11-3 on Page 58 of meto-in-006-report-body 1, the sponsor stated the following: "Analysis was performed using a mixed-effects model with natural log-transformed values of AUC0-t, AUC0-inf, and Cmax as the dependent variable and terms for treatment, sequence, and period as fixed effects and subject nested in sequence as a random effect. Terms for group, sequence-by-group interaction, and period nested in group fixed effects were tested and dropped from the model, as they were not significant at α 0.10, where group effect was defined as Group 1, Group 2, and Group 3, grouping subjects that were dosed on the same day in Period 1 (but not always on the same day in subsequent periods)."

1.6 Statistical comments on sponsor's results

Based on the Sections 1.4 and 1.5, the sponsor's biased data, in which low values from Gimoti group were deleted, were used to demonstrate the bioequivalence between the Gimoti and Reglan. It seems that the sponsor assumed no carryover effect since the sponsor included some subjects with missing cells. This assumption is stronger than the assumption of equal carry over effect in the Latin square design. Note that PROC mixed uses the period with observation and ignores the period without observation. After understanding this, we should not drop off the subjects with missing cell due to the absence of Reglan group. There is also an inconsistence about model specification in the sponsor's report. The complete cases should be used for the analyses with a correct model. Hence, the sponsor's results listed in Tables 4 and 5 below are not statistically valid.

Table 4 Sponsor's Bioequivalence Analyses for Metoclopramide (Overall Pharmacokinetic Population)

Treatment	Parameter	Test		Reference[a]		Ratio (%) (Test/Reference)	90% CI	
		N	Geometric LS Means	N	Geometric LS Means		Lower	Upper
Gimoti 15 mg	AUC_{0-t} (h*ng/mL)	97	274.73	102	304.41	90.25	79.480	102.480
Gimoti 16 mg		98	279.32			91.76	80.842	104.148
Gimoti 17 mg		98	295.33			97.01	85.477	110.110
Gimoti 15 mg	AUC_{0-inf} (h*ng/mL)	95	301.54	101	317.56	94.96	85.436	105.535
Gimoti 16 mg		96	307.26			96.75	87.089	107.492
Gimoti 17 mg		93	354.77			111.72	100.446	124.255
Gimoti 15 mg	C_{max} (ng/mL)	97	31.58	102	39.31	80.32	69.288	93.108
Gimoti 16 mg		98	31.59			80.37	69.361	93.119
Gimoti 17 mg		98	33.13			84.27	72.735	97.636

Table 5 Sponsor's Bioequivalence Analyses for Metoclopramide (Females only)

Treatment	Parameter	Test		Reference[a]		Ratio (%) (Test/Reference)	90% CI	
		N	Geometric LS Means	N	Geometric LS Means		Lower	Upper
Gimoti 15 mg	AUC_{0-t} (h*ng/mL)	41	354.53	44	344.40	102.94	86.069	123.122
	AUC_{0-inf} (h*ng/mL)	41	367.97	43	358.08	102.76	88.733	119.008
	C_{max} (ng/mL)	41	43.53	44	46.77	93.08	76.595	113.109
Gimoti 16 mg	AUC_{0-t} (h*ng/mL)	42	350.98	44	344.40	101.91	85.284	121.782
	AUC_{0-inf} (h*ng/mL)	42	363.42	43	358.08	101.49	87.696	117.462
	C_{max} (ng/mL)	42	40.90	44	46.77	87.44	72.022	106.165
Gimoti 17 mg	AUC_{0-t} (h*ng/mL)	43	363.82	44	344.40	105.64	88.551	126.026
	AUC_{0-inf} (h*ng/mL)	41	430.91	43	358.08	120.34	103.884	139.400
	C_{max} (ng/mL)	43	43.40	44	46.77	92.79	76.563	112.459

1.7 Statistical reviewer's results

To show the effect of removal of some subjects in particular periods, the statistical reviewer analyzed the data with or without these subjects and the complete cases. The final model includes terms for treatment, sequence, group, period as fixed effects and subject as a random effect since interaction

terms group*sequence, group*period, group*trtp are dropped off from the model due to their corresponding p-values>0.1. In FDA's analyses in **Tables 6 to 9**, no subjects with Percentage of AUCext was >20% (shown in Table 3) is excluded for analysis of AUCIFO.

1). For overall population in **Table 6**, without subjects whose pre-dose >5% Cmax, the 90% confidence interval lower limit for AUCLST between Gimoti 15 mg and Reglan increased from 75.1% to 79.5%; Without subjects whose pre-dose >5% Cmax, the 90% confidence interval lower limit for AUCLST between Gimoti 16 mg and Reglan increased from 78.6% to 80.9%. Without subjects whose pre-dose >5% Cmax, the 90% confidence interval lower limit for Cmax between Gimoti 15 mg and Reglan increased from 64.4% to 69.3%; Without subjects whose pre-dose >5% Cmax, the 90% confidence interval lower limit for Cmax between Gimoti 16 mg and Reglan increased from 67.2% to 69.4%.

2). Similarly for females only in **Table 7**, without subjects whose pre-dose >5% Cmax, the 90% confidence interval lower limit for AUCLST and Cmax between Gimoti and Reglan increased by 2 to 7%. Note that for females only (including subjects with Percentage of AUCext was >20%) , the 90% confidence interval upper limit for AUCIFO between Gimoti 17 mg and Reglan can be 132% , greater than 125%. Note that the sponsor's results in Table 3 (taking away subjects with Percentage of AUCext was >20%) shows that the 90% confidence interval upper limit for AUCIFO between Gimoti 17 mg and Reglan is 124.25%, less than 125%.

3). If the missing cells are not imputed, complete cases should be used for analyses. The results for overall population listed in **Table 8** show that 90% confidence interval for the Cmax ratio of Gimoti versus Reglan is much smaller than 80%; 90% confidence interval for the AUCLST ratio of Gimoti versus Reglan is smaller than 80% or larger than 125% for some cases . Table 8 shows that the bioequivalence of Gimoti against Reglan cannot be concluded for overall population. The results for females only are listed in Tables 9. Table 9 shows that the bioequivalence of Gimoti against Reglan cannot be concluded for females only either.

Table 6 FDA's Bioequivalence Analyses using data including subjects with missing cells* for Metoclopramide (Overall Pharmacokinetic Population)

Comparison	Ratio	90% CI		Subjects with C0>5% Cmax	PK Parameter
		Lower	Upper		
Gimoti 15 mg vs Reglan	0.861	0.751	0.987	Y	AUCLST
Gimoti 16 mg vs Reglan	0.901	0.786	1.031	Y	
Gimoti 17 mg vs Reglan	0.970	0.846	1.111	Y	
Gimoti 15 mg vs Reglan	0.903	0.795	1.025	N	
Gimoti 16 mg vs Reglan	0.918	0.809	1.042	N	
Gimoti 17 mg vs Reglan	0.970	0.855	1.101	N	
Gimoti 15 mg vs Reglan	0.755	0.644	0.885	Y	CMAX
Gimoti 16 mg vs Reglan	0.787	0.672	0.923	Y	
Gimoti 17 mg vs Reglan	0.842	0.718	0.988	Y	
Gimoti 15 mg vs Reglan	0.804	0.693	0.931	N	
Gimoti 16 mg vs Reglan	0.804	0.694	0.932	N	
Gimoti 17 mg vs Reglan	0.843	0.727	0.976	N	
Gimoti 15 mg vs Reglan	0.920	0.815	1.038	Y	AUCIFO
Gimoti 16 mg vs Reglan	0.923	0.819	1.041	Y	
Gimoti 17 mg vs Reglan	1.027	0.910	1.159	Y	
Gimoti 15 mg vs Reglan	0.935	0.832	1.050	N	
Gimoti 16 mg vs Reglan	0.941	0.838	1.056	N	
Gimoti 17 mg vs Reglan	1.027	0.914	1.153	N	

* Subjects with missing cells were included if these subjects have Reglan data.

Table 7 FDA's Bioequivalence Analyses using data including subjects with missing cells* for Metoclopramide (Female Subgroup)

Comparison	Ratio	90% CI		Subjects with C0>5% Cmax	PK Parameter
		Lower	Upper		
Gimoti 15 mg vs Reglan	0.957	0.786	1.165	Y	AUCLST
Gimoti 16 mg vs Reglan	1.026	0.844	1.248	Y	
Gimoti 17 mg vs Reglan	1.053	0.865	1.280	Y	
Gimoti 15 mg vs Reglan	1.029	0.860	1.230	N	
Gimoti 16 mg vs Reglan	1.020	0.853	1.218	N	
Gimoti 17 mg vs Reglan	1.055	0.885	1.259	N	
Gimoti 15 mg vs Reglan	0.847	0.679	1.057	Y	CMAX
Gimoti 16 mg vs Reglan	0.879	0.705	1.095	Y	
Gimoti 17 mg vs Reglan	0.923	0.741	1.151	Y	
Gimoti 15 mg vs Reglan	0.930	0.765	1.130	N	
Gimoti 16 mg vs Reglan	0.875	0.721	1.062	N	
Gimoti 17 mg vs Reglan	0.927	0.765	1.123	N	
Gimoti 15 mg vs Reglan	1.025	0.869	1.211	Y	AUCIFO
Gimoti 16 mg vs Reglan	1.027	0.872	1.210	Y	
Gimoti 17 mg vs Reglan	1.118	0.948	1.319	Y	
Gimoti 15 mg vs Reglan	1.026	0.868	1.212	N	
Gimoti 16 mg vs Reglan	1.019	0.863	1.202	N	
Gimoti 17 mg vs Reglan	1.118	0.948	1.320	N	

* Subjects with missing cells were included if these subjects have Reglan data.

Table 8 FDA's Bioequivalence Analyses Using Complete Cases* for Metoclopramide (Overall PK population)

Comparison	Ratio	90% CI		PK parameter
		Lower	Upper	
Gimoti 15 mg vs Reglan	0.874	0.762	1.003	AUCLST
Gimoti 16 mg vs Reglan	0.914	0.796	1.048	
Gimoti 17 mg vs Reglan	0.992	0.864	1.138	
Gimoti 15 mg vs Reglan	0.772	0.657	0.908	CMAX
Gimoti 16 mg vs Reglan	0.805	0.685	0.947	
Gimoti 17 mg vs Reglan	0.865	0.736	1.017	
Gimoti 15 mg vs Reglan	0.936	0.829	1.057	AUCIFO
Gimoti 16 mg vs Reglan	0.938	0.831	1.058	
Gimoti 17 mg vs Reglan	1.052	0.932	1.188	

* Subjects with any cell missing are excluded.

Table 9 FDA's Bioequivalence Analyses Using Complete Cases* for Metoclopramide (Females only)

Comparison	Ratio	90% CI		PK parameter
		Lower	Upper	
Gimoti 15 mg vs Reglan	0.961	0.791	1.167	AUCLST
Gimoti 16 mg vs Reglan	1.068	0.879	1.298	
Gimoti 17 mg vs Reglan	1.059	0.871	1.287	
Gimoti 15 mg vs Reglan	0.851	0.683	1.059	CMAX
Gimoti 16 mg vs Reglan	0.918	0.737	1.143	
Gimoti 17 mg vs Reglan	0.924	0.742	1.151	
Gimoti 15 mg vs Reglan	1.036	0.881	1.219	AUCIFO
Gimoti 16 mg vs Reglan	1.070	0.911	1.258	
Gimoti 17 mg vs Reglan	1.131	0.961	1.331	

* Subjects with any cell missing are excluded.

1.8 Conclusion and recommendation

The sponsor on purpose excluded low values for Gimoti group and increased the 90% confidence interval low limit for the (AUCLST, Cmax, or AUCIFO) ratio of Gimoti versus Reglan close to the lower equivalence margin 80%. Hence the sponsor's statistical analyses are not valid.

In conclusion, based on the FDA's complete cases, the bioequivalence of Gimoti against Reglan cannot be concluded for overall population. The bioequivalence of Gimoti against Reglan cannot be concluded for females only. The bioequivalence analyses for Females Subgroup are post-hoc analyses, which can be used for hypothesis generating, not for a final decision. The sponsor may update the sample size for a prospective study design based on the estimates from the current study. FDA can review the protocol for a future study once it is submitted to the FDA.

Based on data distributions in Figures 1 to 3, the sponsor should reformulate Gimoti for better matching Reglan distributions. We recommend the sponsor select an appropriate dose first and conduct a standard 2-sequence 2-period 2-treatement crossover study in order to increase the number of the complete cases compared to 4-sequence 4-period 4-treatement Latin Square.

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/s/

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