Safety and Efficacy of Low-dose Domperidone for Treating Nausea and Vomiting Due to Acute Gastroenteritis in Children

*Gerhard Leitz, *Peter Hu, *Carlos Appiani, *Qing Li, †Essack Mitha, ‡Maria Garces-Sanchez, and §Rajeev Gupta

See "It Is Ok to Be Negative!" by Di Lorenzo and Nurko on page 393.

ABSTRACT

Background: This study was conducted based on a request from the European Medicines Agency to generate robust data on domperidone efficacy in children in the relief of symptoms of nausea and vomiting by assessing the effect of a low-dose and short treatment duration.

Methods: In this randomized, double-blind, phase 3 study, children ages 6 months to 12 years with acute gastroenteritis randomly (1:1) received oral domperidone 0.25 mg/kg with oral rehydration therapy (ORT) or matching placebo thrice daily for 2 to 7 days. The proportion of patients with no vomiting episodes (primary endpoint) and patients ages ≥4 years with no nausea episodes (key secondary endpoint) within 48 hours of first treatment administration were evaluated.

Results: The study was terminated early following futility analysis. At early termination, 292 patients randomly received domperidone (n = 147) or placebo (n = 145). The proportion of patients with no vomiting episodes within 48-hours of first treatment administration was similar between domperidone (32.0%) and placebo groups (33.8%). Similarly, there was no significant difference in proportion of patients ages ≥4 years with no nausea episodes within 48 hours of first treatment administration between domperidone (35.7%) and placebo (38.6%). Total 13 patients (domperidone, 3.4% [5/147] vs placebo, 5.5% [8/145]) reported ≥1 treatment-emergent adverse events. No deaths or adverse events of special interest (extrapyramidal symptoms and QT prolongation) were reported.

Conclusions: Low-dose of domperidone with ORT did not significantly differ from placebo in reducing vomiting and nausea episodes in pediatric patients with acute gastroenteritis (AG), and the safety profile was similar between both groups.

Key Words: acute gastroenteritis, domperidone, nausea, vomiting

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What Is Known

- The European Medicines Agency recommended that domperidone should be used at the lowest effective dose (0.25 mg/kg) and for the shortest duration, not exceeding 1 week.
- There are limited data available on the efficacy of domperidone at a low dose and short-treatment duration in the relief of symptoms of nausea and vomiting in children.

What Is New

- In this phase 3, randomized study, low-dose domperidone did not significantly differ from placebo in reducing vomiting and nausea episodes in children with acute gastroenteritis.
- Owing to the lack of efficacy, the indication in children <12 years and ≤35 kg has been removed from the domperidone label.

Domperidone, a D2 receptor antagonist with antiemetic properties, has been marketed for >40 years and is available in >100 countries. Until 2014, domperidone was used to treat nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort, and regurgitation of gastric contents in adults at doses up to 80 mg/day and in children up to 2 $mg \cdot kg^{-1} \cdot day^{-1}$ for up to 4 weeks. On the basis of pharmacovigilance information and epidemiologic studies suggesting that domperidone exposure is associated with an increased risk for serious ventricular arrhythmia and sudden cardiac death, the European Medicines Agency's

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From the *Janssen Research & Development, NJ, the †Newtown Clinical Research Centre, Johannesburg, South Africa, the ‡Nazaret Health Center, Valencia, Spain, and the §Barnsley Foundation Hospital NHS Trust, Barnsley, England.

Address correspondence and reprint requests to Gerhard Leitz, MD, PhD, Clinical Leader, Internal Medicine, Established Products, Janssen Research & Development, LLC, 1125 Trenton-Harbourton Road, Mail stop K20 905, Titusville, NJ 08560 (e-mail: GLeitz@its.jnj.com).

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Pharmacovigilance Risk Assessment Committee (PRAC) reviewed available data in 2013 and 2014 and concluded that there is an increased risk of serious and potentially life-threatening cardiac adverse drug reactions associated with domperidone use (1). The risks are increased in patients ages >60 years, in patients who are using doses >30 mg/day, and/or are using concomitant QT-prolonging drugs or Cyp3A4 inhibitors that can increase plasma levels of domperidone.

The PRAC concluded that domperidone should be used at the lowest effective dose and for the shortest duration possible, which does not usually exceed 1 week. The PRAC further concluded that in adults, the benefit-risk balance remains favorable only for the relief of the symptoms of nausea and vomiting at doses up to 30 mg/day. However, for children, there were limited data available supporting efficacy for the newly recommended dose of 0.25 mg/kg up to a maximum of 10 mg thrice-daily (t.i.d) and the PRAC recommended that further data be generated to confirm efficacy in this patient population (1). This study was conducted in pediatric patients with nausea and vomiting because of acute gastroenteritis (AG) using 0.25 mg/kg body weight of domperidone along with standard-of-care therapy (oral rehydration therapy [ORT]). The study design had been selected for various reasons: nausea and vomiting are typical symptoms in children with AG, only short-term treatment is required, earlier studies at higher dose showed promising results in this indication (2–5), and antiemetic drugs, such as domperidone are prescribed in children with gastroenteritis (6,7).

METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel group study (NCT02699385) was conducted from July 07, 2016 to August 03, 2017 at 45 multinational sites (Austria, Belgium, Italy, the Russian Federation, South Africa, Spain, and the United Kingdom) (Fig. 1). After screening, enrolled patients were stratified according to length of time vomiting occurred before baseline (0 to <24 and ≥24 hours), and into 2 age groups (6 months to <4 years or 4–12 years). Patients were randomized (1:1) to receive 0.25 mg/kg dose of domperidone (1 mg/ml suspension) or matching placebo, using a computer-generated randomization schedule. After the first dose of study medication, ORT was initiated within 30 to 60 minutes, and second and third doses were administered at an interval of 4 to 6 hours on Day 1. From days 2 to 7, oral domperidone suspension 0.25 mg/kg (not exceeding 10 mg/day) or placebo suspension t.i.d. was administered 30 minutes before a meal. Treatment was discontinued if the patient was vomiting-free for 24 hours and also had completed at least a total of 6 doses. If nausea, vomiting or diarrhea worsened during the study, study medication was discontinued and rescue medication (standard-of-care used in the practice/country) or intravenous fluids were initiated.

An Independent Data Monitoring Committee (IDMC) reviewed the unblinded interim data to ensure patients' safety and to assess the futility of the study. An interim analysis was conducted twice, when about 25% of patients were enrolled (to review safety data), and when 50% of the randomized patients had either completed or dropped out from the study (to review safety and efficacy data). The IDMC made recommendations regarding study continuation in accordance with objectives of the interim analysis.

The study protocol was reviewed and approved by Independent Ethics Committee or Institutional Review Board at each study site. The study conformed to Declaration of Helsinki, International Council for Harmonization (ICH) and to Good Clinical Practice guidelines. Written informed consent was obtained from patients or their legally acceptable representatives.

Patients

Female or male children ages 6 months to 12 years (children ages >6 years for the sites in Russian Federation as per the country regulation) with mild-to-moderate dehydration presented with ≥3 episodes of nonbilious, nonbloody vomiting, and at least 1 episode of nonbloody diarrhea within 24-hours before screening, were included in the study. Other inclusion criteria were children with

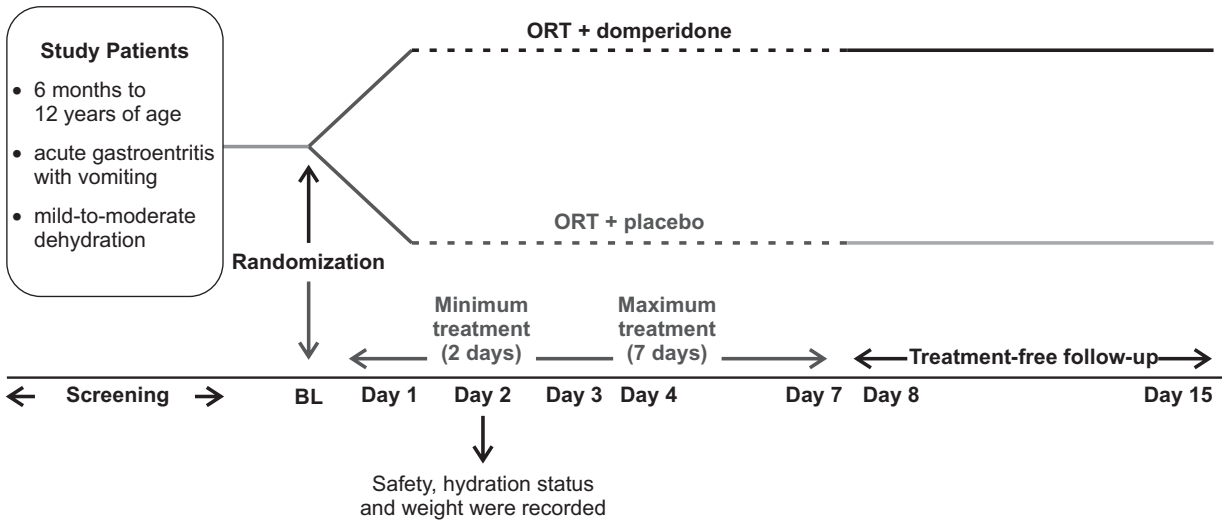

FIGURE 1. Study design, drug dosing, and patient allocation. BL, baseline; ORT, oral rehydration treatment; On days 3, 4, and 8: investigator collected safety data via telephone contact with patients/legal guardian; on days 3, 4, and 8: the study nurse screened for TEAEs of special interest during phone visit, using the checklist and entered the data into the patients' electronic case report form; follow-up visit on day 2: safety, hydration status and weight were recorded. TEAE = treatment-emergent adverse events.

≥2 other signs and symptoms of acute gastroenteritis (fever, nausea, diarrhea, abdominal pain, bloating or discomfort) within 3 hours before screening.

Patients were excluded from the study if they had severe dehydration or severe malnutrition, vomiting, and clinical symptoms for >72 hours before screening or need of intravenous fluid replacement. Additionally, patients who had chronic severe diarrhea, history of *Helicobacter pylori* infection, gastrointestinal disorders, such as active peptic ulcer, celiac disease, Crohn disease, or upper respiratory symptoms were excluded. Other exclusion criteria included history of congenital heart disease, bradycardia, heart failure, long-QT syndrome or other cardiac disorders, obstructive uropathy, pancreatitis, carcinoma, pulmonary, endocrine, neurological, psychiatric, or metabolic disturbances, extrapyramidal symptoms (EPS), hepatic or renal insufficiencies.

Study Objectives and Endpoints

The primary objective was to evaluate domperidone efficacy in children in the relief of symptoms of nausea and vomiting, specifically whether domperidone 0.25 mg/kg (not exceeding 10 mg/day) t.i.d. for up to 7 days with ORT was more effective than placebo with ORT at reducing vomiting associated with acute gastroenteritis within the first 48 hours of treatment administration. The primary efficacy endpoint was the proportion of patients with no vomiting episode within 48 hours of first treatment administration. The key secondary efficacy endpoint was the percentage of patients (≥4 years) with no episode of nausea within 48 hours of first treatment administration.

Other secondary efficacy endpoints included the following: within the 0- to 24-hour, >24- to 48-hour, and >48-hour to 7-day periods after the first treatment administration: number of vomiting episodes, number of nausea episodes (for patients ages ≥4 years), percentage with no episode of vomiting, percentage (ages ≥4 years) with no episode of nausea, and percentage with diarrhea. Within the 7-day treatment period after the first treatment administration, percentage with no episode of vomiting, percentage (ages ≥4 years) with no episode of nausea, percentage taking a rescue medication, percentage with early discontinuation of study drug because of no episodes of vomiting for 24 hours, time to last study drug, percentage referred to an emergency room/hospital for an alternative treatment, and time-to-last vomiting and number of ORT and proportion receiving ≥1 ORT within 0 hours to 7-day period after first successful domperidone administration. Other parameters include change in hydration score from day 1 (baseline) to day 2 (≤24 hours after baseline) and weight change from day 1 (baseline) to day 2.

Study Evaluations

Patients or legal guardians recorded all efficacy assessments including total number and timing of vomiting, nausea and diarrhea episodes, and patient weight in electronic diary (eDiary). Safety assessments included recording of treatment-emergent adverse events (TEAEs; by preferred term using MedDRA version 20.0) and serious TEAEs by severity, duration, and relationship to study drug.

Additionally, the AEs of special interest, which included extrapyramidal signs (EPS) and symptoms associated with QT prolongation were assessed and recorded during screening and frequently during the treatment period. A baseline ECG was not conducted as a single ECG assessment is not considered as a reliable measure to exclude preexisting QT prolongation (8).

In addition, no QT prolongation was expected with the low dose of domperidone (0.25-mg/kg up to a maximum of 10 mg t.i.d) used in this study. Furthermore, patients with a history of cardiac disease were excluded and if any symptoms of QT prolongation were present at screening, the patient was not randomized into the study. Physicians evaluated symptoms associated with QT prolongation at screening before randomization, after the first dose, and at the follow-up visit on days 2 to 4 and 8. During the visits on days 1 and 2, the physician conducted a thorough evaluation for these symptoms and rated them for frequency and severity.

Statistical Analysis

Sample size calculation was based on 2-sided Fisher Exact Test, assuming a type 1 error of 0.05. A total of 480 patients were planned with 240 patients in each treatment group. All efficacy statistical tests were interpreted at the 2-sided 5% level. The primary efficacy analysis was performed in intent-to-treat (ITT) set, defined as all randomized patients. The primary analysis for comparing the primary endpoint between the 2 treatment groups was the Cochran-Mantel-Haenszel test. A sensitivity analysis was performed for the primary efficacy and the key secondary endpoint to assess the effect of early withdrawals (within first 48 hours after first dose). Safety analysis were performed on the safety analysis set, defined as all randomized patients who received ≥1 dose of study agent.

RESULTS

Patient Disposition and Baseline Characteristics

The study was terminated early for futility based on the IDMC recommendations following the planned interim analysis. At the time of early termination of the study, 292 patients were randomized to receive domperidone (n = 147) or placebo (n = 145) and 287 patients completed the study (Supplementary Figure 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/B662*). Before early termination, 5 patients discontinued the study, with AEs being the most common reason for discontinuation (n = 1 in domperidone group and n = 2 in placebo). The demographic and baseline characteristics were comparable across the treatment groups. The median (range) age of patients was 7 (0.67–12) years with 53% boys and the majority were Caucasians (83%) (Appendix 1, Supplemental Digital Content 3, *http://links.lww.com/MPG/B664* and

Supplementary Table 1, Supplemental Digital Content 2, *http://links.lww.com/MPG/B663*). The mean (SD) number of doses was 7.1 (2.29) in domperidone and 7.2 (2.85) in placebo group.

Efficacy

Cessation of vomiting and nausea episodes was observed in a similar proportion of patients in domperidone and placebo groups. There were no vomiting episodes within the first 48 hours of treatment administration in 32.0% of patients in the domperidone and 33.8% in the placebo. Similarly, the proportion of patients with no episodes of nausea in patients ages ≥4 years were similar between domperidone (35.7%) and placebo groups (38.6%) during the first 48 hours of treatment administration (Table 1). No statistical difference was observed for the subgroup analyses based on baseline stratification by age (6 months to 4 years; 4 years to 12 years) or length of time that vomiting occurred before baseline (0 to <24 h or ≥24 hours). The results were consistent with that of the primary analysis for proportion of patients with no vomiting episode.

Within 0 to ≤24 hours of treatment, the mean (SD) number of vomiting episodes was 1.4 (1.35) in the domperidone group versus 1.6 (1.64) in placebo. During >24 to ≤48 hours of treatment, the

TABLE 1. Proportion of patients with no episodes of vomiting and nausea within 48 hours of first domperidone administration (intend-to-treat population)

	Domperidone N = 147	Placebo N = 145
Patients with no episodes of vomiting within 48 hours of treatment		
n (%)	47 (32.0)	49 (33.8)
95% CI	(24.5–40.2)	(26.2–42.1)
CHM *P*-value		0.732
Patients with no episodes of nausea within 48 hours of treatment		
n (%)	46 (35.7)	49 (38.6)
95% CI	(27.4–44.6)	(30.1–47.6)
CMH *P*-value		0.617

CI = confidence interval; CMH = Cochran-Mantel-Haenszel test; ITT = intend-to-treat.

mean (SD) number of vomiting episodes observed was 0.1 (0.45) in domperidone group versus 0.2 (0.55) in placebo. Within the 0 to ≤24-hour timeframe, mean (SD) number of nausea episodes in patients ages ≥4 years was 1.5 (1.72) in the domperidone group versus 1.8 (2.02) in the placebo (Table 2).

The proportion of patients with no episodes of vomiting and nausea were similar in both domperidone and placebo groups for all time periods; i.e., 0 to ≤24 hours, >24 to ≤48 hours and >48 hours to 7 days. The proportion of patients with no episodes of vomiting in the domperidone and placebo groups were 32.7% and 35.9% for the 0 to ≤24 hours period, 89.1% and 86.2% for the ≥24 to ≤48 hours period, and 95.2% and 95.2% for the ≥48 hours to ≤7-day period, respectively. The percentage of patients (ages ≥4 years) with no episodes of nausea were 38.0% and 40.2% for the 0 to ≤24 hours period, 85.3% and 85.8% for the ≥24 to ≤48 hours period, and 96.9% and 92.9% for the ≥48 hours to ≤7-day period in the domperidone and placebo groups, respectively.

TABLE 2. Vomiting and nausea episodes within 0 to <24 hours, >24 to ≤48 hours, and >48 hours to ≤7 days after first treatment administration

	Domperidone N = 129	Placebo N = 127	*P*-value*
Number of nausea episodes, mean (SD)			
0 to ≤ 24 hours	1.5 (1.72)	1.8 (2.02)	0.413
>24 to ≤ 48 hours	0.2 (0.69)	0.2 (0.58)	
>48 hours to ≤ 7 days	0.1 (0.44)	0.1 (0.67)	
Proportion of patients with no episodes of nausea, %			
0 to ≤ 24 hours	38.0	40.2	0.680
> 24 to ≤ 48 hours	85.3	85.8	
> 48 hours to ≤ 7 days	96.9	92.9	
Number of vomiting episodes, mean (SD)			
0 to ≤ 24 hours	1.4 (1.35)	1.6 (1.64)	0.835
> 24 to ≤ 48 hours	0.1 (0.45)	0.2 (0.55)	
> 48 hours to ≤ 7 days	0.1 (0.26)	0.0 (0.25)	
Proportion of patients with no episodes of vomiting, %			
0 to ≤ 24 hours	32.7	35.9	0.707
> 24 to ≤ 48 hours	89.1	86.2	
> 48 hours to ≤ 7 days	95.2	95.2	
Proportion of patients with diarrhea, %			
0 to ≤ 24 hours	68.7	72.4	0.562
> 24 to ≤ 48 hours	30.6	30.3	
> 48 hours to ≤ 7 days	17.7	20.2	

Generalized linear models for treatment comparison (domperidone vs placebo) was used for the number of vomiting episodes with factors for treatment, time period (0 to ≤24 hours, >24 to ≤48 hours, >48 to ≤7days), and stratification factors of the length of time that vomiting occurred before baseline (0 to <24, or ≥24 hours) and age (6 months to <4 years of age vs 4–12 years of age). SD = standard deviation.

*P value indicates 0-hour to 7-day time period.

Within the 7-day treatment period, the proportion of patients with no episodes of vomiting in domperidone group (30.6%) was similar when compared with placebo (32.4%; $P = 0.707$). Similarly, the percentage of patients (ages ≥4 years) with no episodes of nausea within 7-day treatment period were comparable between domperidone (35.7%) and placebo groups (37.8%; $P = 0.680$; Table 2). There was no difference in mean (SD) time-to-last vomiting within the 7 days of treatment between domperidone (16.87 [25.39] hours) and placebo group (16.88 [20.74] hours; $P = 0.837$).

The percentage of patients who had early treatment discontinuations because of no episodes of vomiting in 24-hour timeframe within the 7-day treatment period was comparable between both treatment groups (99.3% in domperidone vs 97.2% in placebo, $P = 0.169$). There was no difference in mean time (SD) to last study drug within the 7-day treatment period in both the treatment groups (46.4 [20.1] and 48.3 [25.6] hours in domperidone and placebo groups, $P = 0.382$). Within 7-day treatment period, rescue medication was taken by 0.7% and 1.4% of patients in the domperidone and placebo groups, respectively. The proportion of patients referred to emergency room or were hospitalized for further management within the 7-day treatment period was 0.7% in both treatment groups.

A mean change of −1.1 in total hydration score from days 1 to 2 was observed in both the treatment groups. Within 7-day treatment period, 97.3% (domperidone) and 95.9% (placebo) of patients received ≥1 ORT, with total mean (SD) dose of ORT being 287.4 (332.2) mL in the domperidone and 343.6 (408.0) ml in the placebo group. The mean change in body weight from baseline to day 2 was −0.01 kg in the domperidone group versus −0.03 kg ($P = 0.372$) in the placebo.

The proportion of patients with diarrhea was similar in both the treatment groups at all timepoints. The percentage of patients with diarrhea in the domperidone and placebo groups was 68.7% and 72.4% from 0 to ≤24 hours period, 30.6% and 30.3% from ≥24 hours to ≤48 hours period, and 17.7% to 20.0% from ≥48 hours to ≤7-day period, respectively. In timeframe 0 hour to 7-day treatment period, there were 74.1% and 76.6% of patients with diarrhea in the domperidone and placebo group ($P = 0.562$), respectively.

Safety

Overall, 13 patients reported 17 TEAEs during the study, with the majority of events being mild in severity. The TEAEs observed were similar in the domperidone group (n = 5, 3.4%) and placebo (n = 8, 5.5%) (Table 3). Two TEAEs reported as severe were gastroenteritis salmonella in 1 patient in the domperidone group, and headache in 1 patient in the placebo. All TEAEs reported in both groups with exception of 2 TEAEs, fatigue and rash reported in the placebo group, were considered to be unrelated to the study treatment. In each treatment group, there was 1 serious TEAE leading to treatment withdrawal: gastroenteritis salmonella in domperidone and dehydration in placebo. No serious TEAE was considered related to study treatment, and no deaths or AEs of special interest occurred during the study.

TABLE 3. Treatment-emergent adverse events observed in safety analysis set

	Domperidone N = 147	Placebo N = 145
Any TEAE, n (%)	5 (3.4)	8 (5.5)
Abdominal pain	1 (0.7)	1 (0.7)
Vomiting	2 (1.4)	0
Fatigue	0	1 (0.7)
Pyrexia	0	1 (0.7)
Gastroenteritis salmonella	1 (0.7)	0
Rhinitis	0	1 (0.7%)
Viral upper respiratory tract infection	0	1 (0.7%)
Fall	1 (0.7)	0
Lip injury	1 (0.7)	0
Headache	0	1 (0.7)
Bruxism	1 (0.7)	0
Sleep talking	1 (0.7)	0
Bronchospasm	0	1 (0.7)
Oropharyngeal pain	0	1 (0.7)
Rash	0	1 (0.7)
Serious TEAEs, n (%)	1 (0.7)	1 (0.7)
Gastroenteritis salmonella	1 (0.7)	0
Dehydration	0	1 (0.7)
TEAEs leading to discontinuation, n (%)	1 (0.7)	2 (1.4)
Gastroenteritis salmonella	1 (0.7)	0
Dehydration	0	1 (0.7)
Rash	0	1 (0.7)

TEAE = treatment-emergent adverse event.

DISCUSSION

On the basis of a review of the literature, the European Medicines Agency's PRAC concluded that there is an increased risk of serious and potentially life-threatening cardiac adverse drug reactions associated with domperidone use. They also concluded that the benefit-risk balance of domperidone-containing products remains favorable when used at the lowest effective dose and for the shortest duration possible, which does not usually exceed 1 week. In order to maintain marketing authorization for the pediatric population and to continue providing domperidone for children in need of treatment they requested a study be conducted to generate robust data on the efficacy of domperidone in the relief of symptoms of nausea and vomiting in children with the new posology (0.25 mg/kg up to a maximum of 10 mg thrice-daily).

This study design followed domperidone-dosing regimen in accordance to the PRAC recommended dose to minimize any potential AEs and generate robust efficacy data for a short treatment duration of 7 days in children with acute gastroenteritis. The indication, acute gastroenteritis, was selected as it required short-term intervention and nausea and vomiting are common symptoms in children with this indication. Both nausea and vomiting are considered clinically relevant endpoints and these symptoms showed improvement with domperidone treatment in several prior clinical studies in children (2,4,5,9,10). However, nausea is difficult to measure because of its subjective nature, especially in younger children. Endpoints based on subjective measures are generally not selected as primary endpoints, and thus, nausea was selected as key secondary endpoint and vomiting as the primary endpoint. At the time this study was designed, no validated instrument was available to assess nausea intensity in children below the age of 4 years (11). Therefore, nausea in children ages 6 months to <4 years was not assessed, and patients were stratified by age: 6 months to <4 years versus 4 to 12 years. Only children with acute gastroenteritis and mild-to-moderate dehydration were enrolled in the study. Children with severe dehydration were excluded as they might frequently have electrolyte disturbances including hypokalemia, which may increase the risk for QT prolongation. Subsequently, the reported phase 3 study investigated the efficacy and safety of domperidone in pediatric patients with nausea, vomiting, and mild-to-moderate dehydration because of AG.

The primary endpoint of the study was the percentage of patients with no vomiting episodes within the first 48 hours of the first treatment administration. The prespecified futility analysis showed that the percentage of patients with no vomiting episodes during the first 48 hours after the first treatment administration was similar between the domperidone and placebo groups (32.0% and 33.8%, respectively). Due to prespecified futility criteria, the IDMC recommended to stop the study as it was unlikely that a significant difference in the primary endpoint would be achieved by enrolling additional patients.

Although the primary endpoint was not met at the time the study was stopped, the mean number of vomiting episodes was 1.4 in the domperidone group versus 1.6 in the placebo for the 0 to ≤24-hour period and 0.1 in the domperidone group and 0.2 in the placebo for the >24- to ≤48-hour period. Also, the mean number of nausea episodes for patients ages ≥4 years within the 0 to ≤24-hour timeframe was 1.5 in the domperidone group versus 1.8 in placebo.

The overall TEAEs were similar in domperidone and placebo (3.4% vs 5.5%), and there was only 1 (0.7%) serious TEAEs in each treatment group: gastroenteritis salmonella in domperidone and dehydration in placebo. None of the TEAEs were considered related to domperidone treatment, and no AEs of special interest (EPS and symptoms associated with QT prolongation) were reported during the entire course of the study.

A prerequisite of this study was to provide ORT as standard-of-care treatment that could be taken at home and before entering the study. ORT has significantly improved over time and seems to be a sufficient remedy to treat mild to moderately dehydrated children with AG, a possibility supported by the low rate of nausea/vomiting episodes and low number of hospitalizations in the placebo group. The average number of vomiting episodes in the placebo group within 0 to 24 hours, >24 to 48 hours, and >48 hours to ≤7 days after the first dose was 1.6, 0.2 and 0, respectively. The percentage of patients referred to an emergency room/hospital for treatment within the 7-day treatment period was 0.7%. This study indicates that nausea and vomiting in pediatric patients with acute gastroenteritis and mild-to-moderate dehydration is self-limiting and well managed by ORT.

The efficacy of domperidone in treating acute gastroenteritis in several studies have shown inconsistent results (11,12). A more recent study in children who failed initial oral rehydration administration showed that a single dose of domperidone (0.5 mg/kg of body weight) was not effective in reducing vomiting episodes or the need for intravenous rehydration (13). Older studies demonstrated that domperidone suppositories and oral solutions significantly decreased the number and severity of vomiting episodes compared with placebo in a variety of indications (4,5,9,10). However, the dose used in those studies exceeded the dose of the new posology.

CONCLUSIONS

In conclusion, a low dose of domperidone (0.25-mg/kg up to a maximum of 10-mg t.i.d for up to 7 days) in combination with ORT in 6-month to 12-year-old pediatric patients with nausea/vomiting and mild-to-moderate dehydration did not make more children vomiting-free within 48 hours as compared with placebo. Given the lack of efficacy and negative benefit risk ratio, the

company in consultation with health authorities removed from the domperidone label the indication in children less than 12 years old and $\leq$35 kg.

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