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ORIGINAL ARTICLE

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A double-blind randomized, multicenter, placebo-controlled study of itopride in functional dyspepsia postprandial distress syndrome

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Abstract

Background: Itopride, a mixed D2 antagonist and cholinesterase inhibitor, has prokinetic effects on gastric motility. The Leuven Postprandial Distress Scale is a validated patient-reported outcome instrument for functional dyspepsia (FD) postprandial distress syndrome (PDS). We aimed to use the LPDS to assess treatment outcome in PDS and PDS/EPS (epigastric pain syndrome).

Methods: Patients with PDS, with or without non-predominant EPS symptoms, were enrolled in an 8-week double-blind placebo-controlled multi-center trial with itopride (100 mg t.i.d.). Patients completed LPDS diaries and questionnaires to assess treatment response. Mann–Whitney test and mixed models were used.

Results: One hundred patients (79% females, 39.1 ± 1.5 yo) were included. No significant difference was observed between treatment arms ($p = 0.6$). Compared to baseline, itopride treatment significantly improved the LPDS score ($p = 0.001$) and all individual symptoms ($p < 0.0001$). In the placebo arm, this was only the case for belching and epigastric pain ($p < 0.05$). In an exploratory analysis, outcomes in "pure" PDS ($n = 45$) and overlapping PDS/EPS ($n = 55$) patients were assessed and showed that the latter subgroup has the largest benefit with itopride compared to placebo ($p = 0.03$).

Conclusion: Using the LPDS score in a pilot controlled trial in FD, itopride shows no therapeutic benefit over placebo after 8 weeks of treatment. In an exploratory post hoc analysis, itopride but not placebo was associated with improvement of symptoms compared to baseline, and this was most prominent in patients with overlapping PDS/EPS. The efficacy of itopride in this subgroup needs to be evaluated in a large study using the same outcome measure. (clinialtrials.org ref.: NCT04647955).

KEYWORDS
dopamine antagonist, functional dyspepsia, itopride, Leuven postprandial distress scale, patient-reported outcome

1 | INTRODUCTION

Functional dyspepsia (FD) is defined by the Rome consensus as "the presence of symptoms in the epigastric region in the absence of any structural or metabolic disease that is likely to explain the symptoms."[1–5] To improve clinical management, FD is subdivided into Postprandial Distress Syndrome (PDS), characterized by bothersome postprandial fullness and/or early satiation, and Epigastric Pain Syndrome (EPS), characterized by bothersome epigastric pain and/or burning.[2,5,6]

In 2016, the Rome III criteria were updated to Rome IV, and these included postprandial epigastric pain and postprandial nausea as common accessory symptoms contributing to the symptom pattern of PDS, which is more prevalent than EPS.[3,4]

FD is a commonly occurring functional gastrointestinal disorder affecting up to 8% of the population worldwide.[7] The chronic character of the disease, together with the increase number of clinical consultations and tests, and co-morbidities such as anxiety and depression, results in an important decrease in quality of life and a high socio-economic impact.[8–11]

The lack of effective treatments for FD is partially addressed to the inappropriate use of endpoints and the lack of validated instruments to assess of symptoms and their responsiveness in this patient group.[12] Therefore, we developed and validated, in line with FDA regulatory guidelines,[13] a new Patient-Reported Outcome (PRO) questionnaire, the Leuven Postprandial Distress Scale (LPDS), for the PDS subgroup.[14,15] The validation of the LPDS was based on the blinded analysis of a placebo-controlled study of itopride (100 mg t.i.d.) in FD PDS patients, and established the construct validity, known groups criterion validity, convergent validity, reproducibility, internal consistency and responsiveness to change during an intervention. Furthermore, the study also allowed to determine whether the minimally clinically important difference (MCID) obtained with the LPDS instrument.[8] These results led to a letter of support from the European Medicines Agency (EMA) for the use of LPDS as a valid tool to assess therapeutic outcome in clinical trials.[16]

For the evaluation of the measurement properties of the LPDS, the blinding to the allocated treatment was not broken. In this case, the use of a treatment trial allows the evaluation of responsiveness to change of the LPDS instrument by inducing treatment-induced changes in symptom intensity in some patients.[14] However, the EMA requested to include breaking of the treatment allocation blinding and to report the results evaluating the efficacy of itopride for further documenting the validity of the LPDS instrument in a clinical study setting.

Based on this request, the study protocol based on the PRO analysis on the first 60 patients and included the assessment to the efficacy of itopride with the LPDS score as a secondary aim in a cohort of 100 patients. In the present manuscript, we report additional results of the LPDS validation study, including data on the treatment efficacy using the LPDS questionnaire and impact on quality of life after treatment with itopride in the full cohort of FD/PDS patients enrolled in the trial.

Key points

What is known

- The LPDS (Leuven Postprandial Distress Scale) is a validated Patient-Reported Outcome (PRO) instrument for Functional dyspepsia —Postprandial Distress Syndrome (PDS).
- Itopride is a mixed dopamine-2 antagonist and cholinesterase inhibitor with inconsistent efficacy results in previous treatment trials in functional dyspepsia.

What is new here

- In this 8-week pilot study using the LPDS, itopride but not placebo improved the LPDS score relative to baseline.
- The LPDS PRO for treatment outcome is also applicable in ROME IV PDS.

Itopride is not approved for this indication and thus the paper describes off-label use in functional dyspepsia.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was a double-blind randomized, multi-center, placebo-controlled study of PDS patients receiving either itopride 100 mg t.i.d. or placebo as previously described[14] (Figure 2) (see CONSORT checklist in the Supplementary Materials). Itopride is a prokinetic benzamide derivative with dopamine-2 antagonistic and cholinesterase inhibitory properties, which exerts a stimulatory effect on gastric motility.[17–21] The treatment period (8 weeks) and administered dose was chosen based on previously reported studies.[17,19,20]

After selection according to Rome III criteria, FD PDS patients entered a 2-week run-in period in which they completed the LPDS questionnaire as a daily diary to assess eligibility. If eligible, based on the symptom pattern and frequency (see below, patient selection section), patients were randomized into parallel treatment arms with itopride (100 mg t.i.d) or placebo.

Patients completed the LPDS diary daily through the entire trial, for 8 weeks. For the purpose of validation of a PRO instrument, anchor questionnaires are used.[14] For this reason, the protocol included multiple additional assessments, with patients completing the Overall Treatment Evaluation (OTE), Overall Symptom Severity (OSS), Patient's Assessment of GastroIntestinal Symptoms (PAGI-SYM), and Short Form Nepean Dyspepsia Index (SF-NDI) questionnaires at the end of the run-in period and every 2 weeks during the treatment period. Three outpatient clinic visits (visit 3, 4, and 6) and one telephone call (visit 5) were planned.[15] Finally, patients

were encouraged to continue an open-label period with itopride for 8 weeks, during which one additional telephone call (visit 7) and a last outpatient clinic visit (visit 8) were planned (Figure 1).

All study procedures were approved by the Ethics Committee of Leuven University Hospital, Belgium (ref. number: S54963; date: 2013) and were performed in accordance with the Declaration of Helsinki. The study is publicly available in clinicaltrials.org (ref. number: NCT04647955). All authors had access to the study data and had reviewed and approved the final manuscript.

2.2 | Study aims

The primary aim of this study, as described in the protocol, was to evaluate the validity of the LPDS questionnaire. For the analysis of this assessment, 60 patients were recruited and these results without breaking the randomization code are already published.[14]

For the current itopride efficacy analysis, the secondary aim of the study, the number of patients was increased to 100 to evaluate the treatment efficacy of Itopride with the LPDS score.

Finally, an exploratory analysis with the LPDS score was performed in the pure PDS subgroup and the overlap subgroup with postprandial pain. For exploratory purposes, we also report the outcome of symptom assessments with the anchor questionnaires OSS, OTE, PAGI-SYM, and the SF-NDI questionnaires. Results of the PAGI-SYM and SF-NDI questionnaires are described as Supplementary Results.

2.3 | Patient selection and subgroups

Consecutive outpatients (18–70 years old) diagnosed with FD PDS according to the Rome III criteria were recruited from 11 secondary- and tertiary-care gastroenterology practices in Belgium. FD patients were included in the trial if the symptomatic PDS pattern was confirmed and they reported at least moderate postprandial fullness and/or early satiation symptoms on at least 4 days during the 2 weeks of eligibility period.[14]

Patients were subdivided into FD subgroups as per Rome III criteria following the outcome of the Rome III questionnaire. The "pure" PDS patients included those patients suffering from of bothersome postprandial fullness and/or early satiation at least several times per week with no occurrence of severe epigastric pain. The overlap PDS/EPS subgroup included those patients with postprandial fullness and/or early satiation at least several times per week and epigastric pain at least once a week. Furthermore, patients were asked to clarify whether the epigastric pain was frequently occurring after the ingestion of a meal, which would classify them as PDS according to Rome IV criteria.[4,5]

2.4 | Randomization and blinding

Randomization was performed by the hospital pharmacy (independent from the trial) by means of the web tool randomization.com. Subjects were randomized to a single treatment by using randomly permuted blocks of 10. The allocation of the subjects was blinded to the patients and investigators involved in the trial.

The sequence was concealed using a sealed envelope that was kept by the hospital pharmacy until the study was completed. The envelope was open after all subjects have finalized the study and after the data for the LPDS validation study were analyzed and published.

2.5 | Questionnaires

Symptom severity was assessed with a daily diary and with questionnaires that were completed at fixed time points during the trial as previously described.[14] The following questionnaires were used in this study: the LPDS diary, OSS, OTE, PAGI-SYM, and the SF-NDI.[22–26] The rationale for each of this questionnaire and their use (secondary outcome) is available in the Supplementary Materials.

The LPDS diary instrument consisted of 3 cardinal PDS symptoms needed for the assessment of treatment outcome: early satiation, postprandial fullness, and upper abdominal bloating. The

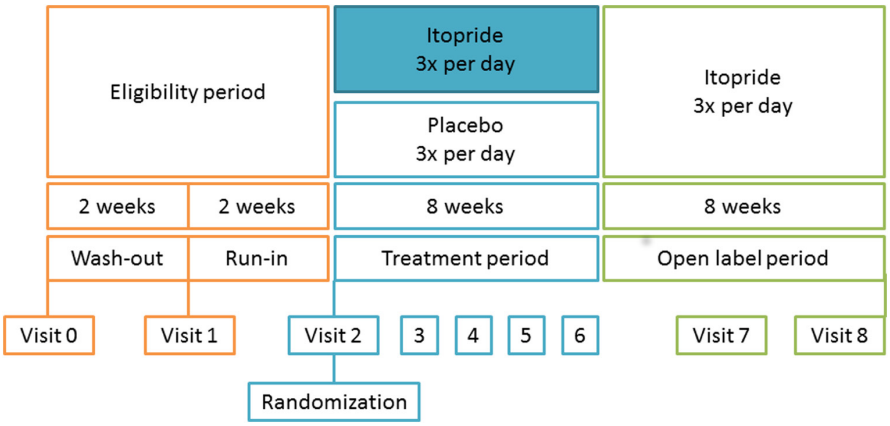

FIGURE 1 Study design

question items addressed in the LPDS questionnaire were defined during focus groups and during a validation analysis.[14,15]

In addition, 5 accessory epigastric symptoms were also scored: epigastric pain, epigastric burning, nausea, belching, and heartburn.[14] The rating of the items is expressed as verbal descriptors (5 levels per item, ranging from absent, 0, to very severe, 4) accompanied by "smiley faces." (☺ to ☹).

2.6 | Statistical analysis

Baseline characteristics include medical history (diagnosis of FD) and demographic parameters (age, weight, height, and BMI). Qualitative measures were compared using the Pearson Chi-Squared test while quantitative measures were compared using the Mann–Whitney test.

After subdividing FD subgroups, reported frequency of all symptoms was analyzed and compared between the groups by means of the Chi-squared test.

In the results reporting, the label "PDS symptoms" refers to the average of LPDS symptom scores for postprandial fullness, early satiation, and upper abdominal bloating together. The label "EPS symptoms" refers to the average of LPDS symptom scores for epigastric pain and epigastric burning together.

Within each treatment arm, the change from baseline (average of the run-in period of 2 weeks) to week 8 (end of treatment) and the difference between baseline and end of therapy was compared between Itopride and control groups using mixed models. As the assumption of normality was violated, formal statistical inference employed the non-parametric bootstrap statistical inference with the parameter for interaction between group and time used to estimate effect size.

The distribution of OTE and OSS scores following treatment was compared between Itopride and placebo groups with the Pearson Chi-Squared test.

The MCID is established at 0.5 of the mean LPDS scores for the PDS cardinal symptoms (postprandial fullness, early satiation, and upper abdominal bloating).[14] We calculated the number of patients that reached the LPDS MCID (≥0.5) and at a higher response threshold (≥0.7) and differences between proportions were analyzed with the Chi-squared test.

Post hoc power analysis is available in the Supplementary Materials. For this study, $p < 0.05$ was considered significant. All data are presented as mean ± standard error of the mean (SEM) or standard deviation (SD).

3 | RESULTS

3.1 | Study population

After eligibility, a total of 100 PDS patients (79% females, 39.1 ± 1.5 years old, 22.2 ± 0.4 kg/m^2) were randomized. Of these, 91 completed the entire study. Nine patients dropped out in the last few weeks (week 7 or week 8) of treatment (itopride $n = 4$, placebo $n = 5$). The main reason for dropout was lack of efficacy. No adverse reactions were observed in this trial (Figure 2).

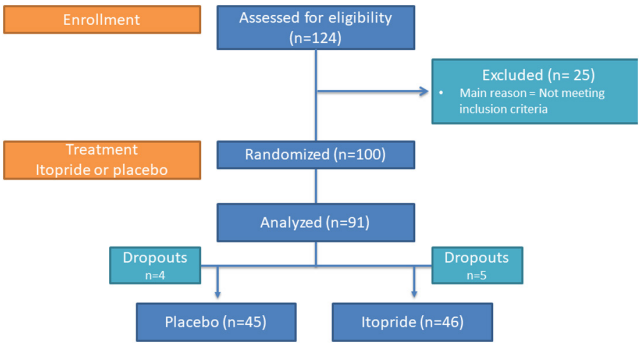

FIGURE 2 Flow diagram

All patients reported postprandial fullness (97%) and/or early satiation (73%) several times per week. Upper abdominal bloating and nausea were reported by 80% and 38% of the patients, respectively. Non-predominant EPS symptoms were allowed during the study. The Rome III criteria classify patients with EPS if symptoms are occurring at least once a week, which was observed in 55% of the study population. Moreover, in this subgroup, 47 patients reported epigastric pain to be mostly meal-related.

When subdividing the FD patients, 45 patients were identified as "pure" PDS (70% females, 41.2 ± 2.6 years old, 22.5 ± 0.5 kg/m^2) and 55 patients were identified with overlapping PDS and EPS symptoms (80% females, 37.3 ± 1.8 years old, 22.3 ± 0.4 kg/m^2). PDS symptoms were the dominant symptoms in both subgroups (Figure 3).

3.2 | Demographics of treatment groups and treatment adherence

At baseline, both treatment arms were similar: placebo: 79% females, BMI 21.8 ± 0.6 kg/m^2 and itopride: 76% females, BMI 22.0 ± 0.6 kg/m^2. However, the patients in the placebo arm were younger than the patients in the itopride arm (35.4 ± 2.1 vs. 42.4 ± 2.1 years old, $p = 0.02$). In keeping with the inclusion criteria, FD subjects ($n = 100$) generally displayed high intensity levels of PDS symptoms (postprandial fullness, early satiation, and upper abdominal bloating) while EPS symptoms of epigastric pain and burning were generally of low intensity (Table 1).

Treatment adherence was assessed by counting the number of tablets at each visit and dividing it by the total number of tablets. For this study, the adherence to the Itopride treatment was 92% and to placebo 88%.

3.3 | Within-group changes evaluated with the LPDS

The change in LPDS score from baseline to week 8 did not show a significant difference between treatment arms (Itopride 0.6 ± 0.2 vs.

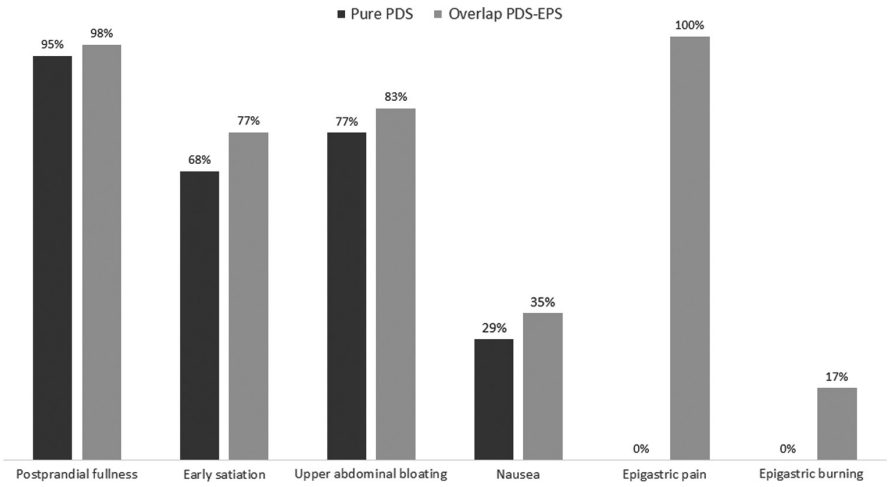

FIGURE 3 Symptom pattern in FD subgroups with pure PDS and overlapping PDS with EPS. Meal-related symptoms of postprandial fullness, early satiation, and upper abdominal bloating are the most common symptoms in both subgroups. Epigastric pain after meals is predominant in the overlap subgroup

TABLE 1 Overview of baseline LPDS score and individual scores in all FD patients

	Placebo ($n = 49$) Mean (SE)	Itopride ($n = 51$) Mean (SE)	p-value
PDS score	5.82 (2.74)	6.53 (2.77)	0.20
EPS score	1.50 (1.52)	2.10 (1.82)	0.10
Postprandial fullness	2.09 (0.92)	2.43 (0.86)	0.06
Early satiation	1.85 (1.17)	2.02 (1.17)	0.48
Bloating	1.89 (0.97)	2.08 (1.10)	0.36
Epigastric pain	1.08 (1.06)	1.42 (1.16)	0.13
Epigastric burning	0.42 (0.70)	0.68 (0.91)	0.12

placebo 0.4 ± 0.1, $p = 0.6$). In the itopride arm, 50% of the patients showed an improvement from baseline equal to or larger than the LPDS MCID (0.5), compared to 40% of the patients in the placebo arm ($p = 0.6$). Taking into account a threshold difference of 0.7 on the LPDS, 37% of the patients improved substantially with itopride compared to 24% with placebo ($p = 0.2$).

Mixed models analysis showed that the overall PDS score and the EPS score was improved after itopride (Table 2). This was not the case for placebo. In terms of individual symptoms assessed by the LPDS diary, the analysis showed a significant improvement for all dyspepsia symptoms ($p < 0.01$) overtime with itopride. Placebo showed only significant improvement for epigastric pain ($p = 0.03$) and belching ($p = 0.006$) (Table 2, Figure 4).

Detailed results of the explorative analysis with OTE, OSS, PAGI-SYM, and SF-NDI questionnaires are available in the Supplementary Materials.

3.4 | Evaluation of treatment in FD subgroups

Subdivision of PDS patients as per Rome III criteria between "pure" PDS ($n = 43$) and overlap PDS/EPS ($n = 48$) showed no significant difference at baseline in LPDS scores.

In the "pure" PDS subgroup, the PDS symptom scores at baseline were comparable between treatments (placebo: 5.8 (2.3) vs. itopride: 6.0 (2.4), $p = 0.9$), but, even though their severity was minimal, the score of accessory EPS symptoms was higher in the itopride group (placebo: 0.5 (0.8) vs. itopride: 1.4 (1.7), $p = 0.03$). In the overlap EPS–PDS subgroup, the treatment arms were similar for the PDS (placebo: 6.7 (2.7) vs. itopride: 7.4 (2.6), $p = 0.3$) and EPS symptom scores (placebo: 2.5 (1.6) vs. itopride: 2.8 (2.0), $p = 0.6$).

Mixed models analysis showed a significant improvement in the LPDS score after 8 weeks of treatment in the overlap PDS/EPS subgroup ($p < 0.001$) and compared to placebo ($p = 0.03$) (Table 3, Figure 5A). This was not observed for the pure PDS subgroup (Table 4, Figure 5B). In the overlap subgroup, itopride led to improvements of early satiation ($p < 0.001$), postprandial fullness ($p < 0.001$), upper abdominal bloating ($p = 0.001$), epigastric pain ($p < 0.001$), heartburn ($p = 0.01$), and borderline epigastric burning ($p = 0.05$).

4 | DISCUSSION

In this manuscript, we report the results of a double-blind placebo-controlled study of itopride in a cohort of 100 FD/PDS patients. This study, with a limited sample size, was primarily set up for the development and validation of a new PRO questionnaire, the LPDS, in line with FDA regulatory guidelines, and this was performed on the first 60 patients without breaking treatment allocation codes.[14] In the present manuscript, however, we focused on the efficacy of itopride (secondary study aim of the original protocol) in the entire 100-patient cohort as a treatment option for PDS, with or without co-existing EPS according to the Rome III criteria.

After 8 weeks, no significant difference was found in the itopride treatment arm compared to placebo. However, mixed models analysis within treatments groups showed that significant improvement in the LPDS score from baseline occurred in the itopride and not in the placebo group. In addition, after 8 weeks of treatment, a beneficial effect of itopride was observed for the change in severity scores of all individual symptoms, whereas placebo only achieved significant

TABLE 2 Change within groups in PDS and EPS scores and individual scores

	Group	Mean change	SE	*p*-value
LPDS score	Placebo	−0.20	0.13	0.10
	Itopride	**−0.51**	**0.16**	**0.001**
	Difference	−0.30	0.20	0.13
EPS score	Placebo	−0.11	0.07	0.11
	Itopride	**−0.37**	**0.12**	**0.002**
	Difference	−0.24	0.14	0.08
Early satiety	Placebo	−0.18	0.14	0.19
	Itopride	**−0.48**	**0.16**	**0.002**
	Difference	−0.30	0.21	0.15
Postprandial fullness	Placebo	−0.24	0.13	0.07
	Itopride	**−0.49**	**0.20**	**0.01**
	Difference	−0.24	0.24	0.31
Upper abdominal bloating	Placebo	−0.20	0.11	0.06
	Itopride	**−0.56**	**0.12**	**<0.001**
	Difference	−0.36	0.21	0.08
Epigastric pain	**Placebo**	**−0.22**	**0.10**	**0.03**
	Itopride	**−0.49**	**0.15**	**0.001**
	Difference	**0.33**	**0.14**	**0.02**
Epigastric burning	Placebo	0.00	0.06	0.9
	Itopride	**−0.24**	**0.10**	**0.01**
	Difference	−0.23	0.14	0.11
Nausea	Placebo	−0.20	0.14	0.16
	Itopride	**−0.38**	**0.16**	**0.02**
	Difference	−0.17	0.21	0.41
Belching	**Placebo**	**−0.28**	**0.10**	**0.006**
	Itopride	**−0.20**	**0.10**	**0.04**
	Difference	0.08	0.14	0.58
Heartburn	Placebo	0.06	0.10	0.57
	Itopride	−0.15	0.13	0.24
	Difference	−0.19	0.16	0.22

Note: Bold values indicates statistically significant.

improvement from baseline for two symptoms (epigastric pain and belching).

Itopride acts as a prokinetic compound by interacting with dopamine D2 receptors in an antagonizing manner and by inhibiting acetylcholine esterase. However, to date, its exact mode of action on gastrointestinal motility is not fully elucidated as studies were not able to confirm a distinctive effect on gastric emptying rate, nutrient volume tolerance,[27] or gastric accommodation.[27,28] Only a low dose of 50-mg Itopride seemed to decrease gastric accommodation,[28] and it has been previously observed that itopride may improve the occurrence of postprandial reflux and alter plasma levels of gastrointestinal key hormones such as so somatostatin, motilin, and CCK.[29,30]

Itopride was previously shown to be well tolerated and more effective than placebo in FD phase II studies.[20] Efficacy was also suggested in a number of open-label or comparator trials.[20,21,31–33] Nevertheless, two large phase III trials involving 1170 FD patients failed to show a significant improvement with itopride compared to placebo for symptoms that were assessed by the Leeds Dyspepsia Questionnaire.[17] It has been argued that the discrepancy between phase II and phase III results is due to patient entry criteria, with co-inclusion of GERD in phase II and a strict exclusion of co-existing heartburn in phase III leading to selection of a high dyspeptic symptom severity at inclusion and a large placebo response.[12,17] On the other hand, at the time, no validated PRO questionnaire to evaluate symptom severity and treatment outcome for this condition existed, and the scale used, the Leeds Dyspepsia Questionnaire, includes several non-dyspeptic symptoms such as retrosternal pain, dysphagia, belching, and regurgitation.[14,17,34]

In the current study, these issues were addressed by including patients with predominant symptoms of FD/PDS as defined by the Rome III criteria, and using the LPDS diary to assess the outcome measures. Patients were screened with the help of a validated

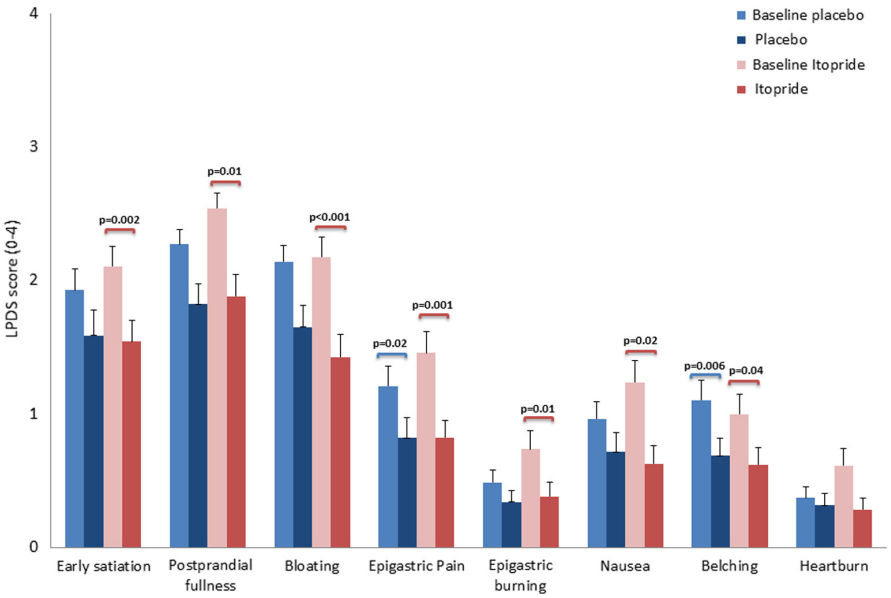

FIGURE 4 Itopride vs placebo. Compared to baseline, mixed models analysis showed that LPDS score was improved after 8 weeks of treatment with itopride ($p = 0.001$) and not with placebo ($p = 0.10$). Also, all symptoms showed clear improvement after treatment with Itopride. Significant improvement for epigastric pain and belching was also shown in the placebo arm. Data are shown as averaged LPDS score with SEM

TABLE 3 Overview effect of itopride compared to placebo in the pure PDS subgroups

Scores	Group	Change	SE	*p*-value
LPDS score	Placebo	−0.23	0.18	0.20
	Itopride	−0.20	0.22	0.37
	Difference	0.04	0.27	0.88
EPS score	Placebo	−0.08	0.05	0.16
	Itopride	−0.24	0.18	0.17
	Difference	−0.14	0.19	0.46
Early satiety	Placebo	−0.18	0.20	0.38
	Itopride	−0.16	0.22	0.47
	Difference	0.02	0.31	0.95
Postprandial fullness	Placebo	−0.24	0.18	0.17
	Itopride	−0.04	0.31	0.90
	Difference	0.21	0.36	0.57
Upper abdominal bloating	Placebo	−0.26	0.19	0.16
	Itopride	−0.35	0.24	0.13
	Difference	−0.09	0.30	0.76
Epigastric pain	Placebo	−0.11	0.10	0.27
	Itopride	−0.32	0.24	0.19
	Difference	−0.19	0.27	0.48
Epigastric burning	Placebo	−0.04	0.02	0.096
	Itopride	−0.14	0.17	0.41
	Difference	−0.08	0.18	0.65
Nausea	Placebo	−0.13	0.16	0.42
	Itopride	−0.34	0.21	0.1
	Difference	−0.21	0.26	0.42
Belching	Placebo	**−0.33**	**0.13**	**0.01**
	Itopride	−0.11	0.12	0.37
	Difference	0.22	0.18	0.24
Heartburn	Placebo	0.12	0.10	0.25
	Itopride	0.16	0.15	0.29
	Difference	0.09	0.20	0.63

Note: Bold values indicates statistically significant.

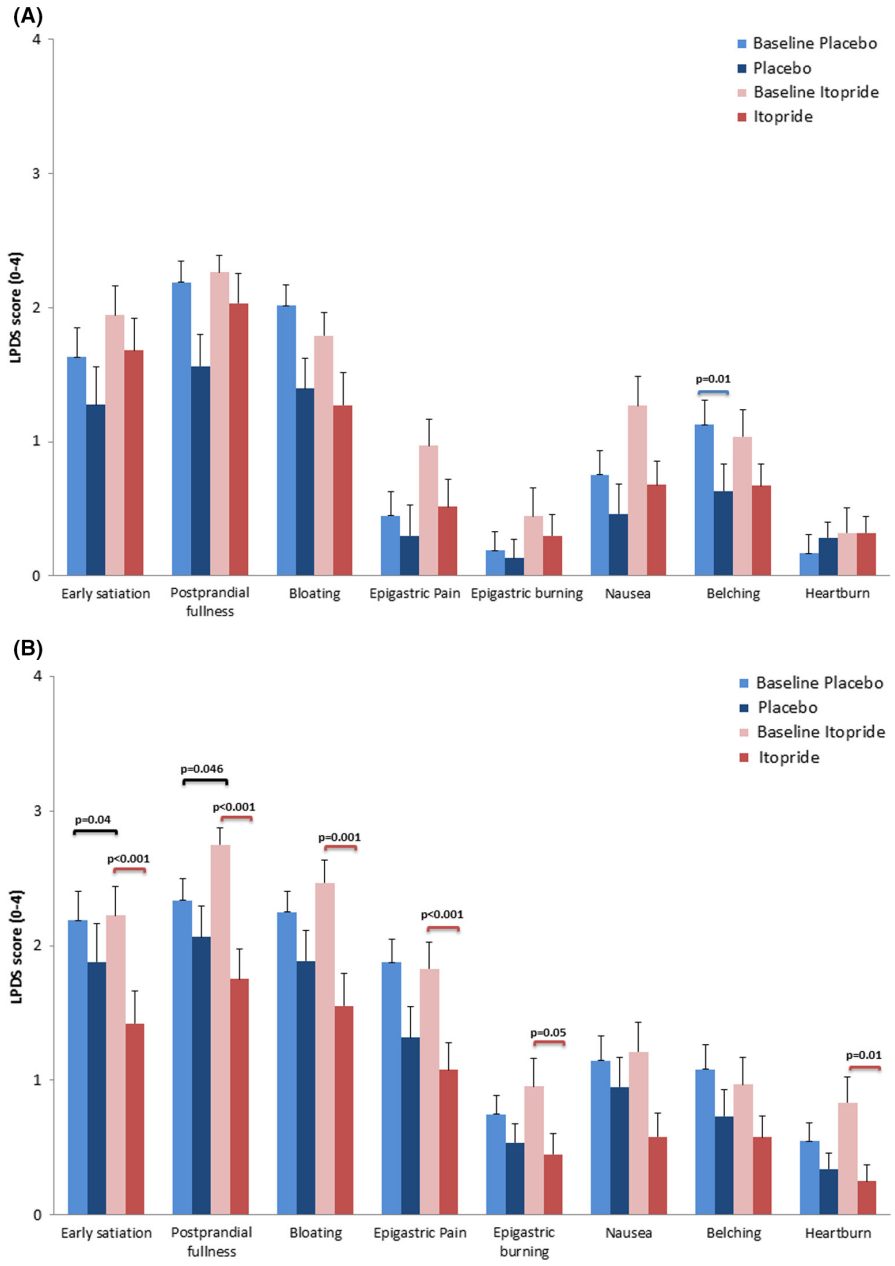

FIGURE 5 (A) Itopride vs. placebo in pure PDS. Exploratory mixed models analysis of subgroups. Only the placebo arm ($n = 22$) showed significant improvement of belching ($p = 0.01$) in the PDS subgroup ($n = 43$). Data are shown as averaged LPDS score with SEM. (B) Itopride vs. placebo in PDS/EPS overlap. Exploratory mixed models analysis of subgroups. In the overlap PDS/EPS group, the itopride arm ($n = 25$) showed significant improvement of the LPDS score after 8 weeks of treatment with itopride ($p < 0.001$) and compared to placebo ($p = 0.03$). Significant improvement was also seen for early satiation (also compared to placebo $p = 0.04$), postprandial fullness (also compared to placebo $p = 0.046$), upper abdominal bloating, epigastric pain, epigastric burning, and heartburn ($p < 0.05$). Nausea and belching showed a tendency ($p = 0.06$) to improvement with itopride. Data are shown as averaged LPDS score with SEM

"waiting room questionnaire'" which uses pictograms.[35] Patients were eligible for participation in the study if they scored at least moderate severity of postprandial fullness and/or early satiation in the LPDS diary at least twice a week during the 2-weeks run-in period.[1-5] Furthermore, treatment outcome was assessed by the LPDS PRO questionnaire, which was specifically developed and validated for the selected FD patient population.[14]

Even though the results of this study did not show a significant difference in symptom severity after 8 weeks of itopride compared to placebo, probably at least in part due to the limited sample size, the LPDS scores in the itopride but not the placebo arm showed significant improvement compared to baseline. This tendency of symptom benefit in favor of itopride should be cautiously considered and requires confirmation in a larger-sized trial. Nevertheless, these findings highlight the applicability of the LPDS score as valid tool to assess treatment outcome in FD/PDS.

The Rome III subdivision of FD patients in EPS and PDS subgroups showed good separation in studies in the general population but was hampered by major overlap in consulting FD patients, rendering application of a strict separation highly problematic in a clinical research setting.[2,36,37] Nowadays, the Rome IV criteria also categorized patients with postprandial occurring epigastric pain and nausea as part of the PDS subgroup, thereby improving the separation between categories.[4,5,37,38] In the present study, 100 PDS FD patients were included, of which 53 showed overlapping non-dominant EPS symptoms (as per Rome III), mainly (>80%) based on meal-related epigastric pain. The exploratory subgroup analysis showed that the Rome III PDS/EPS overlap displayed the most beneficial response to itopride treatment. Using the Rome IV subdivision, these patients would have been classified as PDS patients.[4,5] In summary, the findings in the current study support the validity and reliability of LPDS PRO instrument

TABLE 4 Overview effect of itopride compared to placebo in the overlap subgroup

Scores subgroup	Group	Change	SE	*p*-value
LPDS score	Placebo	−0.18	0.17	0.29
	Itopride	**−0.76**	**0.20**	**<0.001**
	Difference	**−0.58**	**0.26**	**0.03**
EPS score	Placebo	−0.14	0.12	0.25
	Itopride	**−0.49**	**0.15**	**<0.001**
	Difference	−0.35	0.20	0.08
Early satiety	Placebo	−0.17	0.19	0.36
	Itopride	**−0.73**	**0.20**	**<0.001**
	Difference	**−0.55**	**0.27**	**0.04**
Postprandial fullness	Placebo	−0.23	0.19	0.23
	Itopride	**−0.84**	**0.24**	**<0.001**
	Difference	**−0.60**	**0.30**	**0.046**
Upper abdominal bloating	Placebo	−0.14	0.20	0.48
	Itopride	**−0.72**	**0.22**	**0.001**
	Difference	−0.58	0.31	0.06
Epigastric pain	Placebo	−0.32	0.17	0.06
	Itopride	**−0.65**	**0.19**	**<0.001**
	Difference	−0.33	0.24	0.18
Epigastric burning	Placebo	0.03	0.14	0.82
	Itopride	**−0.34**	**0.17**	**0.05**
	Difference	−0.37	0.22	0.1
Nausea	Placebo	−0.27	0.23	0.25
	Itopride	−0.40	0.21	0.06
	Difference	−0.13	0.32	0.69
Belching	Placebo	−0.24	0.16	0.13
	Itopride	−0.27	0.14	0.06
	Difference	−0.03	0.21	0.89
Heartburn	Placebo	−0.01	0.16	0.97
	Itopride	**−0.42**	**0.16**	**0.01**
	Difference	−0.42	0.23	0.07

Note: Bold values indicates statistically significant.

not only in the PDS group as described by the ROME III criteria but also as described in the Rome IV criteria, hence including postprandial epigastric pain. This observation should facilitate the recruitment of FD patients for therapeutic trials aimed at improving PDS patients.

This study is not without limitations. The primary objective of this study was the validation of LPDS as a new tool for treatment outcome of PDS FD and therefore, it was not powered to assess treatment efficacy. Nevertheless, post hoc power analysis showed that the acquired data were suitable to address the current efficacy analysis, and provide a template for a larger-scale itopride study in PDS according to the Rome IV criteria.

In conclusion, at 8-week endpoint of a pilot 8-week controlled trial, FD patients treated with itopride were not significantly better than those treated with placebo. However, compared to baseline, the itopride-treated patients showed a significant improvement in FD symptoms as evaluated by the LPDS questionnaire and this was not the case in the placebo group. Exploratory analysis indicates that the potential beneficial effect of itopride may be most pronounced in the PDS group with overlapping EPS. The study highlights therefore the LPDS instrument as a valid tool for the treatment outcome assessment of PDS symptoms in Rome III FD/PDS patients with overlapping EPS, which correspond to Rome IV PDS. The efficacy of itopride in Rome IV PDS should be confirmed in a large-scale multicentre study using the same selection criteria and endpoint.

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CONFLICT OF INTEREST

Abbott Pharmaceuticals provided itopride for this study.

AUTHOR CONTRIBUTIONS

JT takes responsibility for the integrity of the work as a whole, from inception to published article. Authors involved with the manuscript: JT, LH, MJ, AV, and FC are involved in study concept and design; JT, LH, AV, FC, TV, HP, JA, PC, DS, PV, PM, TDR, FW, VL, VL, and PL are involved in acquisition of data; JT, MJ, and FC are involved in analysis and interpretation of data; MJ and FC are involved in statistical analysis; JT, MJ, and FC are involved in drafting of the manuscript; All authors are involved in the critical revision of the manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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