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ORIGINAL ARTICLE

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Long-term safety and efficacy of acotiamide in functional dyspepsia (postprandial distress syndrome)—results from the European phase 3 open-label safety trial

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Abstract

Backgrounds: Acotiamide is a novel acetylcholinesterase inhibitor for treatment of postprandial distress syndrome (PDS) symptoms of functional dyspepsia (FD).

This European phase 3 open-label safety trial has been conducted to evaluate the long-term safety of acotiamide and explore the efficacy of acotiamide on PDS symptoms using the validated LPDS, quality of life using SF-36 and SF-NDI, and work productivity using WPAI.

Methods: FD-PDS patients (defined by ROME III criteria) aged ≥18 years with active PDS symptoms and without predominant overlapping symptoms of epigastric pain syndrome and related disorders were enrolled to receive 100 mg acotiamide three times daily for 1 year. Patients' safety profile and efficacy of acotiamide were monitored.

Key Results: The majority of patients (81.6%) maintained exposure to acotiamide for >50 weeks, with a mean duration of 320.3 days. No specific clinically significant safety concerns have been shown, with no deaths, treatment-related severe/serious adverse events, or any clinically significant laboratory test results.

Although being an open-label trial, acotiamide showed a change in severity larger than the minimum clinically important difference at weeks 1 and 2 for postprandial fullness and early satiation (meal-related symptoms), and showed improvement of quality of life and work productivity from the first measurement (at week 12) up to 1 year.

Conclusions & Inferences: The long-term safety of acotiamide treatment was confirmed. A clinically important change for PDS symptoms, QoL, and work productivity was suggested; however a controlled trial is required to confirm this hypothetic efficacy of acotiamide. (NCT01973790).

KEYWORDS

acotiamide, functional dyspepsia, motility, phase 3, postprandial distress syndrome

1 | INTRODUCTION

Functional dyspepsia (FD) is defined in the ROME III criteria[1] and the updated ROME IV criteria[2] as the presence of one or more bothersome symptoms (postprandial fullness [PPF], early satiation [ES], epigastric pain, epigastric burning) that are unexplained after a routine clinical evaluation. The global prevalence rate of FD is reported to range between 5% and 11% when using the ROME III criteria.[3] FD encompasses two subgroups in both ROME III and ROME IV criteria, namely the Postprandial distress syndrome (PDS), which is characterized by meal-induced dyspeptic symptoms, and epigastric pain syndrome (EPS), which refers to epigastric pain or epigastric burning that does not occur exclusively postprandially. The overlap of PDS and EPS is also recognized.

The quality of life (QoL) in FD patients is known to be impaired due to symptoms causing emotional distress, problems with food and drink, and impaired vitality.[4]

Furthermore, FD produces a considerable economic impact on both direct and indirect cost. In a retrospective study conducted in USA, the adjusted mean annual cost for employees with FD was more than US$5000 higher than those without FD.[5] More recent studies that directly obtained information from patients showed an estimated US$80 000 per 1000 population in USA,[6] and nearly US$60 000 per 1000 population in urban Malaysia.[7] Using the Work Productivity and Activity Impairment scale, which has also been utilized in this study, an economic loss of 99 600 Japanese Yen per patient per month has been reported in a Japanese ROME III FD patient population.[8]

Acotiamide is a novel compound with fundus-relaxing and gastroprokinetic properties based on antagonism of the inhibitory muscarinic type 1 and type 2 autoreceptors on cholinergic nerve endings and acetylcholinesterase inhibition.[9] Results from clinical trials conducted in Japan have been summarized in previous review articles.[10,11] In the pivotal Japanese phase III trial, acotiamide has shown significant improvement of overall efficacy, meal-related symptoms and QoL, with a good safety profile in patients with FD-PDS.[12] This has led to the marketing approval of acotiamide in Japan, and the inclusion of acotiamide as a treatment option in ROME IV.[13] Notably, the same trend for improvement of meal-related symptoms has been shown from the European phase IIb trial post-hoc analysis.[14] As there has been no trial conducted in the western population that assesses the long-term safety of acotiamide, the primary objective of this trial was set to evaluate the safety of acotiamide for 1 year, and secondary objectives set to explore the effect of 1 year acotiamide treatment on FD symptoms, QoL and work productivity.

Key Points

- Functional dyspepsia is defined as unexplained upper gastrointestinal symptoms. It is highly prevalent worldwide and produces a considerable economic impact, however, no medication on the market has clinical trial evidence, thus comprising an unmet medical need.
- A novel acetylcholinesterase inhibitor, acotiamide, shown long-term safety in Functional dyspepsia patients.
- This result would provide additional input in the clinical data accumulated for acotiamide in Europe, a novel treatment that would meet the unmet clinical need against Functional dyspepsia.

2 | MATERIALS AND METHODS

2.1 | Trial design

This phase III, multicenter, single-arm, open-label clinical trial was conducted at 62 investigative sites in 10 countries (Belgium, Bulgaria, Latvia, Lithuania, Romania, Russia, Slovakia, Sweden, Ukraine, United Kingdom) from March 2014 to August 2016. The trial was designed and conducted in accordance with the ethical principles originating in the Declaration of Helsinki, and are consistent with the International Council for Harmonization Good Clinical Practice guidelines, applicable national/regional laws and regulatory requirements. Patients signed an Ethical Committee approved written informed consent before any trial procedure initiated (ClinicalTrials.gov ID: NCT01973790).

The trial comprised a screening period of up to 3 weeks, a 1 week run-in period, a 52 weeks open-label treatment period, and a 2 weeks adverse event follow-up period (Figure 1).

2.2 | Trial population

Key criteria for being eligible to enter the run-in period were: Adult patients aged 18 years or over; diagnosed as FD (PDS) following the ROME III criteria; most bothersome symptom being postprandial fullness (PPF) or early satiation (ES); having a normal endoscopy result; able to discontinue drugs affecting gut motility, sensitivity and/or acid secretion; without predominant symptoms of irritable bowel syndrome, gastroesophageal reflux disease or chronic idiopathic nausea. Female patients of childbearing potential were required to agree to use acceptable contraceptive methods during the trial.

During the run-in period, patients recorded their symptoms of FD using the electronic version of the Leuven Postprandial Distress Scale (LPDS) on a daily basis. To be eligible for treatment, patients were required to fulfil the following criteria during the run-in period: at least moderate symptoms of PPF or ES for at least 2 days; without any severe/very severe heartburn; mild/moderate heartburn for less than or equal to 1 day; severe/very severe nausea for less than or equal to 2 days; weekly average of less than or equal to mild for epigastric pain and epigastric burning.

2.3 | Outcome measures

2.3.1 | Demographic outcomes

Information on patient demographics, medical/surgical history, prior/concomitant medication, body weight/height, and pregnancy was

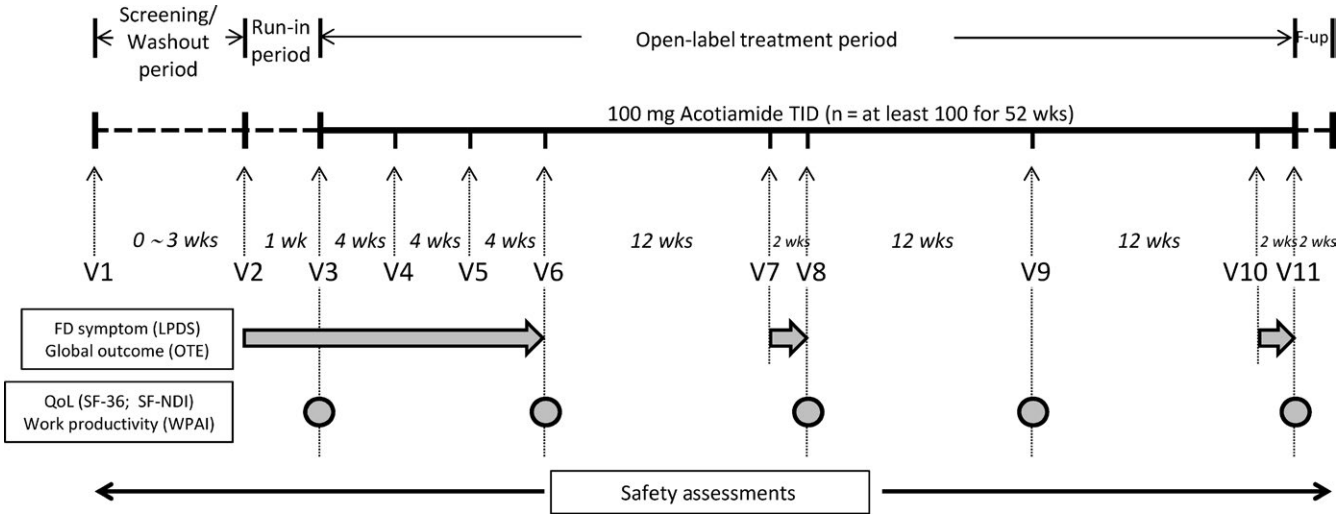

FIGURE 1 Trial scheme. FD, functional dyspepsia; F-up, follow-up; LPDS, Leuven Postprandial Distress Scale; OTE, Overall Treatment Evaluation; QoL, quality of life; SF-36, Short Form-36 survey; SF-NDI, Short Form-Nepean Dyspepsia Index; V, study visit; WPAI, Work Productivity and Activity Impairment

collected. Status of *H. pylori* was determined at baseline. A result of upper gastrointestinal endoscopy was required, and results obtained up to 6 months (for *H.pylori* negative patients) or 3 months (for *H.pylori* positive patients) prior to obtaining informed consent could be used.

2.3.2 | Safety outcomes

The primary objective of this trial was to confirm the long-term safety of 100 mg acotiamide three times daily. By this means, adverse events, ECGs, laboratory variables, vital signs, and physical examination results were recorded throughout the trial.

2.3.3 | Efficacy outcomes

The secondary objective of this trial was to explore the efficacy of acotiamide on FD symptoms, QoL and work productivity, by a range of validated patient reported outcome measures.

The LPDS is a validated 8-item symptom severity scale (early satiation, PPF, upper abdominal bloating, epigastric pain, epigastric burning, nausea, excessive belching, heartburn) that is recorded on a daily basis, with a grading of 0 to 4 on a 5-point Likert scale for each individual symptom, with higher scores indicating greater severity.[15] The weekly score of each symptom was calculated by taking the average of each 7-day period. The weekly change in each individual symptom score was summarized.

A patient's overall assessment of treatment efficacy was evaluated by the Overall Treatment Evaluation scale, a 7-point Likert scale ranging from "1-severely worsened" to "7-strongly improved." Recording was conducted once per week. Improvement was defined as scoring either "6-moderately improved" or "7-strongly improved."

Both generic and disease specific QoL was measured in this trial. Short Form-36 scale is a 36-item instrument widely used to measure generic QoL. Short Form-Nepean Dyspepsia Index is a 10-item instrument that has two questions each in five subscales, with a grading of 0 to 5 on a 6-point Likert scale, with higher scores indicating greater impairment of QoL.[16] Both scales were recorded on baseline, week 12, 26, 38, and 52.

Impact of FD on work and daily activities were assessed by the Work Productivity and Activity Impairment scale, a 6-item questionnaire relating to employment status, absenteeism/presenteeism, work productivity, and activity impairment. Work productivity and activity impairment was assessed by an 11-point Likert scale, with higher scores indicating greater impediment.[17] This scale was recorded on baseline, week 12, 26, 38, and 52.

2.4 | Statistical analyses

The sample size has been set based on the ICH E1 guideline[18] rather than from statistical justifications. The guideline states that 100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety data base.

Two analysis sets were defined in this trial: a safety analysis set and a full analysis set (FAS). The safety analysis set included all enrolled patients who received at least one dose of treatment and the FAS included all patients in the safety analysis set who had at least one post-baseline efficacy assessment.

3 | RESULTS

3.1 | Demographics

Between March 2014 and September 2015, 354 patients were screened, 297 patients proceeded to the run-in period, and 207 patients were enrolled (Figure 2). Among the enrolled population, 185 patients (89.4%) completed 12 weeks, 175 patients (84.5%) completed 28 weeks, and 168 patients (81.2%) completed 52 weeks of

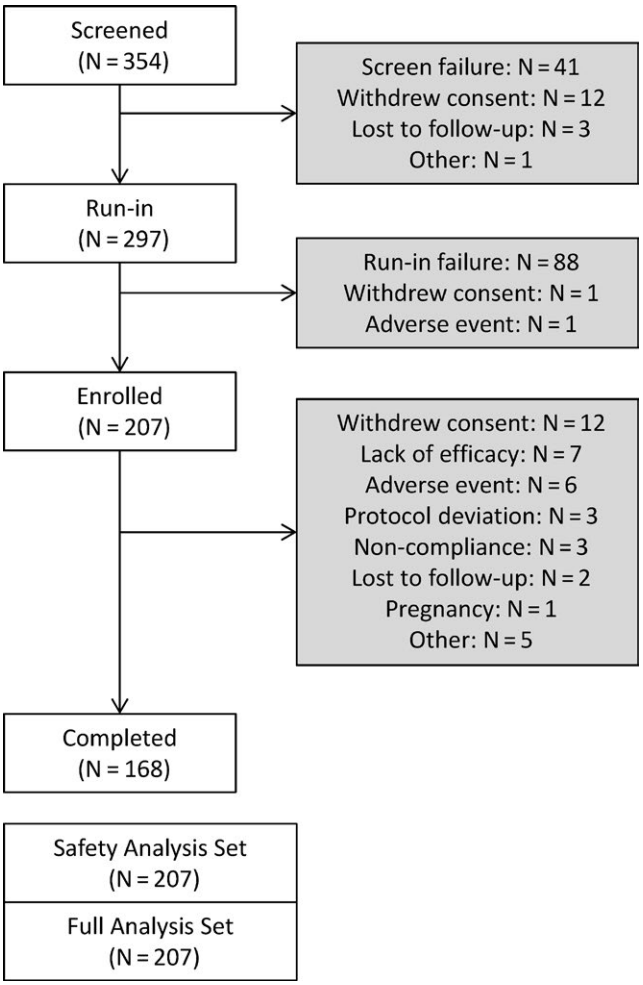

FIGURE 2 Patient disposition

treatment. All enrolled patients were included in both Safety and Full analysis sets.

Patient demographics are shown in Table 1. The majority of the patients were female (69.1%), the mean age of the patients was 42.6 ± 13.02 years and the mean BMI was 24.47 ± 3.490. Most patients were *H.pylori* negative (77.3%).

3.2 | Safety

The majority of patients (81.6%) maintained exposure to acotiamide for >50 weeks with a period of 320.3 ± 111.7 days (mean ± SD). The compliance to acotiamide was very high, with 91.3% of the patients having a compliance of between 80 and 120%.

The incidence of treatment-emergent adverse events (TEAEs) was 44.4%. Severity was classified as mild or moderate in 98.2% of them. TEAEs reported in ≥4% of the total population were influenza (7.2%), headache (6.8%), and nasopharyngitis (5.8%). No chronological trend of AE occurrence was observed.

A total of 18 (8.7%) patients reported at least one treatment-related TEAE, and events that were reported in ≥1% of the total population were nausea (1.4%), abdominal distension (1.0%), and constipation (1.0%).

TABLE 1 Patient demographics and disease characteristics (SAF)

Parameter	100 mg acotiamide (N = 207)
Gender, n (%)	
Male	64 (30.9)
Female	143 (69.1)
Race, n (%)	
White	207 (100.0)
Age, years, mean (SD)	42.6 (13.02)
BMI, kg m^{-2}, mean (SD)	24.5 (3.49)
H.pylori test, n (%)	
Positive	47 (22.7)
Negative	160 (77.3)
Baseline weekly LPDS symptom severity score, mean (SD)	
Early satiation	1.77 (0.919)
Postprandial fullness	2.13 (0.801)
Upper abdominal bloating	1.27 (0.887)
Epigastric pain	0.17 (0.280)
Epigastric burning	0.05 (0.126)
Nausea	0.18 (0.338)
Belching	0.45 (0.657)
Heartburn	0.01 (0.039)

LPDS, Leuven Postprandial Distress Scale.

Four patients experienced severe TEAEs (feces discolored, ileus, lumbar vertebral fracture, ovarian cancer), and six patients experienced serious TEAEs (ileus, lumbar vertebral fracture and rib fracture, ovarian cancer, ligament rupture, uterine hemorrhage, prostate cancer); however, none of these were considered related to the trial drug. There were no deaths during the trial.

Regarding adverse events that led to discontinuation of the study drug, 7 (3.4%) patients experienced a total of 11 TEAEs. This included three cases of nausea, two cases of dyspepsia, and one case each of constipation, eructation, gastrointestinal sounds abnormal, reflux gastritis, decreased appetite, and dysgeusia. One patient discontinued treatment with study drug due to pregnancy.

There has been no country specific difference regarding treatment-related TEAEs, and the total number of serious TEAEs, severe TEAEs or adverse events that led to discontinuation of the study drug was too small to conclude any country specific differences.

No clinically significant laboratory values or notable trends in vital signs and ECG were seen during the trial.

3.3 | Efficacy

3.3.1 | PDS symptom scores

At baseline, the LPDS weekly mean severity scores of PDS symptoms were 1.77 for early satiation, 2.13 for PPF, and 1.27 for upper abdominal bloating. Scores of all other symptoms were less than 0.5.

During the validation of the LPDS, the minimum clinically important difference (MCID) has been determined as −0.5 on the 0-4 range.[11] Clinically important reductions from baseline in mean severity symptom score were observed from week 2 for early satiation, week 1 for PPF, and week 8 for upper abdominal bloating (Figure 3).

Moreover, each symptom showed a continuous decrease in score throughout the 52 weeks treatment period.

3.3.2 | Overall treatment evaluation

The overall improvement rate [95%CI], which is the rate of patients who showed moderate or strong improvement, increased from 13.1% [8.6%, 18.9%] at Week 1 to 41.5% [30.7%, 52.9%] at Week 12, then increased further to 70.2% [62.2%, 77.4%] at Week 52 (Figure 4).

3.3.3 | Quality of life

The mean T-score and the mean change from baseline for the component summaries and each domain of SF-36 are listed in Table 2. All domains except "Bodily pain" and "Role limitations due to emotional problems" showed an increase (improvement) over the minimally important difference[19] at Week 12 and onwards. "Bodily pain" and "Role limitations due to emotional problems" showed an increase (improvement) over the minimally important difference at Week 26 and onwards.

For the FD-specific QoL scale SF-NDI, though no statistical comparison between baseline and each timepoint has been conducted, the mean value of each domain have decreased (improvement) for all five subscale scores, with a mean change ranging between −0.8 and −1.2 at Week 12 to −0.9 and −1.5 at Week 52. The eating/drinking domain showed the largest decrease in score among the five domains (Figure 5).

3.3.4 | Work productivity

The percentage of patients employed remained stable during the trial, within the range from 72.9% to 76.6%. Although absenteeism (work time missed) remained stable during the 52 week treatment period, presenteeism (impairment at work), work productivity and activity impairment have all shown decrease (improvement) at week 12 and onwards (Figure 6).

4 | DISCUSSION

Following the market withdrawal of cisapride and the restriction against domperidone and metoclopramide, there is no evidence-based medication in Europe for a safe long-term usage against meal-related symptoms of FD. Multiple treatments[2,20] and management strategy schemes[21] have been suggested, however, it is of note that treatments such as empirical use of proton-pump inhibitors are given to a large

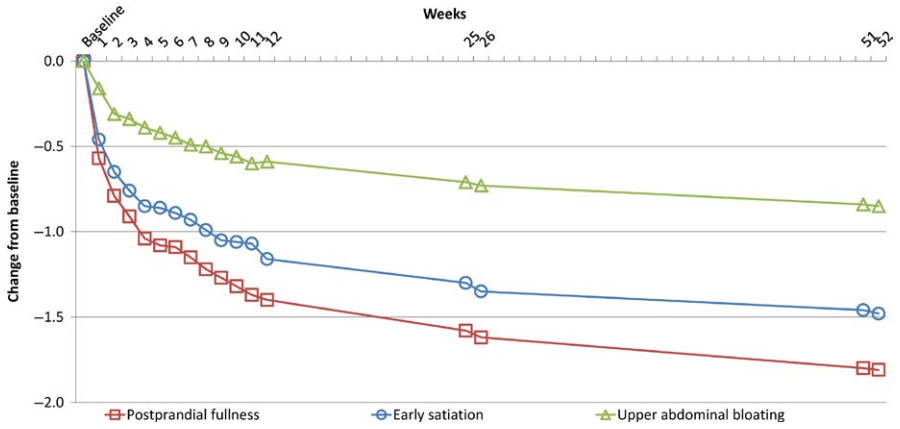

FIGURE 3 Postprandial distress syndrome (PDS) symptom score change from baseline (Full analysis set)

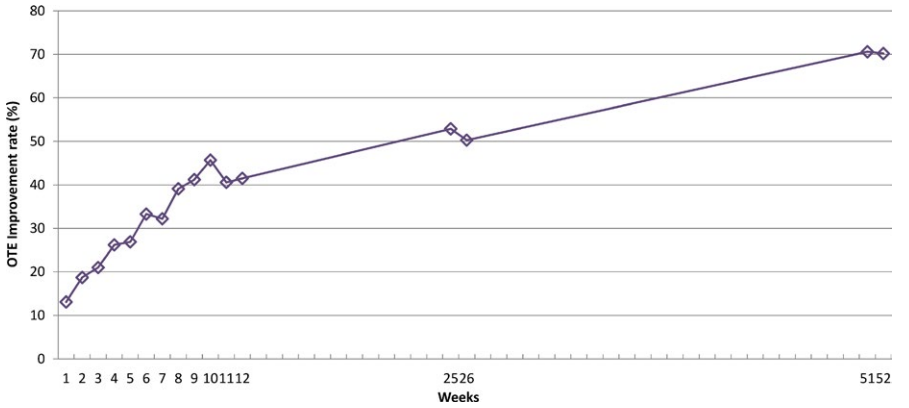

FIGURE 4 OTE improvement rate (Full analysis set)

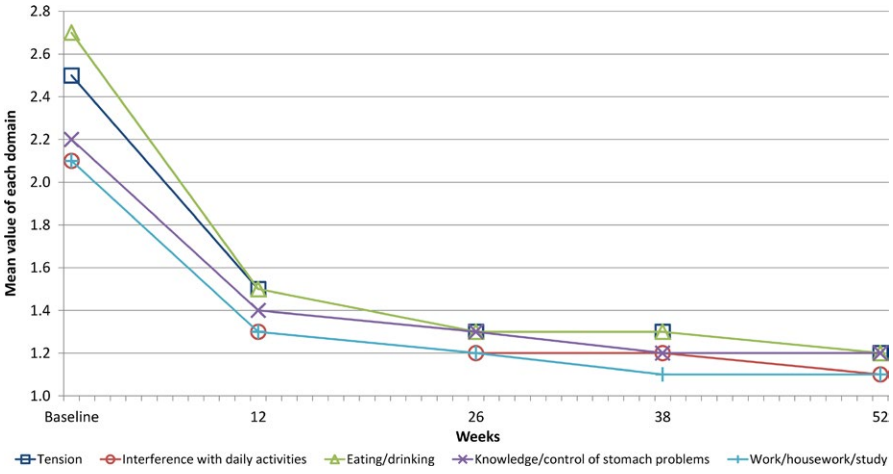

FIGURE 5 SF-NDI mean domain score

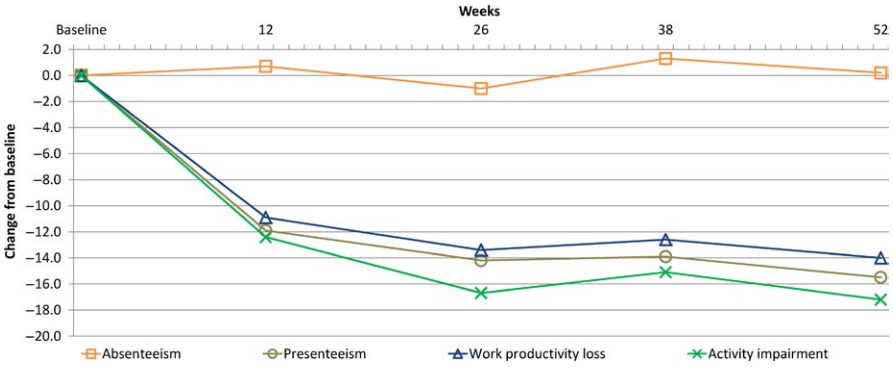

FIGURE 6 WPAI score change from baseline (Full analysis set)

TABLE 2 SF-36 mean T-score and mean change from baseline (FAS)

		Mean T-score (mean change from baseline)				
		Baseline	Week 12	Week 26	Week 38	Week 52
Variables	MID	N = 207	N = 185	N = 175	N = 170	N = 168
Physical component	2	50.1	53.7 (3.4)	55.0 (4.5)	55.0 (4.4)	55.6 (5.2)
Mental component	3	44.4	48.8 (4.2)	50.8 (6.5)	50.7 (6.1)	52.0 (7.6)
Physical functioning	3	50.7	54.1 (3.3)	54.9 (3.9)	55.3 (4.3)	55.8 (4.9)
Role limitations due to physical health problems	3	47.1	51.1 (3.8)	53.2 (6.0)	52.5 (5.1)	53.9 (6.9)
Bodily pain	3	52.7	55.8 (2.7)	57.4 (4.0)	56.8 (3.3)	57.9 (4.6)
General health	2	41.5	47.2 (5.3)	48.9 (7.1)	49.4 (7.6)	49.7 (7.9)
Vitality	2	50.1	54.5 (4.1)	56.2 (5.7)	56.7 (6.0)	57.7 (7.1)
Social functioning	3	45.7	50.6 (4.7)	52.6 (6.9)	52.1 (6.2)	52.9 (7.1)
Role limitations due to emotional problems	4	44.9	48.6 (3.3)	51.8 (6.7)	50.9 (5.5)	52.1 (7.1)
General mental health	3	45.2	49.7 (4.3)	50.3 (5.2)	50.6 (5.4)	52.1 (7.2)

The mean change has been calculated for patients with data for both baseline and each timepoint.
MID, Minimally important difference.

number of patients and there is an unmet need for evidence-based treatment to be given. There have been multiple attempts of establishing an effective treatment for meal-related symptoms, however, many have resulted in disappointment, including the antidepressants amitriptyline and escitalopram,[22] tegaserod,[23] itopride,[24] and mosapride.[25] Moreover, when sub-grouped by FD subtypes, there were no differences in the effect of proton-pump inhibitors versus placebo, H2 receptor antagonists or prokinetics for meal-related symptoms.[26]

In this article, we report the result of the first clinical trial of acotiamide that has shown the safety of acotiamide when continuously

administered for a long-term. Such findings align with the result of past clinical trials for acotiamide.[10-12,14,27,28] There has been a long-term safety trial conducted in Japan,[28] but due to the criteria for treatment cessation, only around 25% of the patients which participated in that trial had uninterrupted treatment. The current trial adds information regarding the safety of continuous acotiamide administration.

The incidence rate of overall, treatment-related, serious, or severe TEAEs were all at a low level, comparable to that of the long-term safety trial conducted in Japan.[28] One reason for this highly safe profile would be the specificity of acotiamide to the muscarinic type 1 and type 2 autoreceptors and acetylcholinesterase. Acotiamide shows no affinity on dopamine D_2 or serotonin 5-HT_4 receptors,[29] which distinguishes this drug from other gastroprokinetics that have cardiovascular side effects. The effect of acotiamide on cardiac repolarization in healthy volunteers has also been evaluated, showing favorable pharmacodynamic results (ClinicalTrials.gov ID number: NCT00850746). As far as we are aware, there is no knowledge of ethnical or regional differences related for receptors and enzymes related to the mode of action of acotiamide, which may be the reason why no country specific differences in safety have been observed.

It must be noted that when discussing the efficacy of acotiamide, the major limitation of this trial is the open-label design, as a high placebo effect is commonly observed in clinical trials for Functional gastrointestinal disorders. For example, a meta-analysis of clinical trials in Irritable bowel syndrome (IBS) shows a pooled placebo response rate of 37.5%.[30] Therefore, to confirm the efficacy of acotiamide a double-blind controlled trial would be needed in a similar study population. However, taking this limitation in account, it is notable that the mean value for the change in the two cardinal meal-related symptoms (PPF and early satiation) both met the MCID at 1-2 weeks of treatment, which may be similar to the result of the Japanese phase III study where significant improvement of acotiamide over placebo has been shown in 2 weeks.[12] In addition, the level of the mean symptom severity change from baseline was sustained over the 1 year treatment period. General QoL, disease specific QoL and work productivity have all shown a decrease (improvement) at the first observation on week 12. Another limitation to this trial is that the target population is limited to FD patients with active meal-related symptoms and without major overlapping symptoms or diseases such as epigastric pain symptoms, IBS, Gastrooesophageal reflux disease (GERD) and Chronic idiopathic nausea (CIN), which are commonly found in the real-world setting.[31-34] Therefore, further information will be required to assess the efficacy and safety of acotiamide on such overlap population and the usage in real-world settings.

To summarize, this long-term safety trial is the first to demonstrate that acotiamide can safely be administered continuously for 1 year. Rapid changes from baseline have been shown for the meal-related symptom severity, overall treatment evaluation, QoL and work productivity, however to conclude about this hypothetical efficacy of acotiamide, a double-blind controlled clinical trial will be required. As being a European trial, this result would provide additional input in the clinical data accumulated for acotiamide in Europe and could lead to conducting further clinical trials to obtain marketing authorization of a novel treatment that would meet the unmet clinical need against meal-related symptoms of FD.

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DISCLOSURE

Jan Tack has given Scientific advice to Abide Therapeutics, AlfaWassermann, Allergan, Christian Hansen, Danone, Genfit, Ironwood, Janssen, Kiowa Kirin, Menarini, Mylan, Novartis, Nutricia, Ono Pharma, Rhythm, Shionogi, Shire, SK Life Sciences, Takeda, Theravance, Tsumura, Yuhan, Zealand and Zeria pharmaceutical, has received Research grant or support from Abide Therapeutics, Shire, Tsumura, Zeria and has served on the Speaker bureau for Abbott, Allergan, AstraZeneca, Janssen, Kiowa Kirin, Menarini, Mylan, Novartis, Shire, Takeda and Zeria. Gediminas Urbonas served as a speaker for Amgen, Bayer, MSD, Servier, Sanofi, AstraZeneca, a consultant and an advisory board member for Sanofi. Hans Törnblom served as a speaker, a consultant and an advisory board member for Almirall, Allergan, Shire and Tillotts. Masaru Tsuchikawa and Tomoharu Miyagawa is an employee of Zeria Pharmaceutical. Juris Pokrotnieks, Christian Banciu, Vladimir Yakusevich, Ivan Bunganic, Yaroslav Kleban, and Patrick Eavis declare no competing interests.

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