

Randomised clinical trial: the 5-HT₄ agonist revexepride in patients with gastro-oesophageal reflux disease who have persistent symptoms despite PPI therapy

N. J. Shaheen*, J. Adler[†], S. Dedrie[‡], D. Johnson[§], P. Malfertheiner[¶], P. Miner^{**}, A. Meulemans[‡], L. Poole^{††}, J. Tack^{‡‡}, L. Thielemans[‡], S. Troy^{§§}, N. Vakil^{¶¶}, F. Zerbib^{***} & M. Ruth[‡]

*Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, Chapel Hill, NC, USA.

[†]Hahn & Adler Gastroenterology & Internal Medicine, LLC, Plantation, FL, USA.

[‡]Shire-Movetis NV, Turnhout, Belgium.

[§]Division of Gastroenterology, Eastern Virginia Medical School, Norfolk, VA, USA.

[¶]Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University, Magdeburg, Germany.

^{**}Department of Digestive Diseases, Oklahoma Foundation for Digestive Research, Oklahoma City, OK, USA.

^{††}Shire, Basingstoke, UK.

^{‡‡}UZ Leuven, Leuven, Belgium.

^{§§}Global Clinical Pharmacology and Pharmacokinetics, Shire, Wayne, PA, USA.

^{¶¶}School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA.

^{***}CHU de Bordeaux, Hôpital Saint André, Bordeaux, France.

Correspondence to:

Dr N. J. Shaheen, Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, Chapel Hill, NC 27599-7080, USA.
E-mail: nicholas_shaheen@med.unc.edu

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SUMMARY

Background

A substantial proportion of patients with gastro-oesophageal reflux disease (GERD) have only a partial response to proton pump inhibitor (PPI) therapy. Prokinetic drugs may improve reflux symptoms by enhancing oesophageal motility and gastric emptying.

Aim

To evaluate the effect of revexepride, a novel prokinetic 5-hydroxytryptamine type 4 (5-HT₄) receptor agonist, compared with placebo, in patients with GERD who have a partial response to PPIs.

Methods

A phase 2b, double-blind, parallel-group study was conducted, in which patients were randomised to one of three revexepride treatment groups (0.1, 0.5 and 2.0 mg three times daily) or placebo (1:1:1:1 ratio). Daily e-diary data captured patients' symptoms over an 8-week treatment period. The primary efficacy outcome was the weekly percentage of regurgitation-free days in the second half of the study (weeks 5–8).

Results

In total, 480 patients were randomised and 477 received treatment (mean age 47.9 years; 61% women). The mean percentage of regurgitation-free days increased from baseline (range, 15.0–18.8%) to week 8 (62.3–70.5%) in all four study arms; however, there were no statistically significant differences in this change between placebo and the three treatment arms. No dose-dependent relationship in treatment effect was observed for any of the study endpoints. The incidence of treatment-emergent adverse events (TEAEs) was revexepride dose-dependent. Only one serious TEAE occurred and none resulted in death.

Conclusions

Revexepride was no more effective than placebo in controlling regurgitation in patients with GERD symptoms partially responsive to PPIs. Revexepride was well tolerated. ClinicalTrials.gov Identifier: NCT01472939.

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INTRODUCTION

Gastro-oesophageal reflux disease (GERD) is a chronic and recurrent condition. It is a highly prevalent disorder, particularly in Western countries (10–20%),¹ and impacts significantly on the health-related quality of life (HRQoL) of affected patients.² GERD is characterised by reflux of gastric contents into the oesophagus, resulting in tissue damage or troublesome symptoms.³ The most commonly detected endoscopic manifestation of oesophageal injury is reflux oesophagitis (which occurs in approximately one in three patients with GERD).⁴ There is also a broad spectrum of associated extra-oesophageal manifestations, such as chronic cough, asthma, laryngeal disorders and chest pain.⁵ The presence and severity of reflux symptoms are best assessed using patient-reported outcome (PRO) instruments.⁶

Proton pump inhibitors (PPIs) are widely considered the most effective treatment for reflux symptoms;^{7,8} however, approximately 20–40% of patients with GERD experience persistent, troublesome heartburn or regurgitation despite PPI therapy.⁹ Heartburn appears to be more responsive to PPI therapy than is regurgitation, which persists more frequently.¹⁰ Treating patients with partial response to PPI therapy remains one of the most challenging problems in the management of GERD. Acid exposure is controlled in most of these patients, suggesting that their persistent symptoms may be caused by a different mechanism.^{11, 12} Therefore, the development of novel therapeutic agents has targeted the underlying mechanisms of GERD such as transient lower oesophageal sphincter relaxations, dysmotility, lack of mucosal integrity and oesophageal hypersensitivity.

Impaired oesophagogastric motility may be improved by prokinetic drugs.¹³ These agents may improve reflux symptoms by enhancing oesophageal motility and gastric emptying. However, previous studies have found disappointing results with respect to upper gastrointestinal symptoms with motility agents such as cisapride.^{14, 15} Revexepride is a member of a new class of highly specific prokinetic 5-hydroxytryptamine type 4 (5-HT₄) receptor agonists and has been shown to accelerate gastric emptying in healthy humans and animal models (Shire, unpublished data). It enhances the physiological release of acetylcholine, the main stimulator of gastrointestinal motility, at the myenteric plexus, and therefore may be suitable for the targeted treatment of conditions with a disordered motility in the upper gastrointestinal tract. Revexepride has been developed as an add-on therapy to PPI to treat symptoms associated with GERD, specifically

for those patients who have persistent symptoms of regurgitation, with or without heartburn, while on PPI therapy.

The aim of this study was to evaluate the effect of revexepride compared with placebo on regurgitation in patients with GERD who have persistent symptoms while on PPI treatment. The study concentrated on patients who had regurgitation rather than heartburn as their primary symptom as this may be due to oesophageal dysmotility, which could be targeted by a prokinetic agent. This study also investigated the effects on heartburn and evaluated the pharmacokinetics, safety and tolerability of revexepride in the target population.

MATERIALS AND METHODS

Patients

Enrolled patients were men or nonpregnant women aged 18–70 years who had a body mass index (BMI) of 18.5–37.0 kg/m² and at least a 6-month history of reflux symptoms (i.e. heartburn or regurgitation). Patients had to have been on optimised PPI therapy, defined as the once-daily dosing regimen (the approved dose for GERD-related conditions) achieving the best symptom control, for at least 8 weeks (twice-daily dosing not permitted in the previous 4 weeks). Participants were also required to have had persistent symptoms of regurgitation for 2 or more days in the 7 days before the screening visit, with or without heartburn, reported using the Gastroesophageal Reflux Disease Questionnaire (GerdQ).¹⁶ If patients had a previous diagnosis of reflux oesophagitis [Los Angeles (LA) grade A, B, C or D],¹⁷ they were required to have been treated with a healing dose of PPI (i.e. a PPI dose indicated for the treatment of reflux oesophagitis according to the country label) for at least 8 weeks before screening.

Individuals who had no upper endoscopy results available for the 2 years before the screening visit, who had an endoscopy in this period but who experienced new or worsening symptoms in the time between that endoscopy and the screening visit, or who had evidence of reflux oesophagitis at that endoscopy, underwent endoscopy at screening. If the screening endoscopy showed evidence of LA grade B, C or D oesophagitis, the patient was excluded from the study. Patients were also excluded if they had no symptom response to PPI therapy, or if they had symptoms of dyspepsia (epigastric pain or nausea as determined by the GerdQ) that were more frequent than their heartburn and/or regurgitation during the 7 days before the screening visit.

Other exclusion criteria were: a documented history of eosinophilic oesophagitis, active gastric or duodenal ulcer, oesophageal dysplasia or large (>5 cm) hiatus hernia; a diagnosis of oesophageal, gastric, endocrine, neurological or rheumatological disorders that may affect motility (e.g. scleroderma, achalasia, nutcracker oesophagus or gastroparesis); having undergone an endoscopic anti-reflux procedure or major gastrointestinal surgery (with the exception of appendectomy or laparoscopic cholecystectomy); and a history of cardiovascular disease. Patients could not use cytochrome P450 3A4 inhibitors, drugs known to prolong the QT interval, drugs that delay gastrointestinal motility, prokinetic drugs, histamine-2 receptor antagonists, oral bisphosphonates or anti-neoplastic drugs in the 7 days before the run-in period.

All participants provided written consent before the initiation of study-related activities, and the study was carried out in accordance with local ethical and legal requirements, and the Declaration of Helsinki.

Trial design

This was a phase 2b, 17-week, placebo-controlled, double-blind, parallel-group study (ClinicalTrials.gov Identifier: NCT01472939), in which patients were randomised to one of four treatment groups (1:1:1:1). Randomisation was stratified by country and PPI dose. The study design is presented in Figure 1. The study was conducted at 76 sites across eight countries (Czech Republic, France, Germany, Hungary, Latvia, Poland, Romania and the USA) from 27 February 2012 to 14 May 2013. Patients who were eligible following a screening period (of 1–21 days; to allow for potential endoscopy and washout period) were enrolled in a 4-week run-in period to establish symptom frequency and to document adherence to PPI therapy. Patients were issued electronic diaries (e-diaries) to enable them to score GERD-related

symptoms daily during this period, as well as PPI and rescue medication usage. Individuals were instructed to record their symptoms each evening using a newly developed questionnaire [Persistent Reflux Integrated Symptom Measurement (PRISM) v5.5]. The outcome of symptom scoring during the last 2 weeks of the run-in period was used as the basis for randomisation into the treatment groups.

PRISM is a validated 20-item PRO instrument¹⁸ used to measure the frequency and severity of regurgitation, heartburn, nausea, vomiting and burping, and the presence of nocturnal reflux. The items cluster into four domains: liquid and food symptoms, burning sensations, nausea and vomiting, and upper abdominal gas-related symptoms. Patients completed the PRISM questionnaire during the run-in and treatment periods. After 58 patients had completed 4 weeks of treatment, initial assessment of the PRO instrument (PRISM v5.5 A) was performed. This resulted in some minor modifications that resulted in the final revised PRO instrument (PRISM v5.5 B). The results (pooled PRISM A and B data) for the PRISM domains presented in this study are based on the scoring algorithm defined during the validation of PRISM.

To be eligible for randomisation into the study, patients had to have experienced regurgitation on average at least 3 days per week during the final 2 weeks of the run-in period. In addition, the number of days on which patients had heartburn without regurgitation had to be less frequent than the number of days with regurgitation and could not exceed an average of 3 days per week. Patients were also required to have an average of no more than 2 days of vomiting per week during the last 14 days of the run-in period. These parameters were assessed from individual PRISM questions. Patients who met these criteria at the end of the run-in period were randomised to receive an oral administration of revexe-

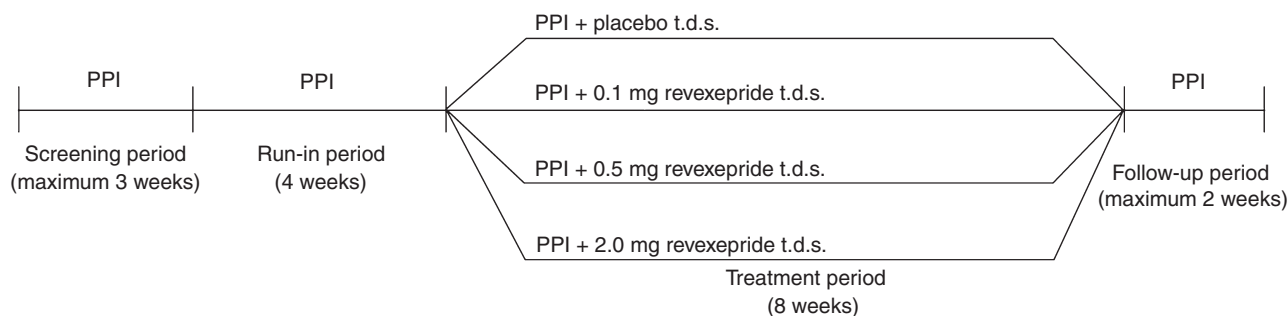


Figure 1 | Study design. PPI, proton pump inhibitor.

pride 0.1, 0.5 or 2.0 mg, or a matching placebo, three times a day (30 min before breakfast, lunch and dinner), in addition to their PPI treatment.

The treatment period was 8 weeks (with visits at week 2, week 4, week 6 and week 8), followed by a 2-week follow-up period for safety evaluation. While the duration of treatment necessary to ascertain efficacy of an add-on treatment for GERD in patients with a partial response to PPIs is not clear, the 8-week treatment period was based on the treatment paradigm of PPIs, specifically for symptomatic GERD, in which patients are given 4 weeks of initial therapy and an additional 4 weeks if symptoms continue. The 8-week period was therefore chosen to give sufficient time to determine treatment response. Additionally, in a subset of patients, the pharmacokinetics of revexepride were investigated after multiple dosing of investigational product, at the week 2 visit.

Study endpoints

The primary efficacy endpoint was the change from baseline in the weekly percentage of regurgitation-free days reported through PRISM during the second 4 weeks of the treatment period (weeks 5–8). Secondary efficacy endpoints included: PRISM liquid and food domain scores; other PRISM domain scores (burning sensations, nausea and vomiting, and upper abdominal gas-related symptoms); percentage of regurgitation-free days per week; percentage of heartburn-free days per week; percentage of both regurgitation and heartburn-free days per week (i.e. complete relief of classical reflux symptoms); proportion of patients with a reduction of 3 or more days with regurgitation compared with the run-in period; proportion of participants with a reduction of 3 or more days with heartburn compared with the run-in period; proportion of participants with a reduction of 3 or more days with heartburn and regurgitation compared with the run-in period; and percentage of days per week on which antacid rescue medications were used. All efficacy endpoints were evaluated for the overall treatment period (weeks 1–8), and separately for weeks 1–4 and weeks 5–8.

Efficacy assessments

The efficacy endpoints for this study were assessed using the responses to the PRISM questionnaire, which patients completed every evening in the e-diary. The primary efficacy endpoint was assessed using the following PRISM question: 'In the past 24 h, how often did liquid or food come back into your oesophagus or throat but without vomiting?'. At baseline and at the end of each

week, additional anchor questions assessed overall reflux symptoms experienced over the previous 7 days. These included questions on both severity and relief of overall GERD (reflux) symptoms and, more specifically, liquid and food symptoms (sour or acid taste in the mouth or food coming back up). The anchor questions were used in the validation of PRISM and for the calculation of minimally clinically important difference. The minimal clinically important criterion was defined as a 10-point difference in PRISM domain scores between revexepride and placebo. Patients were also required to record their daily use of investigational product, PPIs and antacid rescue medications in the e-diary. For all PRISM questions, baseline was calculated using the 14 days before the first intake of investigational product. If a participant had fewer than 4 days of data in a week, the weekly percentage was considered to be missing.

Pharmacokinetics

Blood samples for the determination of steady-state nominal peak and trough concentrations of revexepride were taken from all patients at the week 2 visit. Full pharmacokinetic profiles were obtained for a subset of patients (full pharmacokinetic subset) at the week 2 visit or later. Pharmacokinetic parameters were determined from the plasma concentration–time data for revexepride by noncompartmental analysis. The pharmacokinetic parameters recorded included: maximum plasma concentration at steady state (C_{ssmax}); minimum plasma concentration at steady state (C_{ssmin}); time to reach maximum observed concentration sampled during a dosing interval (t_{max}); area under the curve from 0 to 8 h at steady state (AUC_{0-8}); area under the curve within a dosage interval at steady state (AUC_{ss}), where $AUC_{ss} = AUC_{0-8}/2$; and degree of fluctuation [defined as $(C_{ssmax} - C_{ssmin})/C_{average}$, where $C_{average} = AUC_{ss}/4$]. In all patients, steady-state nominal peak and trough concentrations were determined, as represented by plasma concentrations at 1 h after dosing and immediately pre-dosing, respectively, at an appropriate visit (week 2 visit or later) during the 8-week treatment period.

HRQoL and symptom assessments

Patients' HRQoL was assessed using three different previously validated questionnaires. GERD-specific HRQoL was assessed using the Quality of Life in Reflux And Dyspepsia (QOLRAD)¹⁹ questionnaire, which is based on a 1-week recall period. The Reflux Disease Questionnaire (RDQ),²⁰ a validated self-assessment scale, was employed to document the course of symptoms in

patients with GERD. It uses a 1-week recall period to assess the severity and frequency of six items covering heartburn and regurgitation. Finally, overall HRQoL was assessed using the 12-item Short-Form Health Survey (SF-12),²¹ which is also based on a 1-week recall period. The scores from these three questionnaires at baseline, week 4 and week 8 were analysed.

Safety measurements

The occurrence of adverse events (AEs) was assessed throughout the study. Vital signs (systolic and diastolic blood pressure and pulse rate), and biochemistry and haematology assessments were recorded at each study visit. Urinalysis was conducted at baseline, week 4 and week 8. A 12-lead electrocardiogram (ECG) was recorded at all study visits.

Statistical methods

With a sample size of 109 patients per treatment group, a difference as small as 10% in the primary outcome between placebo and a (minimal) active dose could be detected at a significance level of 1.67% (Bonferroni correction for three comparisons) with 80% power [assumed standard deviation (SD) of 22%]. Assuming that 5% of patients had insufficient e-diary data for a proper evaluation, 115 patients were required per treatment group (i.e. 460 randomised patients in total). The following analysis sets were defined.

(i) Safety analysis set: all patients who took at least one dose of investigational product.

(ii) Full analysis set: all patients in the safety analysis set who had at least one post-baseline value for the primary efficacy assessment (i.e. e-diary data).

(iii) Per-protocol set: all patients in the full analysis set who had at least 14 days with e-diary information on symptoms in the second 4 weeks of the treatment period (weeks 5–8) and who did not have any major protocol deviations.

(iv) Pharmacokinetic set: all patients in the safety analysis set for whom the primary pharmacokinetic data were considered sufficient and interpretable (based on a limited pharmacokinetic assessment of pre-dose and post-dose blood samples).

The primary efficacy endpoint was analysed using a mixed-effects model for repeated measures (MMRM), with treatment arm, country, PPI use, visit and the interaction between treatment arm and visit as fixed factors, baseline as a covariate, and further adjusted for the interaction between baseline and visit. The primary comparison

between each treatment group and placebo was performed over weeks 5–8. Sensitivity analyses were performed using two methods: placebo-multiple-imputation and pattern-mixture model. In the placebo-multiple-imputation, missing values after dropout (not intermittent missing values) were imputed under the assumption that patients in the placebo arm stay on placebo after dropout, while participants in the active arm take placebo after dropout. In the pattern-mixture model, pattern was imputed as an extra parameter and a pattern-averaged (overall) treatment effect was calculated.

The comparisons for each secondary endpoint between each treatment group and placebo were also performed across weeks 5–8. Continuous data were analysed statistically using MMRM. A five-point or higher scale qualified as a continuous variable. Binary data were analysed using a generalised linear mixed model for repeated measures, including the terms treatment arm, country, PPI use at baseline, visit and the interaction between treatment arm and visit as fixed factors. Statistical analyses were performed using Version 9.1 or higher of SAS (SAS Institute, Cary, NC, USA).

RESULTS

Patient population

Of 1283 patients screened, 480 were randomised to receive one of the four investigational doses, of whom 477 received investigational product and were therefore included in the safety analysis set: revexepride 0.1 mg, $n = 119$; revexepride 0.5 mg, $n = 118$; revexepride 2.0 mg, $n = 118$ and placebo, $n = 122$. The majority of patients failed screening because they did not have predominant regurgitation at baseline. The analysis population is presented in Figure 2. Most patients (415; 86.5%) completed the study; a total of 65 (13.5%) patients discontinued, of whom 31 (6.5%) discontinued owing to AEs.

Patient demographics and other baseline characteristics were similar across the treatment groups (Table 1). The mean age of participants was 47.9 years and just over 60% were women. At baseline, patients had a mean frequency of regurgitation of 5.8 days/week, of heartburn alone of 0.6 days/week and of vomiting of 0.2 days/week. Approximately 30% of participants were receiving a healing PPI dose (i.e. a PPI dose indicated for the treatment of reflux oesophagitis according to the country label) at baseline (depending on the type of PPI, total daily dose ranged from >20 to ≥ 60 mg); the remaining individuals were receiving a symptomatic dose (i.e. a PPI

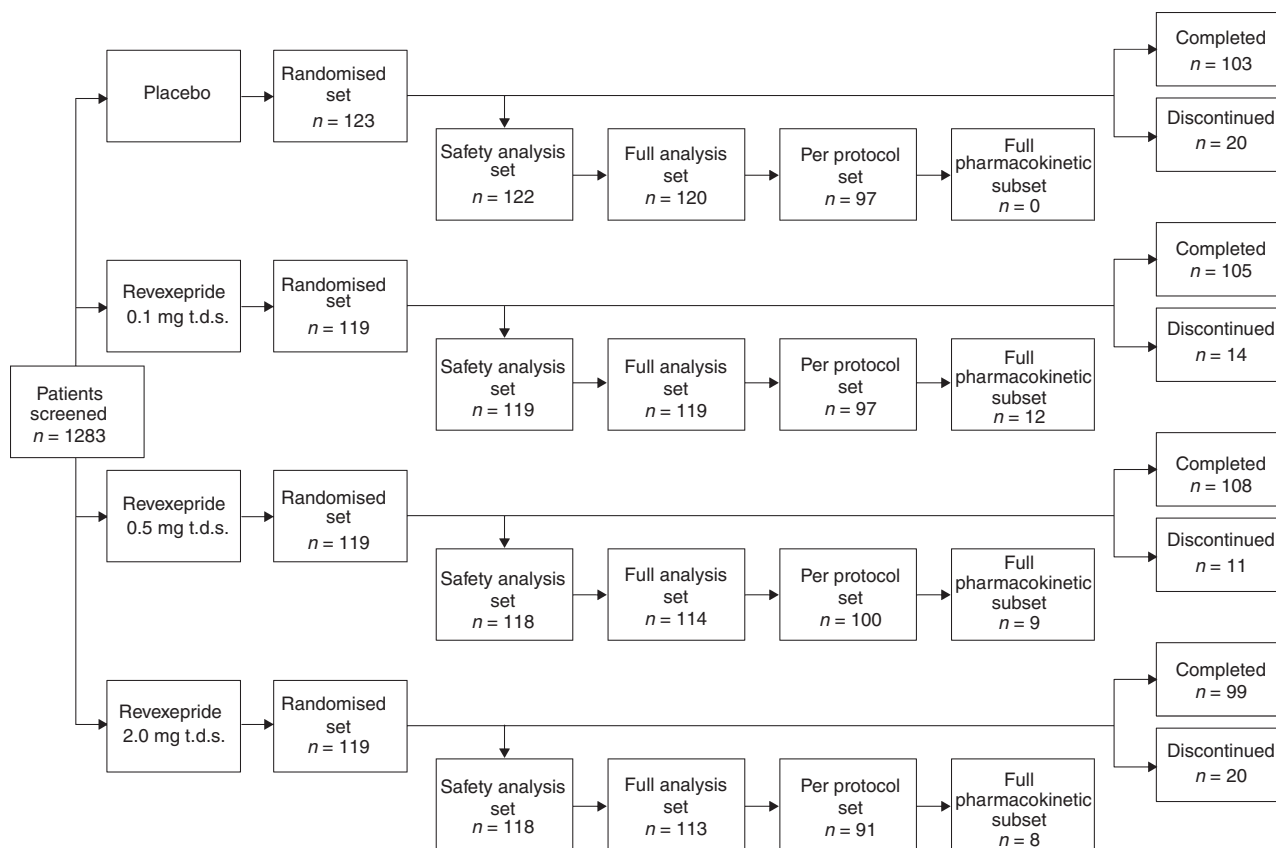


Figure 2 | Study analysis population. *n*, number of patients.

dose indicated for the treatment of non-erosive reflux disease according to the country label) at baseline. Upper endoscopy revealed oesophagitis grade A in 8% of patients at screening. Most patients in each treatment group (75–85%) were taking at least one concomitant medication (excluding PPI and rescue medications), with the most common medications being acetylsalicylic acid, ibuprofen and multivitamins. There was no significant difference in the proportion of patients taking healing doses of PPI between the groups. Most individuals were compliant with investigational product and mean compliance for each treatment group ranged from 87% to 91% (data not shown).

Primary efficacy results

The mean percentage of regurgitation-free days increased from baseline (range, 15.0–18.8%) to week 8 (62.3–70.5%) in all four study arms. The mean change from baseline in the percentage of regurgitation-free days per treatment group over the treatment period are presented in Figure 3a. The least-squares (LS) mean \pm SE change in the primary efficacy endpoint (weekly percentage of

regurgitation-free days from baseline over weeks 5–8) was numerically greater for each dose of revexepride (0.1 mg, $43.0 \pm 3.7\%$; 0.5 mg, $44.4 \pm 3.7\%$; 2.0 mg, $38.8 \pm 3.7\%$) than placebo ($37.0 \pm 3.6\%$). The differences in LS means between placebo and each of the three revexepride doses were not, however, statistically significant (0.1 mg, $P = 0.128$; 0.5 mg, $P = 0.062$; 2.0 mg, $P = 0.650$). Sensitivity analyses using placebo-multiple-imputation and a pattern-mixture model were consistent with the results of the primary efficacy analysis (data not shown).

Secondary efficacy results

Each dose of revexepride was associated with a numerically greater LS mean decrease than placebo in PRISM liquid and food domain score from baseline over weeks 5–8. The difference in LS means between placebo and revexepride 0.5 mg (-3.20 , 95% CI: -5.82 , -0.57) was statistically significant ($P < 0.05$), whereas the differences in LS means for the 0.1 mg (-2.47 , 95% CI: -5.09 , 0.14) and the 2.0 mg (-2.15 , 95% CI: -4.81 , 0.52) dose groups were not statistically significant ($P = 0.064$ and

Table 1 | Patient demographics and other baseline characteristics (safety analysis set)

Characteristic*	Placebo n = 122	Revexepride 0.1 mg t.d.s. n = 119	Revexepride 0.5 mg t.d.s. n = 118	Revexepride 2.0 mg t.d.s. n = 118	Total n = 477
Age, years†	46.2 (12.10)	48.8 (12.59)	49.2 (12.31)	47.6 (11.30)	47.9 (12.11)
Sex					
Male	48 (39.3)	41 (34.5)	46 (39.0)	53 (44.9)	188 (39.4)
Female	74 (60.7)	78 (65.5)	72 (61.0)	65 (55.1)	289 (60.6)
BMI, kg/m ² ‡	27.5 (4.74)	28.3 (4.40)	28.3 (4.69)	28.4 (4.48)	28.1 (4.58)
Regurgitation, days/week§	5.7 (1.31)	6.0 (1.17)	5.7 (1.35)	5.8 (1.30)	5.8 (1.29)
Heartburn alone, days/week§	0.7 (0.89)	0.5 (0.75)	0.5 (0.78)	0.6 (0.90)	0.6 (0.83)
Vomiting, days/week§	0.2 (0.44)	0.2 (0.41)	0.2 (0.47)	0.2 (0.48)	0.2 (0.45)
PPI dose at baseline					
Healing¶	38 (31.1)	37 (31.1)	35 (29.7)	36 (30.5)	146 (30.6)
Symptomatic**	84 (68.9)	82 (68.9)	83 (70.3)	82 (69.5)	331 (69.4)
Did upper endoscopy reveal oesophagitis?					
Yes	11 (9.0)	10 (8.4)	10 (8.5)	6 (5.1)	37 (7.8)
No	29 (23.8)	27 (22.7)	29 (24.6)	30 (25.4)	115 (24.1)
N/A	82 (67.2)	82 (68.9)	79 (66.9)	82 (69.5)	325 (68.1)

BMI, body mass index; IV/WRS, Interactive Voice/Web Response Service; PPI, proton pump inhibitor; N/A, not applicable; SD, standard deviation.

Data are numbers (%) or mean (SD).

* The baseline value for a characteristic is the last value collected before randomisation.

† Age was calculated as the difference between date of birth and date of informed consent, truncated to years. For participants in Germany, 1 January was used as the day and month of date of birth as only the year of birth was collected.

‡ BMI was calculated as: weight (kg)/height (m)².

§ From IV/WRS, calculated by the e-diary for each participant over the 14 days before the baseline visit. Heartburn alone is heartburn with no regurgitation.

¶ PPI dose indicated for the treatment of erosive oesophagitis according to the country label.

** PPI dose indicated for the treatment of non-erosive reflux disease according to the country label.

0.114, respectively). The differences in the changes from baseline in PRISM liquid and food domain score for each revexepride dose and placebo were not clinically meaningful. Similarly, the differences in the changes from baseline in the other PRISM domains (burning sensations, nausea and vomiting, and upper abdominal gas-related symptoms) between the different revexepride doses and placebo were also not clinically meaningful.

The mean change from baseline to week 8 in the percentage of heartburn-free days per treatment group are presented in Figure 3b. The LS mean \pm SE percentage change in heartburn-free days from baseline over weeks 5–8 was numerically greater for each dose of revexepride (0.1 mg, 28.5 \pm 3.7%; 0.5 mg, 30.7 \pm 3.7%; 2.0 mg, 27.5 \pm 3.8%) than for placebo (21.8 \pm 3.6%). The difference in LS means between placebo and revexepride 0.5 mg was statistically significant ($P < 0.05$), but the corresponding differences between placebo and the remaining dose groups were not statistically significant (0.1 mg, $P = 0.102$; 2.0 mg, $P = 0.175$). The LS mean

percentage changes in heartburn-free and regurgitation-free days from baseline over weeks 5–8 were greater for the three doses of revexepride (0.1 mg, 38.2 \pm 3.6%; 0.5 mg, 38.6 \pm 3.6%; 2.0 mg, 35.7 \pm 3.7%) than placebo (31.8 \pm 3.6%), but the differences in LS means between placebo and revexepride were not statistically significant for any dose group (0.1 mg, $P = 0.135$; 0.5 mg, $P = 0.112$; 2.0 mg, $P = 0.367$).

Figure 4a shows the percentage of patients with a reduction of 3 or more days with regurgitation compared with baseline for each of the four treatment groups over weeks 1–8. Compared with placebo, there was no statistically significant increase from baseline in the proportion of patients with a reduction of 3 or more days with regurgitation over weeks 5–8 in the revexepride treatment groups (0.1 mg, $P = 0.081$; 0.5 mg, $P = 0.060$; 2.0 mg, $P = 0.289$). Figure 4b shows the percentage of patients with a reduction of 3 or more days with heartburn compared with baseline for each of the four treatment groups over weeks 1–8. The proportion of

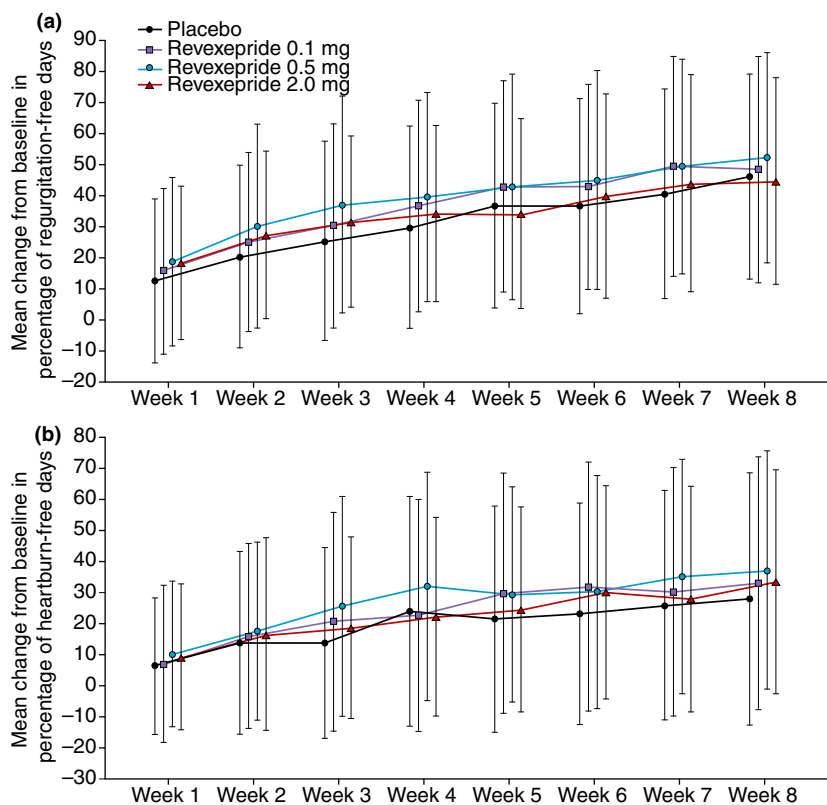


Figure 3 | Mean (\pm standard deviation) change from baseline in percentage of (a) regurgitation-free and (b) heartburn-free days by visit and treatment group (full analysis set). Regurgitation: differences in change from baseline between placebo and the three revexepride treatment groups were not statistically significant. Heartburn: there was a statistically significant difference ($P < 0.05$) between revexepride 0.5 mg and placebo only.

patients with a reduction of 3 or more days with heartburn statistically significantly increased from baseline over weeks 5–8 for the revexepride 0.5 mg treatment group ($P < 0.05$) compared with placebo, but not for the revexepride 0.1 mg ($P = 0.072$) and 2.0 mg ($P = 0.209$) treatment arms. The proportion of patients with a reduction of 3 or more days with regurgitation and heartburn increased statistically significantly from baseline over weeks 5–8 for the revexepride dose groups 0.1 mg and 0.5 mg ($P < 0.05$) compared with placebo (data not shown), but not for the 2.0 mg dose ($P = 0.069$). The numbers of days per week antacid rescue medication was used compared with placebo ($-9.07 \pm \text{SE } 3.1$) were not statistically significantly different, expressed as LS mean (SE) change from baseline over weeks 5–8, per treatment arm (revexepride 0.1 mg, -12.8 ± 3.2 , $P = 0.253$; 0.5 mg, -11.6 ± 3.2 , $P = 0.441$; 2.0 mg, -11.3 ± 3.2 , $P = 0.503$).

HRQoL and symptom questionnaires

The changes in QOLRAD scores from baseline to week 8 are presented in Table 2. The placebo group had smaller LS mean changes for each QOLRAD dimension than any of the three revexepride treatment groups. Differences in LS means between placebo and revexepride 0.1 mg were statistically significant for each QOLRAD

dimension, and for the sleep disturbance and food/drink problem dimensions for the revexepride 0.5 mg group. However, the differences in the mean scores between placebo and these treatment groups were smaller than the adult QOLRAD minimal clinically significant difference standard of 0.5 units.²² Differences in LS means between placebo and revexepride 2.0 mg were not statistically significant for any QOLRAD dimension. Similar trends were observed in the RDQ scores (data not shown). The SF-12 score changes did not differ statistically significantly from baseline to week 8 between placebo and any of the three revexepride treatment groups (data not shown).

Pharmacokinetic results

The mean plasma profiles of revexepride showed that maximal concentrations were attained approximately 5 h after the first daily dose (i.e. 1 h following the second daily dose). Median t_{max} was generally similar for each dose level, ranging from 4.5 to 5.1 h. For the majority of individuals, t_{max} ranged from 4.5 to 5.6 h across all dose levels. Taking into account between-patient variability, systemic exposure to revexepride, as measured by AUC_{ss} and C_{ssmax} (12–44% and 20–47%, respectively) in the pharmacokinetic set and trough and peak concentrations in the full pharmacokinetic subset, increased in an

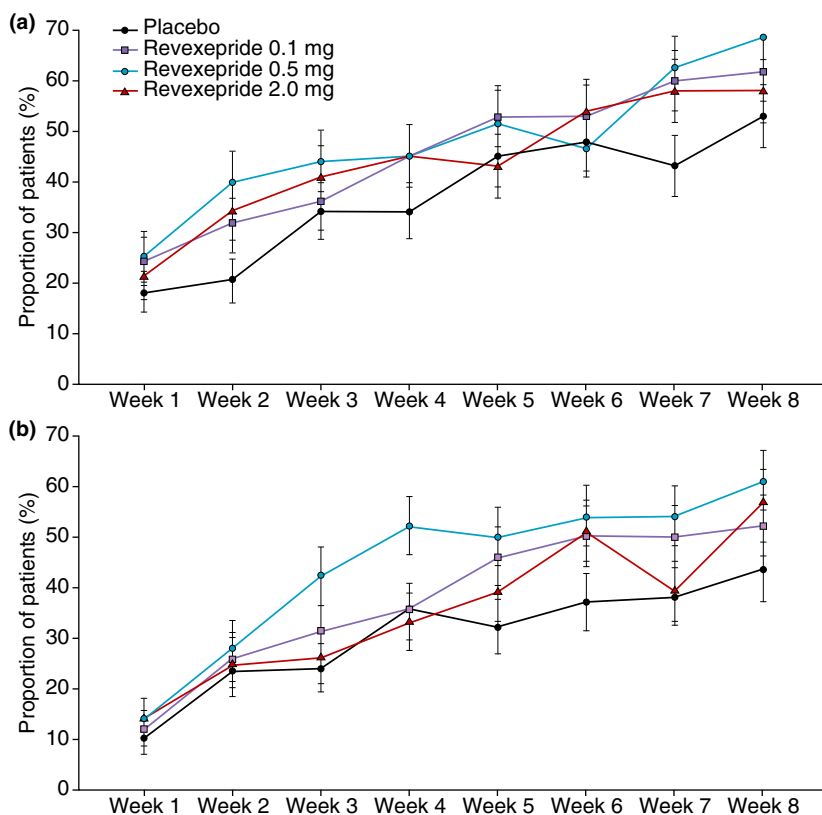


Figure 4 | Percentage (\pm SE) of patients with a reduction of 3 or more days with (a) regurgitation and (b) heartburn, by visit and by treatment group (full analysis set). Regurgitation: differences in change from baseline between placebo and the three revexepride treatment groups were not statistically significant. Heartburn: there was a statistically significant difference ($P < 0.05$) between revexepride 0.5 mg and placebo only.

Table 2 | Analysis of LS mean (SE) changes in QOLRAD score from baseline to week 8 for each treatment group

QOLRAD dimension	Placebo	Revexepride 0.1 mg t.d.s.	Revexepride 0.5 mg t.d.s.	Revexepride 2.0 mg t.d.s.
Emotional distress	1.27 (0.14)	1.68 (0.15)	1.46 (0.15)	1.33 (0.15)
<i>P</i> value		0.006	0.196	0.687
Sleep disturbance	1.14 (0.13)	1.51 (0.14)	1.51 (0.14)	1.29 (0.14)
<i>P</i> value		0.009	0.007	0.274
Food/drink problem	1.47 (0.16)	1.95 (0.16)	1.87 (0.16)	1.77 (0.16)
<i>P</i> value		0.004	0.015	0.075
Physical/social functioning	0.89 (0.12)	1.34 (0.12)	1.10 (0.12)	0.94 (0.12)
<i>P</i> value		<0.001	0.076	0.674
Vitality	1.22 (0.15)	1.69 (0.15)	1.45 (0.15)	1.33 (0.15)
<i>P</i> value		0.002	0.123	0.494

LS, least-squares; QOLRAD, Quality of Life in Reflux and Dyspepsia; SE, standard error. Lower QOLRAD scores indicate a more severe impact on daily functioning. Values in bold indicate statistical significance ($P < 0.05$) in LS mean between revexepride and placebo.

approximately dose-proportional manner across the 20-fold dose range (0.1–2.0 mg). Exclusion of patients experiencing regurgitation or significant diarrhoea within the blood-sampling period did not have any discernible impact on plasma pre-dose and 1-h post-dose revexepride concentrations in the pharmacokinetic set (data not shown).

Safety analysis

A summary of the treatment-emergent adverse events (TEAEs) is presented in Table 3. Within the revexepride treatment groups, the proportion of TEAEs was dose dependent; the 2.0 mg treatment group had the highest rate of TEAEs (59.3%) while the 0.1 mg treatment group had the lowest rate (40.3%). The incidence of TEAEs con-

Table 3 | Treatment-emergent adverse events by treatment group (safety analysis set)

	Placebo <i>n</i> = 122 Number (%), <i>e</i>	Revexepride 0.1 mg t.d.s. <i>n</i> = 119 Number (%), <i>e</i>	Revexepride 0.5 mg t.d.s. <i>n</i> = 118 Number (%), <i>e</i>	Revexepride 2.0 mg t.d.s. <i>n</i> = 118 Number (%), <i>e</i>
Any TEAE	60 (49.2), 113	48 (40.3), 96	61 (51.7), 103	70 (59.3), 168
Serious TEAEs	0	0	0	1 (0.8), 1
TEAEs related to investigational product	21 (17.2), 33	22 (18.5), 30	24 (20.3), 37	42 (35.6), 84
TEAEs leading to investigational product discontinuation	3 (2.5), 3	7 (5.9), 7	7 (5.9), 7	14 (11.9), 14
Severe TEAEs	4 (3.3), 5	2 (1.7), 2	2 (1.7), 3	7 (5.9), 11
TEAEs related to investigational product and of at least moderate severity	7 (5.7), 10	9 (7.6), 12	10 (8.5), 17	22 (18.6), 40
TEAEs leading to death	0	0	0	0
TEAEs by type*				
Diarrhoea	8 (6.6)	12 (10.1)	19 (16.1)	32 (27.1)
Nausea	4 (3.3)	7 (5.9)	5 (4.2)	12 (10.2)
Headache	4 (3.3)	1 (0.8)	7 (5.9)	10 (8.5)
Abdominal pain	2 (1.6)	3 (2.5)	3 (2.5)	10 (8.5)
Upper respiratory tract infection	6 (4.9)	4 (3.4)	7 (5.9)	3 (2.5)
Back pain	7 (5.7)	0	0	0
TEAE by maximum severity				
Mild	40 (32.8)	28 (23.5)	38 (32.2)	34 (28.8)
Moderate	16 (13.1)	18 (15.1)	21 (17.8)	29 (24.6)
Severe	4 (3.3)	2 (1.7)	2 (1.7)	7 (5.9)

e, number of events; *n*, number of patients; TEAE, treatment-emergent adverse event.

* Frequently occurring TEAEs ($\geq 5\%$).

sidered related to the investigational product was also dose dependent, with the revexepride 2.0 mg treatment group having the most related TEAEs (35.6%). Only one serious TEAE occurred during the course of the study (worsening pulmonary hypertension in a patient with a pre-existing condition of pulmonary hypertension; revexepride 2.0 mg treatment group). No TEAEs resulted in death, and no deaths occurred during the study. A higher proportion of patients in the revexepride 2.0 mg treatment group had TEAEs that led to discontinuation of the investigational product than in the other treatment groups.

The most frequently ($\geq 5\%$) occurring TEAEs were diarrhoea, nausea, headache, abdominal pain, upper respiratory tract infection and back pain. The frequency of patients with upper respiratory tract infections was similar across all treatment groups and the TEAE of back pain occurred only in the placebo group. Overall, there were few severe TEAEs across the revexepride dose groups (11 patients; 3.1%).

The numbers of patients with potentially clinically important haematology results and vital signs were minimal and similar across treatment groups (Table S1). One

hour after the first administration of investigational product, there was a dose-dependent mean increase from baseline in heart rate for each revexepride treatment group (mean \pm SD: 0.1 mg, 2.4 ± 7.42 bpm; 0.5 mg, 4.1 ± 8.74 bpm; 2.0 mg, 5.5 ± 8.27 bpm), while the placebo treatment group had a 1.5 ± 6.85 bpm decrease. The changes from baseline for all other ECG parameters and visits were minimal and similar across treatment groups. The numbers of patients with potentially clinically important ECG results are presented in Table S2. The most common potentially clinically important ECG criteria were a QT interval corrected according to Bazett's formula (QTcB) of between 450 and 480 ms, any rhythm other than sinus rhythm (per central reader) and a QTcB interval change from baseline of between 30 and 60 ms. The incidences of these criteria were similar across treatment groups.

DISCUSSION

In this study, we evaluated the efficacy and safety of revexepride (0.1, 0.5 and 2.0 mg three times daily) in patients with GERD who had persistent symptoms of

regurgitation, with or without heartburn, while on optimised PPI treatment. The focus of the study was on patients with primarily regurgitation as opposed to heartburn. Regurgitation may be associated with oesophageal dysmotility, leading to volume reflux.^{23–25} Therefore, prokinetic agents have been proposed to be complementary to PPIs in regurgitation-predominant patients. Previous studies have attributed a reduction in regurgitation to the prokinetic effects of 5-HT₄ receptor agonists (such as cisapride and tegaserod) on oesophageal function.^{15, 26}

There was no significant difference in the primary efficacy endpoint (change from baseline in percentage of regurgitation-free days over weeks 5–8 as measured with the PRISM PRO instrument) between any of the revexepride dose groups and the placebo group. No dose-dependent treatment effects were observed for any of the study efficacy endpoints, and the changes from baseline in PRISM liquid and food domain score for each revexepride dose were not clinically meaningful. The development of revexepride has now been abandoned.

The search for pro-motility agents that have a positive impact on upper gastrointestinal disease has been frustrating. Previous studies have demonstrated that other motility-modifying drugs, such as the 5-HT₄ receptor agonist cisapride, had poor efficacy in relieving symptoms in patients with functional dyspepsia.^{14, 15} Similarly, the reflux inhibitors lesogaberan and arbaclofen placarbil (the pro-drug of the γ -aminobutyric acid-B agonist R-baclofen) demonstrated disappointing results in patients with GERD who were partially responsive to PPI therapy.^{27, 28}

The poor efficacy of revexepride observed in this study may partially reflect difficulty in identifying patients with reflux symptoms on acid suppression that are related to persistent, weakly acidic reflux events or dysmotility that could potentially improve with a prokinetic medication. Furthermore, while the patients included in this study were selected based on persistent, classical reflux symptoms, it is conceivable that their symptoms were not caused by reflux, given that an estimated 20% of patients with reflux symptoms are thought to have functional heartburn.²⁹ In individuals with a partial response to PPI therapy, this proportion may be even higher.³⁰ Patients with functional or nonreflux-related symptoms are unlikely to respond to a prokinetic agent; hence, the potential inclusion of such patients may have limited the ability to detect a statistically significant therapeutic effect of revexepride. However, the extent to which this might have applied in the present

study remains uncertain. The inclusion/exclusion criteria attempted to minimise the number of participants with functional disease in the study group by focusing on regurgitation, a symptom highly correlated with the presence of reflux events. Additionally, by requiring more days with regurgitation than heartburn, and by limiting allowable dyspeptic symptoms and vomiting, the intention was to isolate the group most likely to benefit from the mechanism of action of revexepride. Despite these measures, the study failed to detect a clinically significant effect of the intervention. To what degree this lack of efficacy may be explained by inclusion of participants with functional disease is unclear.

There was a high placebo response observed in the efficacy endpoints. The placebo response rate in trials for functional gastrointestinal disorders has been shown to be substantial.³¹ As this large placebo response rate is similar to those seen in the placebo arms of randomised controlled trials in functional disease, it again raises the possibility of the potential dilution of our patient population with individuals with functional heartburn. While our PRO tool was developed and validated specifically in patients with reflux symptoms partially responsive to PPI, the lack of treatment response in the primary endpoint may additionally reflect limitations of the PRISM instrument and the difficulties associated with identifying the correct symptom descriptions.

Revexepride was generally well tolerated and overall there were few severe, and no fatal, TEAEs. There were no clinically significant safety findings. Of particular interest, and in contrast to other 5-HT₄ receptor agonists, ECG findings did not indicate any cardiac concerns. The evaluation of the patients' safety did not raise any new safety concerns at the doses of revexepride administered in this study.

In conclusion, this study found that revexepride has no significant effect on regurgitation in patients with GERD who have a partial response to PPIs. Revexepride was generally well tolerated. These findings, in association with previous disappointing studies, suggest that altering motility may be an inadequate mechanism to address symptoms in patients with GERD who are partially responsive to PPI therapy. This study also highlights the difficulties involved in selecting patient populations that effectively exclude individuals who have functional or nonreflux-related symptoms.

AUTHORSHIP STATEMENT

Guarantor of the article: Nicholas Shaheen.

Author contributions: NJS, JT, NV, FZ, SD, MR, AM and LT were involved in the conception and design of the study. LP was responsible for the statistical analyses. All authors contributed to data interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Menarini, Novartis, Shire, Takeda and Zeria. Nimish Vakil is a consultant to AstraZeneca, Forest Pharmaceuticals, Ironwood Pharmaceuticals, Otsuka and Takeda, and owns stock in Meridian Bioscience. Frank Zerbib has served as a speaker, consultant and advisory board member for Abbott, Addex Pharma SA, Almirall, Cephalon, AstraZeneca, Given Imaging, Janssen Cilag, Norgine, Pfizer, Reckitt Benckiser, Sanofi-Aventis, Shire-Movetis NV and XenoPort. Peter Malfertheiner has been a lecturer for Abbott, Aptalis, AstraZeneca, Falk and Takeda. Sophie Dedrie, Ann Meulemans, Lynne Poole, Leen Thielemans and Magnus Ruth were employees of Shire at the time of the study. Steven Troy is a Shire employee and holds share/stock options with Shire. Jay Adler has nothing to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Patients with potentially clinically important vital sign results (safety analysis set).

Table S2. Patients with potentially clinically important electrocardiogram results (safety analysis set).

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