Original research

Treatment of non-constipated irritable bowel syndrome with the histamine 1 receptor antagonist ebastine: a randomised, double-blind, placebo-controlled trial

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ABSTRACT

Objective We evaluated the histamine 1 receptor antagonist ebastine as a potential treatment for patients with non-constipated irritable bowel syndrome (IBS) in a randomised, placebo-controlled phase 2 study.

Methods Non-constipated patients with IBS fulfilling the Rome III criteria were randomly assigned to 20 mg ebastine or placebo for 12 weeks. Subjects scored global relief of symptoms (GRS) and abdominal pain intensity (API). A subject was considered a weekly responder for GRS if total or obvious relief was reported and a responder for API if the weekly average pain score was reduced by at least 30% vs baseline. The primary endpoints were the proportion of subjects who were weekly responders for at least 6 out of the 12 treatment weeks for both GRS and API ('GRS+API', composite endpoint) and for GRS and API separately.

Results 202 participants (32±11 years, 68% female) were randomly allocated to receive ebastine (n=101) or placebo (n=101). Treatment with ebastine resulted in significantly more responders (12%, 12/92) for GRS+API compared with placebo (4%, 4/87, p=0.047) while the proportion of responders for GRS and API separately was higher for ebastine compared with placebo, although not statistically significant (placebo vs ebastine, GRS: 7% (6/87) vs 15% (14/91), p=0.072; API: 25% (20/85) vs 37% (34/92), p=0.081).

Conclusions Our study shows that ebastine is superior to placebo and should be further evaluated as novel treatment for patients with non-constipated IBS.

Trial registration number The study protocol was approved by the local ethics committee of each study site (EudraCT number: 2013-001199-39; ClinicalTrials.gov identifier: NCT01908465).

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Mast cell activation and histamine-induced visceral hypersensitivity are considered to be involved in the pathogenesis of irritable bowel syndrome (IBS).

⇒ A previous proof-of-concept pilot study evaluating the effect of the histamine 1 receptor antagonist ebastine showed significant symptom relief and reduced abdominal pain compared with placebo in patients with IBS.

WHAT THIS STUDY ADDS

⇒ This phase 2b trial in 202 non-constipated patients with IBS reveals that 20 mg/day of ebastine is superior to placebo as treatment of non-constipated IBS.

⇒ The proportion of weekly responders (improvement in global symptom relief and reduced abdominal pain) in the ebastine group significantly increases after 6–8 weeks of treatment compared with placebo, indicating that treatment should be maintained for at least 6–8 weeks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study indicates that histamine 1 receptor antagonists such as ebastine should be considered as a potential novel treatment for patients with non-constipated IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most prevalent gastrointestinal (GI) disorders of the gut–brain axis, affecting approximately 4% of the population across the world.[1] Affected individuals suffer from recurrent abdominal pain that is associated with diarrhoea (IBS-D), constipation (IBS-C) or both in an alternating pattern (IBS-M).[2] A small proportion of patients who do not fall into any of these categories are classified as unsubtyped (IBS-U). Additional common complaints are abdominal bloating or distention and faecal urgency. Currently, effective treatment options are rather scarce and mainly act to normalise bowel movements and stool consistency but fail to improve abdominal pain.[3 4]

One of the pathophysiological mechanisms leading to increased abdominal pain in IBS is visceral hypersensitivity, defined as abnormal pain signalling in the viscera, manifested by a painful response to normally innocuous stimuli and/or

an exaggerated response to painful stimuli.[5] Since the papers by Barbara *et al*, evidence indicating mast cell activation as an important mechanism underlying abnormal pain signalling in IBS is accumulating.[6 7] Indeed, several studies describe the enhanced release of mast cell mediators such as tryptase and histamine in the intestinal mucosa of patients with IBS, while in rodent models of IBS, these mediators are known to activate and sensitise afferent nociceptive nerve endings resulting in visceral hypersensitivity.[7–9] Moreover, in a proof-of-concept pilot study, we showed that treatment of patients with IBS with the mast cell stabiliser ketotifen decreased visceral hypersensitivity and improved intestinal symptoms compared with placebo.[10]

Histamine sensitises transient receptor potential vanilloid 1 channels via activation of histamine 1 receptors (H1R) and thereby mediates visceral hypersensitivity in a preclinical model of IBS.[8 11–13] Unlike ketotifen, ebastine is a second-generation antagonist of H1R that is indicated for allergic rhinitis and urticaria. After oral administration, the drug is quickly absorbed and is metabolised into its active metabolite carebastine by CYP3A4 due to extensive first-pass metabolism.[14] Ebastine hardly penetrates the blood–brain barrier and is, therefore, less likely to cause sedation compared with first-generation antihistamines.[14] Previously, we designed a proof-of-concept pilot trial in which 55 patients with IBS were randomised to be treated with the H1R antagonist ebastine or placebo for 12 weeks.[8] Our pilot study showed that 20 mg of ebastine once per day for 12 weeks significantly reduced visceral hypersensitivity, symptoms and abdominal pain compared with placebo, suggesting that H1R antagonists, such as ebastine, might represent a new therapeutic approach for IBS. To further confirm the therapeutic potential of H1R antagonists, we designed a multicentre phase 2b, randomised, placebo-controlled trial comparing ebastine with placebo in patients with non-constipated IBS. The choice to exclude IBS-C patients was based on a post-hoc analysis of the pilot trial suggesting that the effect of ebastine was less pronounced in IBS-C patients.

MATERIALS AND METHODS

Study participants

Patients between 18 and 65 years of age, with a diagnosis of IBS according to the Rome III criteria, were recruited at the outpatient clinic of the participating study centres.[15] Patients did not have an identifiable cause for their GI symptoms (including negative test results for the lactose breath test, faecal parasites, faecal calprotectin and coeliac disease). Bile acid diarrhoea was not excluded systematically, only if suspected clinically. Eligible patients had an average daily abdominal pain score of the worst abdominal pain per day during the 2-week screening phase of ≥3 on a 10-point Visual Analogue Scale. Patients were not involved in the review of the study protocol and were not asked to assess the burden of the intervention or the time required to participate in the study, but are currently involved in the dissemination of the results.

Exclusion criteria were (1) constipation-predominant IBS, (2) medical history of lactose intolerance, giardiasis, inflammatory bowel disease, active intestinal infection, chronic intestinal ischemia, chronic subobstruction, pseudo-obstruction,

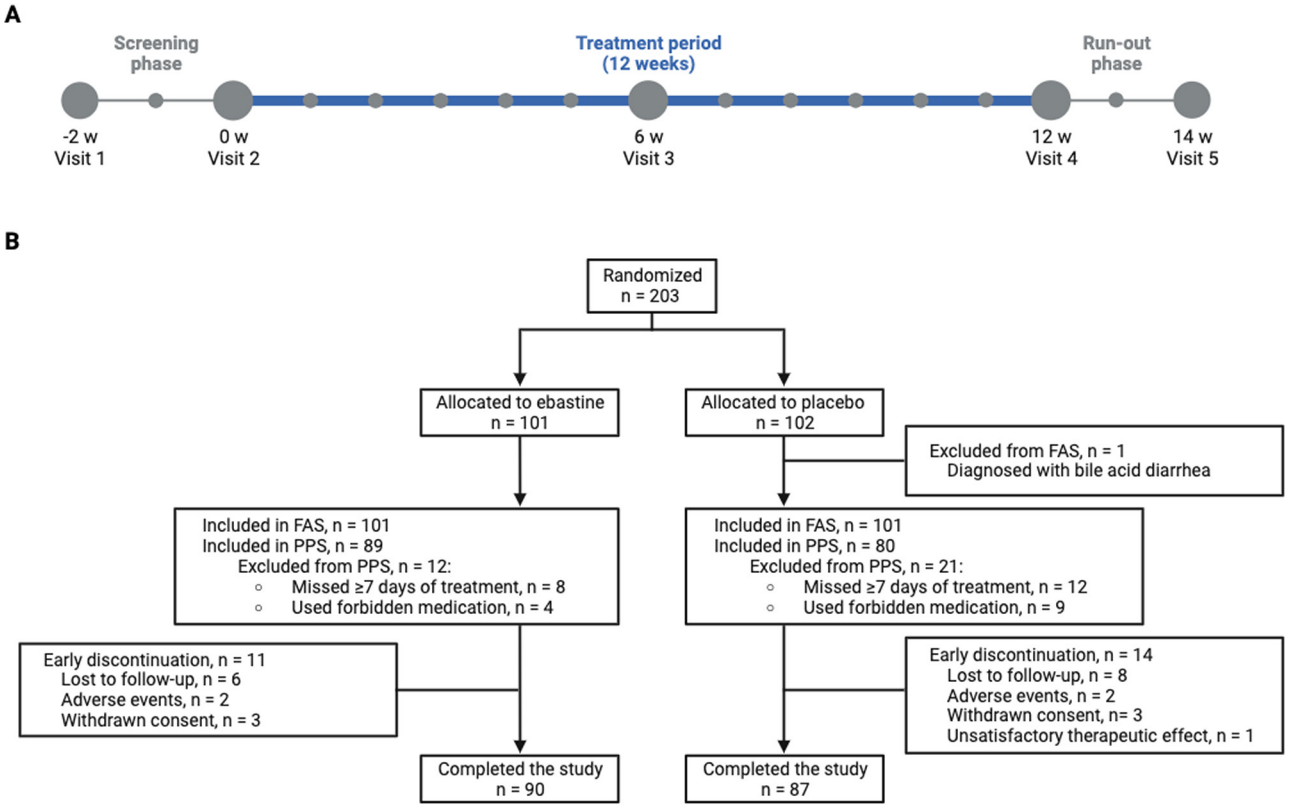


Figure 1 Timeline and flow chart of the study. (A) Overview of the study timeline from the first patient contact at visit 1, minimum 2 weeks before randomisation, until the last patient contact at visit 5, 14 weeks after randomisation. (B) Patient disposition in the study. All randomised patients received the allocated study medication. Patients who did not complete the study until visit 5 were listed as early discontinuation. Patients who missed ≥7 days of study treatment or used medication that is believed to interfere with the effect of the study treatment, were considered to violate the protocol and were therefore excluded from the per-protocol set (PPS). FAS, full-analysis set.

Table 1 Baseline characteristics of study participants (FAS)

Characteristic	Placebo (n=101)	Ebastine (n=101)
Age, mean (SD)	32 years (11)	32 years (12)
Female sex, n (%)	70 (69)	68 (67)
Caucasian, n (%)*	99 (99)	99 (98)
BMI, mean (SD)	24 kg/m^2 (4)	23 kg/m^2 (4)
Allergic rhinitis, n (%)*	15 (15)	23 (23)
Asthma, n (%)*	7 (7)	3 (3)
Eczema, n (%)*	7 (7)	10 (10)
HADS depression score, n (%)		
No depression (0–7)	71 (73)	69 (72)
Possible depression (8–10)	17 (18)	13 (14)
Probable depression (11–21)	9 (9)	14 (15)
PHQ9 depression score, n (%)		
No and minimal depression (0–4)	25 (27)	29 (33)
Mild and moderate depression (5–14)	63 (68)	45 (51)
Severe depression (15–27)	5 (5)	14 (16)
PHQ15 somatic symptom score, n (%)		
Minimal and low (0–9)	16 (17)	19 (20)
Medium (10–14)	40 (42)	38 (40)
High (15–30)	39 (41)	37 (39)
IBS subtype, n (%)		
IBS-D	69 (68)	65 (64)
IBS-M	15 (15)	19 (19)
IBS-U	17 (17)	17 (17)
Frequency of IBS symptoms, n (%)*		
At least three times/month	2 (2)	1 (1)
Less than 1 day/week	0 (0)	1 (1)
1–2 days/week	5 (5)	6 (6)
≥3 days/week	35 (35)	29 (29)
Every day	58 (57)	60 (59)
Unknown	1 (1)	4 (4)
Duration of IBS symptoms, median (Q1; Q3)*	110 (24; 122)	95 (30; 120)
Abdominal pain score at baseline, mean (SD)†	5 (2)	5 (2)

*Self-reported and collected on visit 1. IBS subtype was determined with the bristol stool scale on visit 1. Duration of IBS symptoms was calculated from the date of the first symptoms to the date of visit one and reported in months.
†Average of the daily reported worst abdominal pain (on 0–10 Visual Analogue Scale) during the screening phase.
BMI, body mass index; FAS, full-analysis set; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; PHQ9, Patient Health Questionnaire 9; Q1, first quartile; Q3, third quartile.

Table 2 Primary outcome responder rates: responder data per outcome and per analysis set

Outcome	Placebo	Ebastine	Risk difference (RD)	
Analysis set	n/N proportion (95% CI)		RD (95% CI)	P value
Clinical response				
FAS	4/87 4.3 (1.7 to 10.4)	12/92 12.0 (7.0 to 19.8)	7.7 (0.2 to 15.2)	0.0471
PPS	3/78 3.8 (1.2 to 11.0)	10/88 11.2 (6.2 to 19.6)	7.5 (–0.3 to 15.3)	0.0682
Global relief of symptoms response				
FAS	6/87 6.9 (3.3 to 13.9)	14/91 15.1 (9.2 to 23.7)	8.2 (–0.7 to 17.1)	0.0715
PPS	5/78 6.3 (2.6 to 14.2)	12/87 13.5 (7.8 to 22.3)	7.2 (–1.6 to 16.1)	–
Abdominal pain intensity response				
FAS	20/85 24.8 (17.1 to 34.5)	34/92 36.6 (27.6 to 46.6)	11.8 (–1.4 to 24.9)	0.0813
PPS	18/77 22.6 (14.8 to 32.9)	32/88 36.0 (26.8 to 46.3)	13.4 (–0.2 to 26.9)	–

Data per group are reported as number of responders (n) per total number of those from whom data was collected (N) and the estimated response rate (%) with associated 95% CI. Response rates, (RD, with 95% CI) and p values were determined using multiple imputation with 100 imputations to account for missing data. The p value was obtained using a χ^2 test.
FAS, full-analysis set; PPS, per-protocol set.

dumping syndrome, pancreatic insufficiency, liver, kidney or thyroid dysfunction, moderate to severe cardiovascular disease, extensive gastrectomy and/or bowel resection, active malignant disease, insulin-dependent diabetes mellitus or psychiatric disorders for which medication is needed, (3) onset of GI symptoms after abdominal surgery, (4) pregnancy or breast feeding and (5) use of one or more of the following medications: H1R-antagonists, antidepressants, antipsychotics, anticholinergics, antispasmodics, serotonin receptor 4 agonists, cholinomimetics, loperamide, laudanum, codeine, stimulant laxatives, macrogol, paraffin oil, non-steroidal anti-inflammatory drugs and oral antibiotics. All patients provided written informed consent before study-related procedures were initiated.

Trial design and data collection

The study was designed as a multicentre, randomised, double-blind and placebo-controlled trial to evaluate the efficacy of ebastine (20 mg, once daily) as treatment for IBS. Placebo tablets were made to be identical to the study medication to maintain blinding throughout the study. All study personnel was blinded to the study allocation.

A schematic representation of the study protocol can be found in figure 1A. Following a 2-week screening phase, eligible subjects were randomised to receive either placebo or ebastine for 12 weeks. Randomisation was accomplished via a centralised telephone Interactive Voice Response System at the Leuven Coordinating Center. A computerised algorithm was used and patients were stratified according to the study site. After completing the 12-week treatment period, patients were followed for two additional weeks (run-out phase, weeks 13–14). After the intake visit (visit 1), study visits took place at the start of the first treatment week (visit 2), the end of week 6 (visit 3), week 12 (visit 4) and week 14 (visit 5). Abdominal pain scores and the number of loose stools (type 6–7 on the Bristol Stool Form Scale (BSFS)) were recorded daily in a diary whereas global symptom relief was obtained weekly throughout the entire study. The Hospital Anxiety and Depression Scale (HADS), the 36-item Short-Form Health Survey (SF-36) and the Patient Health Questionnaires (PHQ) 9 and 15 were completed on visit 1 and visit 4.[16–19]

From April 2014 to October 2022, data were collected at five study centres located in Belgium (University Hospital Leuven (central site), University Hospital Antwerp, University Hospital Ghent, Hospital East-Limburg Genk, AZ Sint-Lucas Brugge) and three in the Netherlands (Amsterdam University Medical Centers, Medisch Spectrum Twente, Rijnstate Hospital).

Study outcomes

According to the FDA (Food and Drug Administration, USA) recommendations, a composite primary endpoint was based on the following outcomes[20]:

1. Abdominal pain intensity (API): API was assessed daily using a 10-point Visual Analogue Scale. For each week, an average

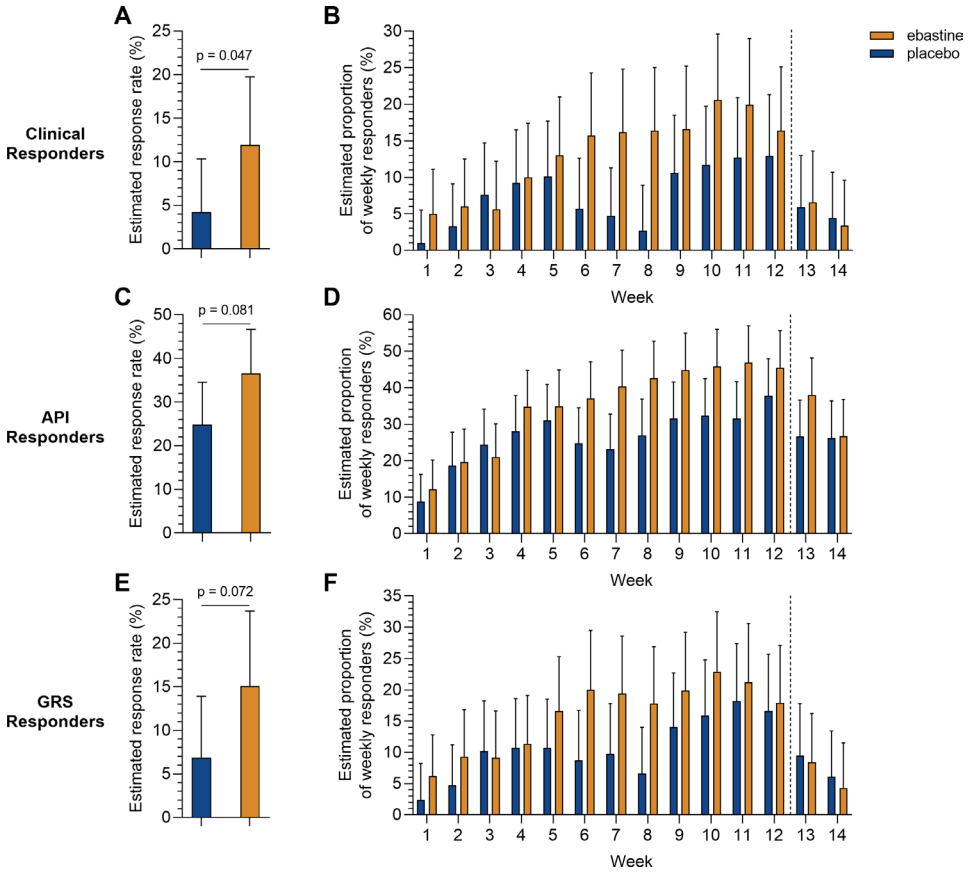


Figure 2 Response rates for the primary outcomes and weekly response rates. (A) Proportion of clinical responders (composite endpoint, 6/12 weeks), (C) Abdominal pain intensity (API) responders (EMA endpoint, 6/12 weeks) and (E) global relief of symptoms (GRS) responders (EMA endpoint, 6/12 weeks) are shown for placebo (blue) and ebastine (orange). P values are shown above each bar plot and were obtained using a χ^2 test. (B) Weekly proportion per treatment arm of clinical responders, (D) API responders and (F) GRS responders. A subject is considered a weekly responder for GRS if total or obvious relief is experienced compared to baseline, and a weekly responder for API if the weekly average pain score is reduced by at least 30% from baseline. A weekly clinical responder is a weekly responder for both GRS and API. The observed responder rates are presented with their associated 95% CI. EMA, European Medicines Agency.

pain score of the worst abdominal pain per day was calculated. Then, the change in weekly pain score was calculated from the average pain score recorded during the screening phase (baseline). An API weekly responder is defined as a subject who had a decrease of≥30% compared with baseline.

2. Global Relief of Symptoms (GRS): GRS was assessed weekly using a 6-point scale for 12 weeks during treatment and run-out. A subject is considered as a GRS weekly responder if he/she scores total or considerable relief of symptoms compared with baseline.

A study subject is considered as a weekly clinical responder for a particular week if the subject was both an API and GRS responder. Using this definition, a study subject will be defined as a 'clinical responder$^{6/12}$' if he/she is a weekly Clinical Responder for at least 6 of the 12 weeks of treatment. Clinical response, thus, refers to the improvement of both GRS and API.

In addition to the composite endpoint, we also determined the primary outcome according to the EMA (European Medicines Agency) guidelines. As dictated by the EMA guidelines for IBS trial design, global assessment of symptoms and abdominal pain should be tested separately.[21] Here, a subject will be defined as a GRS responder$^{6/12}$ if he/she reported total or obvious relief of symptoms compared with baseline for at least 6 of the 12 weeks of treatment. An API responder$^{6/12}$ was defined as a patient who experienced an improvement in weekly average API of ≥30% compared with baseline for at least 6 of the 12 treatment weeks.

As secondary endpoints, we also separately evaluated the effect of ebastine in patients with IBS-D. Here, we included the responder rates for stool consistency. A subject is considered a weekly responder for stool consistency if he/she experiences a ≥50% reduction in the number of days per week with at least one stool of type 6 or 7 on the BSFS compared with baseline.[20] In line with the primary endpoint, IBS-D clinical responders$^{6/12}$ are defined as subjects that were weekly responders for both stool consistency and API during at least 6 of the 12 treatment weeks. Based on the previous pilot study, we also determined response rates during the last 4 weeks of the treatment period referred to hereafter with '$^{2/4}$', as well as during the final week of the treatment period (referred to hereafter with '^{w12}'). Finally, mental health and health-related quality of life questionnaire scores were compared between treatment groups and adjusted for baseline values.

Exploratory endpoints included responder rates for clinical response, GRS, API and stool consistency during at least 3 out of the last 6 weeks of the treatment period (referred to hereafter with '$^{3/6}$').

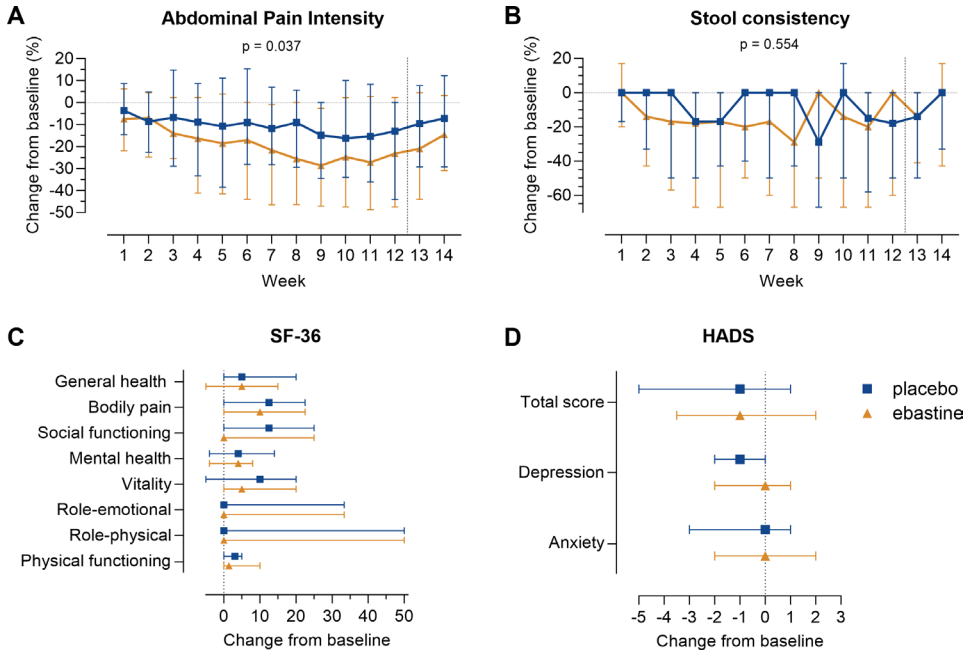


Figure 3 Additional physiological and psychological outcomes. (A) The weekly average of the worst abdominal pain per day and (B) the weekly number of days with 1 or more loose stools (BSFS types 6–7) are shown as a median percentage of change from baseline (week 0), the error bars indicate the upper (75%) and lower (25%) quartiles. P values were obtained using an overall F-test for the effect of treatment over time from a random-intercept linear model. (C) The median change between baseline and week 12 in subscores for the SF-36 questionnaire and (D) in total and subscores for the HADS questionnaire, with errors bars indicating the upper (75%) and lower (25%) quartiles. BSFS, Bristol Stool Form Scale; HADS, Hospital Anxiety and Depression Scale; SF-36, 36-item Short-Form Health Survey.

Statistical analysis

Sample size calculations were based on response rates for GRS and API in the monocentric ebastine trial of respectively 4.3% and 18.2% in the placebo group and 25.0% and 38.1% in the ebastine group.[8] Assuming a kappa coefficient of 0.4 for the association between the two endpoints, it was calculated that 85 patients per group would result in a statistical power of 83% for detecting a statistically significant difference ($\alpha<0.05$) between the treatment groups for both endpoints using two χ^2 tests. Under the same assumptions, the statistical power was estimated to be 87% to assess the clinical response. To compensate for drop-outs, we aimed to enrol 200 patients.

A detailed description of all statistical analyses is provided in the statistical analysis plan (supplemented), which was finalised prior to database lock and unblinding of study treatment. Analysis sets were finalised during a blind review meeting before database lock and unblinding. The full-analysis set (FAS) included all randomised patients, except for one patient who was diagnosed with bile acid diarrhoea during the study. Patients in the FAS who missed >7 days of the investigational medicinal product, or used medication listed in the exclusion criteria, were excluded from the per-protocol set (PPS). During the blind review meeting, it was decided to add response rates for 2 out of the last 4 weeks ('$^{2/4}$') and at week 12 ('^{w12}') as secondary endpoints.

Missing API and GRS scores were accounted for by means of multiple imputation, using a total of 100 imputations. The imputation model was finalised at the blind review meeting and included the following baseline characteristics: age, sex, IBS subtype, frequency of symptoms, average pain score and average stool number during the 2-week screening period. All outcomes of interest were calculated on the imputed datasets.

To control the overall type I error of the trial in the presence of multiple primary endpoints, a hierarchical gatekeeping testing procedure was used whereby first the clinical response was evaluated. If statistically significant, the study was to be considered positive for clinical response, and further testing of API and GRS response as per EMA guidelines could be done at a significance level of 5%. In case of no statistically significant result for clinical response, no further testing of the remaining two endpoints could be performed and the study was to be considered negative for all primary endpoints.

All continuous variables are summarised using means and SD or medians and IQRs, as appropriate. Categorical variables are summarised by their observed frequencies and percentages. Response rates were compared using a χ^2 test and treatment effects were estimated as risk differences (RDs) and presented with their associated 95% CI. All statistical tests were two sided and assessed at a significance level of 5%. All analyses were performed by using SAS V.9.4 for Windows 10 (SAS Institute).

RESULTS

Study participants

203 patients who had IBS symptoms without constipation (mean age of 32 years (SD 11 years), 138 (68%) females) were enrolled and randomised in the study (figure 1B). One patient in the placebo arm was diagnosed with bile acid malabsorption after randomisation and excluded from the FAS. All other 202 randomised patients received at least one dose of the study drug and were therefore included in the FAS. A total of 91% of the patients in the ebastine arm and 87% in the placebo arm completed the 12-week treatment period, and, respectively, 89% and 86% completed the entire study (including run-out phase, figure 1B). The baseline characteristics of the patients in the FAS were similar between treatment groups (table 1). The adherence to the study drug was 88% for the placebo group and 92% for

Table 3 Secondary and additional outcome responder rates (FAS)

Outcome	Placebo	Ebastine	Risk difference (RD)	
	n/N proportion (95% CI)		RD (95% CI)	P value
Clinical response				
Responder data for 2/4 weeks	13/86 13.7 (8.2 to 22.1)	22/90 22.7 (15.5 to 32.0)	9.0 (–1.9 to 19.8)	0.1067
Responder data for 3/6 weeks	8/87 8.5 (4.4 to 15.7)	18/89 18.7 (12.1 to 27.6)	10.2 (0.6 to 19.8)	0.0386
Responder data at 12 weeks	12/87 12.9 (7.6 to 21.3)	16/89 16.4 (10.3 to 25.1)	3.5 (–6.5 to 14.0)	0.4959
Global relief of symptoms response				
Responder data for 2/4 weeks	17/85 19.4 (12.6 to 28.5)	22/88 24.3 (16.7 to 33.9)	4.9 (–6.9 to 16.7)	0.4164
Responder data for 3/6 weeks	11/87 12.8 (7.4 to 21.0)	18/87 20.2 (13.2 to 29.6)	7.5 (–3.3 to 18.2)	0.1748
Responder data at 12 weeks	14/86 16.6 (10.2 to 25.7)	16/86 17.9 (11.3 to 27.1)	1.3 (–9.7 to 12.3)	0.7523
Abdominal pain intensity response				
Responder data for 2/4 weeks	32/86 38.1 (28.9 to 48.3)	48/92 51.2 (41.2 to 61.2)	13.1 (–1.2 to 27.4)	0.0740
Responder data for 3/6 weeks	28/85 34.0 (25.2 to 44.0)	46/92 49.0 (39.0 to 59.0)	15.0 (1.0 to 29.0)	0.0378
Responder data at 12 weeks	31/85 37.8 (28.5 to 48.0)	42/89 45.5 (35.6 to 55.7)	7.7 (–6.7 to 22.0)	0.2966
Stool consistency response (IBS-D population)				
Responder data for 6/12 weeks	17/60 25.9 (16.9 to 37.7)	18/59 27.8 (18.4 to 39.7)	1.9 (–13.3 to 17.1)	0.8046
Responder data for 2/4 weeks	24/60 37.2 (26.3 to 49.5)	23/60 35.9 (25.2 to 48.1)	–1.3 (–18.0 to 15.4)	0.8315
Responder data for 3/6 weeks	21/60 32.2 (22.1 to 44.4)	23/59 36.0 (25.3 to 48.2)	3.7 (–12.7 to 20.1)	0.6510
Responder data at 12 weeks	21/60 32.8 (22.7 to 44.9)	17/58 28.1 (18.6 to 40.2)	–4.7 (–20.7 to 11.3)	0.5652
Stool consistency and abdominal pain intensity response (IBS-D population)				
Responder data for 6/12 weeks	4/60 7.1 (3.0 to 15.9)	10/61 15.4 (8.6 to 26.1)	8.3 (–2.5 to 19.0)	0.1309
Responder data for 2/4 weeks	10/60 16.0 (9.1 to 26.6)	16/61 24.7 (15.8 to 36.5)	8.7 (–5.0 to 22.4)	0.2147
Responder data for 3/6 weeks	8/60 13.0 (6.9 to 23.1)	12/60 20.0 (12.1 to 31.3)	7.0 (–5.6 to 19.6)	0.2771
Responder data at 12 weeks	11/60 17.5 (10.2 to 28.3)	13/59 21.7 (13.3 to 33.2)	4.1 (–9.5 to 17.7)	0.5502

Data per group are reported as number of responders (n) per total number of those from whom data was collected (N) and the estimated response rate (%) with associated 95% CI. Response rates, (RD, with 95% CI) and p values were determined using multiple imputation with 100 imputations to account for missing data. The p value was obtained using a $\chi 2$ test.
FAS, full-analysis set; IBS, irritable bowel syndrome.

the ebastine group. Protocol violations were more common in the placebo group (placebo n=21, ebastine n=12) (figure 1B).

Primary efficacy endpoints

We first evaluated the effect of treatment on the proportion of clinical responders with improvement of both global symptoms (GRS responders) and abdominal pain (API responders) for at least 6 of the 12 treatment weeks. In the FAS, significantly more subjects in the ebastine group (12.0%) were identified as clinical responders[6/12] compared with the placebo group (4.3%; p=0.047; table 2, figure 2A), resulting in a RD of ebastine versus placebo of 7.7% (95% CI 0.2% to 15.2%). In the PPS, 11.2% of patients treated with ebastine were clinical responders[6/12], whereas the placebo group only had a responder rate of 3.8%, the difference between groups was, however, not statistically significant (p=0.068; table 2).

Given statistical evidence for a treatment effect in the first primary endpoint, rates of GRS responders and API responders were evaluated separately, as stipulated by EMA. In the FAS, 36.6% of patients in the ebastine group were API responders[6/12] compared with 24.8% in the placebo group (p=0.081; table 2, figure 2C), resulting in an RD of 11.8% (95% CI −1.4% to 24.9%). Concerning GRS, analyses in the FAS revealed higher GRS responder[6/12] rates for ebastine compared with placebo, although this difference was not statistically significant (15.1% vs 6.9%; p=0.072; table 2, figure 2E, RD=8.2% with 95% CI −0.7 to 17.1). Similar results were seen in the PPS (table 2).

As shown in figure 2B, the weekly proportion of clinical responders increased with time in the ebastine group reaching a plateau by week 6. After 6 weeks of treatment, 15.7% of patients treated with ebastine had both at least considerable relief and a reduction of 30% or more in abdominal pain compared with 5.7% in the placebo group. In contrast, the proportion of weekly clinical responders in the placebo group has a biphasic morphology, dropping to 2.7% in week 8 but increasing again after visit 3 towards the end of the treatment period. As shown in figure 2D,F, the proportion of weekly responders for API and GRS also gradually increased in the ebastine group until it stabilised after 6 weeks of treatment, while a biphasic response was again observed in the placebo-treated group. Moreover, ebastine had a significantly greater effect on the decrease in abdominal pain during the treatment period compared with placebo (p=0.037, figure 3A).

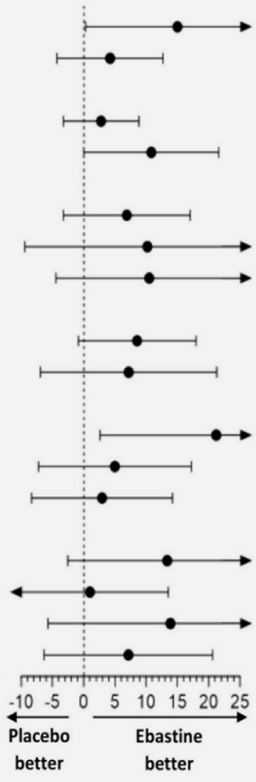
Secondary efficacy endpoints

Of the 202 patients included, 132 patients were classified as IBS-D. In this patient cohort, we evaluated the effect of treatment on stool consistency. Ebastine treatment did not affect response rates for stool consistency when compared with placebo, irrespective of the number of weeks used in the responder definition (table 3 and online supplemental table S1). Additionally, no significant treatment effect was observed with ebastine on the number of days with loose stools per week compared with placebo (figure 3B).

Moreover, we assessed the treatment effect on quality of life using the SF-36, and on anxiety and depression with the HADS questionnaire that was filled in before and after the treatment period. As shown in figure 3C,D, no significant differences were observed between the ebastine and placebo groups.

Table 4 Subgroup analysis part 1 (FAS): responder rates for 6 or more of the 12 treatment weeks per subgroup for clinical response

	Placebo	Ebastine	Risk difference (RD)		Interaction
Subgroup	n/N (proportion %)		RD (95% CI)		P value
Gender					0.3462
Male	1/25 (3.3)	6/30 (18.3)	15.0 (0.3 to 29.7)		
Female	3/62 (4.7)	6/62 (8.9)	4.2 (–4.3 to 12.7)		
IBS subtype					
Non-IBS-D	0/26 (0.2)	1/31 (3.0)	2.8 (–3.3 to 8.8)		
IBS-D	4/61 (6.1)	11/61 (16.9)	10.8 (0.0 to 21.6)		
HADS anxiety score					0.7114
None	1/32 (3.1)	5/47 (10.0)	6.9 (–3.3 to 17.1)		
Possible	2/29 (6.7)	3/17 (16.9)	10.2 (–9.4 to 29.8)		
Probable	1/23 (3.8)	4/25 (14.3)	10.5 (–4.4 to 25.4)		
HADS depression score					0.9146
None	3/62 (4.5)	9/65 (13.1)	8.6 (–0.9 to 17.9)		
Possible and probable	1/23 (4.0)	3/24 (11.1)	7.2 (–6.9 to 21.3)		
PHQ15: somatic symptom severity					0.0895
Minimal and low	0/15 (0.1)	4/17 (21.3)	21.2 (2.6 to 39.8)		
Medium	2/34 (5.5)	4/36 (10.5)	5.0 (–7.3 to 17.2)		
High	2/34 (5.2)	3/34 (8.1)	2.9 (–8.4 to 14.2)		
PHQ9: depression severity					0.2177
None and minimal	1/21 (4.0)	5/28 (17.4)	13.3 (–2.5 to 29.2)		
Mild	2/32 (6.2)	2/26 (7.1)	1.0 (–11.6 to 13.5)		
Moderate	1/24 (3.8)	3/15 (17.7)	13.9 (–5.7 to 33.5)		
Moderate to severe and severe	0/5 (0.0)	1/13 (7.1)	7.1 (–6.4 to 20.6)		



Data per group are reported as number of responders (n) per total number of those from whom data were collected (N) and the estimated response rate (%). Response rates, (RD, with 95% CI) and p values were determined using multiple imputation techniques with 100 imputations to account for missing data. The interaction p value was obtained using a logistic regression that included factors for treatment, subgroup and their interaction.
FAS, full-analysis set; HADS, Hospital Anxiety and Depression Scale; PHQ, Patient Health Questionnaire 9.

Additional post hoc endpoints

Based on our previous pilot trial showing a maximal effect of ebastine in the last weeks of treatment, an additional analysis was performed focusing on the last 4 weeks and the last week of treatment. For the FAS, there was a higher proportion of clinical responders[2/4], GRS responders[2/4] and API responders[2/4] in the ebastine group compared with the placebo group, although this did not reach statistical significance (table 3). In the PPS, the proportion of API responders[2/4] was significantly greater in the ebastine arm compared with the placebo arm (52.0% vs 36.5%; p=0.044; online supplemental table S1). No differences were observed between placebo and ebastine at week 12 (table 3 and online supplemental table S1).

Subgroup analyses and interactions

Subgroups were defined prior to unblinding to determine the effect of ebastine on clinical response[6/12] (table 4), GRS response[6/12] (table 5), and API response[6/12] (table 6). Of interest, significant interactions were found between treatment and HADS (p=0.021) and PHQ9 depression severity (p=0.009) for API response[6/12] (table 6). Moreover, the effect of ebastine tended to be larger in men than in women for clinical response[6/12] (RD in men: 15.0% (95% CI 0.3% to 29.7%) vs 4.1% (95% CI −4.3% to 12.7%) in women; table 4) as well as for API response[6/12] (RD in men 23.9% (95% CI 0.6% to 47.2%) vs 6.0% (95% CI −9.7% to 21.8%) in women; table 6) and GRS response[6/12] (RD in men 15.0% (95% CI −0.3% to 30.3%) vs 5.1% (95% CI −5.8% to 15.9%) in women; table 5) compared with placebo.

Exploratory efficacy outcomes

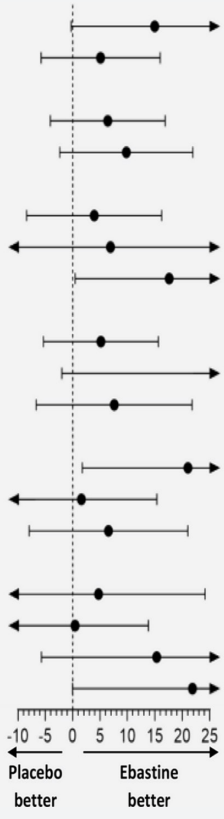
Due to the late onset of the treatment effect, an additional exploratory postunblinding analysis was performed to determine the response rates in the last 6 weeks of treatment ('[3/6]'). In the FAS, treatment with ebastine resulted in a significant increase in the proportion of clinical responders[3/6] compared with placebo (18.7% vs 8.5%; p=0.039; table 3). Also, the API response rate[3/6] was significantly higher in the ebastine group versus the placebo group (49.0% vs 34.0%; p=0.038; table 3). No significant differences were observed for GRS responders[3/6]. In the IBS-D subpopulation, stool consistency was not significantly affected by ebastine compared with placebo. Responder rates[3/6] in the PPS were comparable to those in the FAS for both treatment arms (online supplemental table S1).

Safety data

Similar proportions of patients reported at least one adverse event (AE) that was considered possibly or probably related to the allocated treatment in the placebo group compared with the ebastine group (25% vs 20%). The most common reported AEs were upper respiratory tract infections (placebo: n=9, ebastine: n=6), headache (placebo: n=7, ebastine: n=3), abdominal pain

Table 5 Subgroup analysis part 2 (FAS): responder rates for 6 or more of the 12 treatment weeks per subgroup for GRS Response

	Placebo	Ebastine	Risk difference (RD)	Interaction
Subgroup	n/N (proportion %)		RD (95% CI)	P value
Gender				0.2832
Male	1/25 (3.8)	6/30 (18.8)	15.0 (–0.3 to 30.3)	
Female	5/62 (8.2)	8/61 (13.3)	5.1 (–5.8 to 15.9)	
IBS subtype				0.3908
Non-IBS-D	0/26 (0.9)	2/31 (7.3)	6.4 (–4.1 to 16.9)	
IBS-D	6/61 (9.6)	12/60 (19.4)	9.8 (–2.4 to 21.9)	
HADS anxiety score				0.2421
None	2/33 (6.9)	5/47 (10.8)	3.9 (–8.4 to 16.2)	
Possible	3/28 (10.3)	3/17 (17.2)	6.9 (–13.9 to 27.7)	
Probable	1/23 (4.0)	6/25 (21.6)	17.6 (0.5 to 34.7)	
HADS depression score				0.1671
None	5/62 (8.2)	9/65 (13.3)	5.1 (–5.4 to 15.6)	
Possible	1/15 (6.1)	4/12 (33.0)	26.9 (–2.0 to 55.8)	
Probable	0/8 (0.0)	1/12 (7.6)	7.6 (–6.7 to 21.8)	
PHQ15: somatic symptom severity				0.0771
Minimal and low	0/15 (0.5)	4/17 (21.5)	21.0 (1.7 to 40.3)	
Medium	3/34 (9.2)	4/36 (10.8)	1.6 (–12.2 to 15.4)	
High	3/34 (7.9)	5/34 (14.5)	6.5 (–7.9 to 21.0)	
PHQ9: depression severity				0.1019
None and minimal	3/21 (12.8)	5/28 (17.6)	4.7 (–14.7 to 24.2)	
Mild	2/32 (7.1)	2/26 (7.5)	0.4 (–13.0 to 13.8)	
Moderate	1/24 (4.0)	3/15 (19.4)	15.3 (–5.7 to 36.3)	
Moderate to severe and severe	0/5 (0.0)	3/13 (21.9)	1.9 (0.0 to 43.8)	



Data per group are reported as number of responders (n) per total number of those from whom data was collected (N) and the estimated response rate (%). Response rates, (RD, with 95% CI) and p values were determined using multiple imputation techniques with 100 imputations to account for missing data. The interaction p value was obtained using a logistic regression that included factors for treatment, subgroup and their interaction.
GRS, Global Relief of Symptoms; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; PHQ, Patient Health Questionnaire.

(placebo: n=2, ebastine: n=7) and allergic reactions (placebo: n=5, ebastine: n=4) (table 7). No serious adverse events were reported.

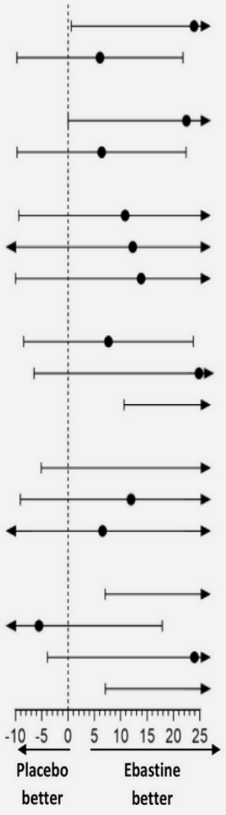
DISCUSSION

IBS causes substantial impairment of the patient's quality of life, affects mental health and work productivity and increases the use of healthcare resources.[1 22] To date, treatment of IBS mainly improves stool pattern but leaves abdominal pain largely unaffected, underscoring the unmet clinical need for novel medical strategies targeting pain signalling. In this study, we evaluated the effect of ebastine on abdominal pain, global symptom relief, stool consistency and quality of life in 202 patients with non-constipated IBS. We show that ebastine treatment significantly increases the proportion of patients with a clinical response$^{6/12}$ and results in more API and GRS responders$^{6/12}$ compared with placebo, although the latter difference was not statistically significant. Moreover, ebastine had a significant treatment effect on the weekly abdominal pain scores compared with placebo, but not on stool consistency and quality of life, suggesting an effect on visceral sensitivity. Taken together, this phase 2b study shows that ebastine is superior to placebo, indicating that selective targeting of H1R should be considered as a novel treatment for patients with non-constipated IBS.

The first-line clinical management of patients suffering from IBS consists of conservative measures such as dietary and lifestyle advice and avoiding symptom triggers, combined with a pharmacological treatment based on the predominant symptom or defaecation pattern.[23] Ideally, however, the choice of treatment should be based on pathophysiology and biomarkers with the ultimate goal to increase treatment efficacy over that seen in this and previous trials and reduce the number needed to treat.[24] Previously, we demonstrated histamine-mediated sensitisation of visceral afferents and improvement of pain responses to colorectal distention by H1R blockade in two murine models of visceral hypersensitivity.[8 12 13] Based on these findings, we next designed a proof-of-concept pilot study in which we showed improvement of visceral hypersensitivity and reduction of abdominal symptoms and abdominal pain following treatment with the H1R antagonist ebastine. Here, we confirm the therapeutic effect of ebastine in non-constipated patients with IBS in a randomised, placebo-controlled, multicentre phase 2b clinical trial. Using a composite endpoint, we show that the percentage of patients with a clinical response$^{6/12}$, defined as improvement of both global symptoms and abdominal pain in 6 or more of the 12 treatment weeks, was significantly higher in the ebastine-treated group (12%) compared with the placebo-treated group (4%). In contrast to previous clinical trials using composite endpoints, these numbers are considerably lower compared

Table 6 Subgroup analysis part 3 (FAS): responder rates for 6 or more of the 12 treatment weeks per subgroup for API response

	Placebo	Ebastine	Risk difference (RD)		Interaction
Subgroup	n/N (proportion %)		RD (95% CI)		P value
Gender					0.2347
Male	5/25 (20.7)	14/30 (44.6)	23.9 (0.6 to 47.2)		
Female	15/60 (26.7)	20/62 (32.7)	6.0 (–9.7 to 21.8)		
IBS subtype					0.2549
Non-IBS-D	4/26 (19.0)	13/31 (41.4)	22.5 (0.0 to 44.9)		
IBS-D	16/59 (27.5)	21/61 (33.9)	6.4 (–9.7 to 22.4)		
HADS anxiety score					0.6890
None	10/32 (29.0)	19/47 (39.8)	10.8 (–9.4 to 31.0)		
Possible	5/28 (18.3)	5/17 (30.6)	12.3 (–14.0 to 38.5)		
Probable	4/22 (22.9)	9/25 (36.7)	13.8 (–10.9 to 38.5)		
HADS depression score					0.0211
None	18/60 (29.7)	25/65 (37.3)	7.7 (–8.5 to 23.8)		
Possible	1/15 (11.2)	4/12 (36.0)	24.8 (–6.5 to 56.1)		
Probable	0/8 (0.0)	4/12 (37.4)	37.4 (10.6 to 64.1)		
PHQ15: somatic symptom severity					0.3498
Minimal and low	3/15 (21.8)	8/17 (48.3)	26.5 (–5.1 to 58.1)		
Medium	9/33 (25.6)	14/36 (37.5)	11.9 (–9.1 to 32.9)		
High	6/33 (21.1)	9/34 (27.6)	6.5 (–13.4 to 26.5)		
PHQ9: depression severity					0.0085
None and minimal	4/20 (18.5)	14/28 (50.0)	31.5 (7.0 to 56.0)		
Mild	11/32 (33.7)	7/26 (28.2)	–5.5 (–28.9 to 17.9)		
Moderate	2/23 (15.3)	6/15 (39.3)	24.0 (–3.9 to 51.9)		
Moderate to severe an severe	0/5 (0.0)	4/13 (32.5)	32.5 (7.0 to 58.0)		



Data per group are reported as number of responders (n) per total number of those from whom data was collected (N) and the estimated response rate (%). Response rates, (RD, with 95% CI) and p values were determined using multiple imputation techniques with 100 imputations to account for missing data. The interaction p value was obtained using a logistic regression that included factors for treatment, subgroup and their interaction.
API, abdominal pain intensity; FAS, full-analysis set; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; PHQ, Patient Health Questionnaire.

with those reported for example for eluxadoline (25%) or linaclotide (34%).[25 26] One potential explanation is the slow onset of response to ebastine treatment, gradually increasing to reach a plateau by week 6 (figure 2). Limiting the responder analysis to the last 6 weeks of treatment indeed reveals higher clinical responder rates of 19% for ebastine compared with 8% for placebo. Notably, also the placebo response is considerably lower compared with previous IBS clinical trials. A meta-analysis even reported a pooled placebo response of 37% in the 73 randomised clinical trials evaluated.[27] Although we have no explanation for the low placebo response, the fact that there was only a single trial visit planned during the entire treatment period may have contributed. The placebo response indeed increased considerably in the weeks following this visit, suggesting that limiting the number of visits might be important to reduce the placebo response.

Separate analysis of GRSs and API, as advised by EMA, revealed a reduction in the GRS and API responder rates, although not statistically significant. Of interest, 37% of patients treated with ebastine had a 30% reduction in abdominal pain score during 6 of the 12 weeks, compared with 25% of patients treated with placebo. Similar to the clinical response rate, the proportion of API responders to ebastine treatment gradually increased with the duration of treatment. As a result, the proportion of API responders[3/6] increased to 49% during the last 6 weeks of ebastine treatment, which was significantly higher than placebo (34%). In line with this observation, the average weekly pain scores were significantly lowered by ebastine compared with placebo, further supporting the visceral analgesic effect of H1 receptor antagonism. We can only speculate on the slow kinetics of abdominal pain and global symptom improvement. Of interest, central sensitisation with phenotypical alterations of neurons in the dorsal root ganglia has been demonstrated in a murine chronic model of visceral hypersensitivity.[28] To what extent normalisation of nociceptor function and thus pain signalling in response to H1R treatment is a slow process remains an interesting topic to further investigate. Irrespective, our data indicate that ebastine effectively reduces abdominal pain scores in a subpopulation of non-constipated patients with IBS and provides evidence that treatment should be maintained for at least 6–8 weeks.

As indicated earlier, abdominal pain remains difficult to treat in the majority of patients with IBS. Antispasmodics are currently the recommended treatment of choice for patients with IBS with abdominal pain, although strong evidence supporting global improvement of IBS symptoms is lacking.[29] More recently approved drugs targeting abdominal pain include linaclotide and lubiprostone for IBS-C, and alosetron, ramosetron and eluxadoline for IBS-D, although only linaclotide is still available in the EU. The therapeutic gain with respect to the responder rates for API for ebastine (12%) is comparable to linaclotide (15%) and ramosetron (8%–14%), but higher than those reported for eluxadoline (4%).[25 30 31] Accordingly, based on our study, ebastine

Table 7 Adverse events (AEs) possibly or probably related to treatment

Adverse events	Placebo (n=101)	Ebastine (n=101)
Upper respiratory tract infection	9 (2 s, 3 mo, 4 m)	6 (1 s, 3 mo, 2 m)
Headache	7 (2 s, 3 mo, 2 m)	3 (2 s, 1 mo)
Allergic reaction*	5 (2 s, 3 m)	4 (1 s, 3 m)
Dry eyes	3 (1 mo, 2 m)	0
Abdominal pain	2 (1 mo, 1 m)	7 (4 s, 2 mo, 1 m)
Gastroenteritis	2 (1 s, 1 mo)	3 (2 s, 1 mo)
Cystitis	2 (2 m)	1 (1 m)
Nausea	1 (1 m)	4 (3 s, 1 m)
Constipation	1 (1 mo)	2 (1 mo, 1 m)
Reflux	1 (1 m)	1 (1 m)
Dry mouth	1 (1 m)	1 (1 m)
Change in taste perception	1 (1 m)	1 (1 m)
Haemorrhoids	1 (1 m)	1 (1 mo)
Fatigue	0	4 (2 mo, 2 m)
Vomiting	0	2 (2 m)

AEs are listed in descending order of frequency in the placebo group and were reported in two or more cases in either treatment group. AEs with missing causality are included as being related, AEs with missing severity are included as being severe.
*Allergic reaction included skin rash, itching skin or eyes, sneezing and swelling of the throat.
m, mild; mo, moderate; s, severe.

should be considered as a potential new treatment for patients with non-constipated IBS. Of interest, preliminary results of an open-label study evaluating the effect of 40 mg ebastine show a further increase in responder rates (unpublished data). To confirm this observation, a new clinical study evaluating 40 mg ebastine in non-constipated patients with IBS is ongoing.

A recent meta-analysis of 12 randomised trials showed that the female gender is mostly associated with improved outcome.[32] Our subgroup analysis, however, revealed that the treatment effect of ebastine tended to be larger in males than females for the three primary endpoints. It must be noted though that the interaction between gender and responder rates was not significant and the number of male participants was relatively small per subgroup (placebo n=25, ebastine n=30). Of interest, a recent study evaluating the effect of amitriptyline in primary care also revealed improved treatment outcome in men.[33] Additionally, we identified depression to be significantly associated with an increased API response rate, a finding that was detected independent of the questionnaire used (HADS or PHQ9). Patients with no or minimal depression on the PHQ9 questionnaire were more likely to respond to ebastine than to placebo (50% vs 19%, respectively), arguing against a centrally central mediated mechanism of action of ebastine. Of interest, Ford *et al* recently reported a larger treatment effect of amitriptyline in patients with a lower baseline HADS-anxiety score, although not significant.[33] Very few studies report depression severity at baseline for randomised trials in patients with IBS and only three studies have used this information for a subgroup analysis.[34–39] All failed to detect an association between psychological symptoms at baseline and treatment outcome.[33 35 39]

Ebastine was introduced in 1990 as treatment of urticaria and allergic rhinitis and has proven good overall safety and tolerability over the past 30 years.[14] The most common reported AEs for ebastine were headache (8%), drowsiness (3%) and dry mouth (2%).[14] In the current trial, abdominal pain (7%), upper respiratory tract infections (6%) and fatigue (4%) were in the top three of most reported AEs. Headache was also reported by 3% of patients in the ebastine arm, but slightly more common in the placebo group (7%). Dry mouth was reported by 1% of patients in both treatment arms. Overall, we can conclude that ebastine has a favourable safety profile. Also the cost of ebastine is favourable, as this is only €0.15 on average in Belgium, thirteen times less than linaclotide.

One of the strengths of our study is the use of strict criteria to define clinical success as advised by the FDA and EMA. Moreover, symptoms and quality of life were assessed using validated questionnaires and detailed statistical analyses were performed to identify subgroups or characteristics associated with treatment response. A weakness of the study is the biphasic placebo response interfering with data interpretation, but this observation is in line with the well-known waxing and waning of symptoms reported by patients with IBS.

In conclusion, our study shows that ebastine is well tolerated and superior to placebo in non-constipated IBS indicating that peripheral H1R antagonism is a potential new treatment for IBS.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this study was approved by the 'Ethische Commissie Onderzoek UZ/KU Leuven', S55485. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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