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Efficacy and tolerability of linaclotide in the treatment of irritable bowel syndrome with constipation in a real-world setting: The Alpine study

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2 LINACLOTIDE ALPINE RWE: MANUSCRIPT

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TITLE PAGE

Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with Constipation in a Real-World Setting: The Alpine study

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Running Title: Linaclotide in IBS-C – The Alpine study

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ABSTRACT

Objectives: The efficacy and safety of linaclotide, a minimally-absorbed guanylate cyclase-C agonist approved for the treatment of moderate-to-severe irritable bowel syndrome with constipation (IBS-C) in adults, has been established in clinical trial settings. Herein, we evaluated the effectiveness and tolerability of linaclotide in routine clinical practice in Austria and Switzerland.

Setting and Measures: This was a multi-center, non-interventional study in adults aged ≥18 years with moderate-to-severe IBS-C, conducted between December 2013 and November 2015 across 31 primary, secondary, and tertiary centers in Austria and Switzerland. Linaclotide treatment decision was at the physician's discretion. Data was collected over two visits in Austria (weeks 0 and 4) and three visits in Switzerland (weeks 0, 4, and 16). Treatment-related adverse events were recorded.

Results: The study enrolled 138 patients with a mean age of 50 years, >75% of whom were female. 128 patients completed the study. Improvements in IBS-C symptoms were observed following a 4-week treatment period, with the mean intensity score of abdominal pain reducing to 2.7 from a baseline score of 5.8, while the bloating intensity score reduced to 3.1 from a baseline score of 5.8 (both indices p<0.001;11-point numeric rating scale [0=no to 10=worst possible pain or bloating]). Moreover, the frequency of mean weekly bowel movements

increased from 2.1 at baseline to 4.5 at week 4 (p<0.001). Global effectiveness and tolerability of linaclotide were assessed as good or excellent in >70% patients by the treating physicians. In total, 31 adverse events were reported in 22 patients, the most common being diarrhoea, reported by 6 (7%) and 8 (15.4%) patients in Austria and Switzerland, respectively.

Conclusions: Linaclotide was effective in treating moderate-to-severe symptoms in routine clinical practice of this IBS-C patient population. Linaclotide was safe and well tolerated and no new safety concerns were raised, confirming results from previous clinical trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first real-world study evaluating the effectiveness and tolerability of an IBS-C treatment in the Alpine region
- This study sought to evaluate whether the efficacy and tolerability of linaclotide that was demonstrated in randomized clinical trials could be recapitulated in clinical practice in a real-world setting
- Results from the physicians' global assessment of efficacy and tolerability will be useful in determining physician comfort level with prescribing linaclotide for their patients
- This was a non-interventional study that lacked a placebo control; thus, the statistical analyses are descriptive and exploratory in nature

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain or discomfort and change in bowel habits [1]. IBS is a common GI ailment, with global prevalence ranging from 3-21% depending on the diagnostic criteria [2]. The prevalence of IBS in Europe is estimated at 12-15% [3]. IBS is subtyped based on the predominant stool pattern, and includes IBS subtype with constipation (IBS-C), diarrhea (IBS-D), mixed stool (IBS-M), or unsubtyped (IBS-U) when stool consistency does not meet criteria for IBS-C, -D, or -M [4]. Of the IBS subtypes, IBS-C is the second most common subtype, comprising approximately 35% of all IBS cases [3].

In addition to abdominal pain and discomfort, patients with IBS-C often experience hard or lumpy stools, straining, feeling of incomplete evacuation, and bloating. Moreover, IBS-C has an undue impact on quality of life, increases healthcare costs, and reduces work productivity [5, 6]. Since IBS-C presents with a constellation of symptoms, therapy options have centered on symptom relief and have generally included dietary and lifestyle modifications, and over-the-counter medications such as fibre supplements and laxatives that aim to relieve constipation. However, these treatments are often ineffective and patients resort to additional therapies, which in turn, drive up healthcare costs and resources, thus underscoring the need to identify efficacious treatment options for IBS-C [7].

Linaclotide is a minimally absorbed, 14-amino acid, guanylate cyclase C (GC-C) receptor agonist structurally related to the guanylin peptide family [8]. Upon binding to GC-C receptors, linaclotide increases the intracellular production of cyclic guanosine monophosphate (cGMP), which in turn activates the cystic fibrosis transmembrane conductance regulator (CFTR) resulting in secretion of chloride and bicarbonate into the intestinal lumen, ultimately accelerating intestinal transit [9]. Linaclotide was demonstrated to increase colonic transit and reduce abdominal pain and constipation in patients with IBS-C in Phase 2 trials [10, 11].

Subsequently, the efficacy and safety of linaclotide for the treatment of IBS-C was established in two placebo-controlled Phase 3 trials that showed improvements in IBS-C symptoms, including abdominal pain and bowel movements [8, 12].

Linaclotide was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C [13, 14]. While the efficacy and safety of linaclotide has been established in clinical trial settings, these may not depict real-life experiences. To address this need, observational studies were undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in Europe. In routine clinical practice, linaclotide has recently been shown to be effective in improving IBS-C symptoms in a post-marketing authorization study conducted in Germany [15]. Herein, we aimed to document the effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C in adults under real-life conditions in the Alpine region of Austria and Switzerland.

METHODS

Study Design

This was a multi-center, non-interventional study evaluating the effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C in adult patients under real-life routine clinical practice conditions in Austria and Switzerland. A total of 200 subjects were planned for enrollment across 40 sites in each country. The study was conducted from December 2013 to March 2015 in Austria and from November 2014 to November 2015 in Switzerland.

The study comprised a 4-week treatment period commencing with visit 1 at treatment initiation and visit 2 occurring approximately 4 weeks after initiation in Austria. In Switzerland, data were collected over the course of three visits, at 0, 4, and 16 weeks after treatment initiation. Linaclotide was administered per the usual therapeutic procedure of the attending physician and in accordance with the indication for the drug (290 µg once daily, taken at least 30 minutes before meals) [14].

The study protocols were approved by local Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each center (study approval numbers: Austria, 26-279 ex 13/14; Switzerland, KEK-ZH-Nr.2014-0137). The study was conducted in accordance with the Declaration of Helsinki, applicable local laws and regulations, and International Conference on Harmonisation E6 Good Clinical Practice guidelines. All participants provided written informed consent prior to study initiation.

Participants

Eligible patients were aged ≥18 years with a diagnosis of moderate-to-severe IBS-C, characterised by clinical evidence of relevant interference of symptoms with well-being and/or daily routines at work or during leisure. The decision to treat a patient with linaclotide was taken solely by the treating physician prior to inclusion in the study. Subjects with known hypersensitivity to the active ingredient or any other component of linaclotide, suspected or

known gastrointestinal obstruction, or who were pregnant or planning to become pregnant were excluded from the study.

Study Assessments

All relevant data collected during routine treatment with linaclotide were recorded in case report forms (CRFs). Patient demographics and medical history were collected, including diagnosis, prior treatment and symptoms of IBS-C, comorbidities, and concomitant medications.

The primary effectiveness endpoints included severity of abdominal pain and bloating measured using an 11-point numeric rating scale (NRS), frequency of bowel movements during the week before each visit, general symptom improvement relative to pre-treatment, satisfaction with linaclotide therapy, sensation of incomplete bowel evacuation, change of predominant stool consistency, and physicians' global assessment of the effectiveness of linaclotide.

Adverse events (AEs) related to linaclotide treatment or whose relation to linaclotide treatment could not be excluded were documented. AEs assessed by the physician as not related to linaclotide treatment were not documented. Other safety measures included physicians' global assessment of the tolerability of linaclotide.

Statistical Analyses

Statistical analysis was performed using SAS™ v9.4 software (SAS Institute, Cary, NC). Data was analyzed using descriptive statistics and no hypotheses were pre-specified. To determine whether the pre–post changes of symptoms were statistically significant, the Wilcoxon Signed-Rank Test was applied. Reported *p*-values are two-tailed, using an alpha level of 0.05 to assess statistical significance. Missing data was imputed using the last observation carried forward (LOCF) method. Visit 1 and 2 efficacy data was compiled for both countries, where applicable.

RESULTS

Patient characteristics

A total of 86 patients in 22 sites and 52 patients in 9 sites were respectively enrolled in Austria and Switzerland. Baseline characteristics were generally comparable between the two countries. Of the enrolled patients, 71 (82.6%) in Austria and 40 (76.9%) were female, and the mean age was 51 and 49 years, respectively (**Table 1**). The mean BMI was 24 kg/m^2 and 23 kg/m^2 in each country. The average time since IBS-C diagnosis for patients in Austria was 2.1 years and 5.2 years for patients in Switzerland. At baseline, more than 90% of patients in both countries reported abdominal pain (mean intensity 6 and 5.4, respectively) and bloating (mean intensity 5.8 and 5.6, respectively). Patients in both countries reported a mean of 2.1 number of bowel movements per week. Prior treatment for IBS-C was reported by 73 (84.9%) patients in Austria and 49 (94.2%) patients in Switzerland, mainly consisting of laxatives and dietary fibres, while 33 (38.4%) patients in Austria and 16 (30.8%) patients in Switzerland received concurrent IBS-treatment. Concomitant diseases were reported by 35 (40.7%) patients in Austria and 10 (19.2%) patients in Switzerland (**Table 1**). Collectively, baseline characteristics of the IBS-C patients in this study were reflective of the general IBS patient population (i.e., approximately 70% of IBS patients are typically female, with high likelihood of majority of patients being 50 years of age or younger).

Over the course of the study, 20 (23.3 %) subjects in Austria and 17 (32.7%) subjects in Switzerland discontinued linaclotide treatment, with the main reason for discontinuation being lack of effectiveness for 13 (15.1%) patients in Austria and adverse events in Switzerland reported in 10 (19.2%) patients. Reasons for treatment discontinuation are summarized in **Table 2**.

Effectiveness outcomes

Effect of linaclotide treatment on symptoms of IBS-C

Linaclotide was administered over 4 weeks in Austria and 16 weeks in Switzerland, and data from the initial 4-week treatment periods is compiled in this analysis. Improvements in abdominal pain, bloating, and bowel movement were observed after 4 weeks of treatment with linaclotide. From a mean intensity score of 5.8 at baseline, abdominal pain reduced to 2.7 after 4 weeks of treatment in both countries (**Fig. 1A**; $p<0.001$ vs. visit 1;11-point NRS, [0=no pain to 10=worst possible pain). In Switzerland, continued reduction in abdominal pain was observed at week 16 with a mean intensity score of 2.5 (SD ±2.0; n=51; $p<0.0001$ vs. visit 1). Improvements in bloating were seen after 4 weeks of treatment in both countries; from a baseline mean intensity score of 5.8, the score reduced to 3.1 at week 4 (**Fig. 1B**; $p<0.001$ vs. visit 1;11-point NRS [0=no bloating to 10=worst possible bloating]), with a mean intensity score of 3.0 (SD ±2.2; n=51; $p<0.0001$ vs. visit 1) at week 16 in Switzerland. Furthermore, the frequency of bowel movements increased from a mean of 2.1 bowel movements per week at baseline to 4.5 at week 4 (**Fig. 1C**; $p<0.001$ vs. visit 1) in both countries, and to 4.7 (SD ±1.6; n=51; p<0.0001 vs. visit 1) at week 16 in Switzerland.

Data was stratified based on patients who received prior IBS-C treatment, and improvements in IBS-C symptoms were observed within the 4-week treatment period regardless of prior IBS-C treatment. Significant reductions from week 1 to week 4 in mean abdominal pain intensity and mean bloating intensity were seen in patients who had received laxative pre-treatment and in those who did not receive prior IBS-C treatment (**Fig. 2A** and **Fig. 2B**, respectively**;** all $p<0.001$ vs. visit 1). Similar degrees of mean reduction in abdominal pain were seen in patients who did not and those who received laxative pre-treatment (both 3.1), while a slightly greater mean reduction in bloating was seen in those who did not receive IBS-C pre-treatment compared to those who received laxative pre-treatment (2.6 and 3.1). Furthermore, the effect of concomitant laxative use with linaclotide was evaluated. Our results showed that significant reduction was achieved after 4 weeks of treatment in mean abdominal pain intensity (**Fig. 3A**; all $p<0.001$ vs.

visit 1) and mean bloating intensity (**Fig. 3B**; all $p<0.001$ vs. visit 1) both in patients who used laxative concomitantly with linaclotide and those who did not. A greater symptom improvement was observed in those who did not use concomitant treatment (mean reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9; **Fig. 3A** and **3B**; all differences $p<0.001$ vs. visit 1).

Patient assessment of improvement of IBS-C symptoms

At each respective end-of-treatment period, patients were asked to indicate their sense of general improvement of symptoms as compared to the pre-treatment period. In Austria, 74 patients (87.1%) reported overall improved symptoms, among which 56 (65.9%) patients experienced improvements in abdominal pain, 60 (70.6%) had improvements in bloating, and 65 (76.5%) reported improvements in constipation at visit 2 compared to baseline (**Fig. 4**). In Switzerland, 45 patients (88.2%) reported overall improved symptoms, consisting of 38 (74.5%) patients with improvements in abdominal pain, 35 (68.6%) with improvements in bloating, and 42 (82.4%) reporting improvements in constipation after 16 weeks of treatment compared to baseline (**Fig. 4**).

Physician assessment of satisfaction and effectiveness of linaclotide therapy

Physicians' satisfaction with linaclotide treatment was assessed on a scale from 0 (very satisfied) to 10 (totally unsatisfied). In Austria, mean satisfaction was 2.9 (SD±3.0; median 2.0) points after 4 weeks of treatment, indicative of "good satisfaction", with at least 60% of the 83 total patients rated by a score of ≤2.0 by their treating physicians. In Switzerland, mean satisfaction was 4.6 (SD±3.2; median 3.0) points after 16 weeks of treatment, indicative of "moderate satisfaction", with at least 50% of the 51 total patients rated with a score of ≤3.0 by their treating physicians (**Fig. 5A**). Furthermore, physicians assessed the global effectiveness of linaclotide treatment at the end of the treatment periods, and at visit 2, linaclotide

effectiveness was evaluated as "excellent" in 33 patients (38.4%), "good" in 30 patients (34.9%), "moderate" in 14 patients (16.3%), and "poor" in 9 patients (10.5%) in Austria. In Switzerland, physicians assessed linaclotide effectiveness as "excellent" in 18 patients (37.5%), "good" in 21 patients (43.8%), and "moderate" in 9 patients (18.8%), with the effectiveness not rated as "poor" in any patient after 16 weeks of treatment (**Fig. 5B**).

Physicians were also asked to indicate the rationale for initiating linaclotide treatment. In Austria, linaclotide was prescribed due to low efficacy of previous medication for 39 (45.4%) patients; for 3 (3.5%) patients, linaclotide was prescribed due to low tolerability of prior medication; and for 52 (60.5%) patients, linaclotide was a new prescription whose treatment rationale was not a consequence of any previous medication. In Switzerland, 31 (59.6%) patients were prescribed linaclotide due to low efficacy of previous medication, 3 (5.8%) patients were prescribed linaclotide due to low tolerability of prior medication, while 20 (38.5%) patients received linaclotide as a new IBS-C prescription and not due to any previous medication.

Use of concomitant medications

Concomitant medication use was reported in 31 (36.1%) and 13 (25.0%) patients in Austria and Switzerland, respectively, with the most common being antihypertensive renin-angiotensin system (RAS) agents in both countries, used by 7 (8.1%) patients in Austria and 6 (11.5%) patients in Switzerland. A summary of concomitant medication use by Anatomical Therapeutic Chemical (ATC) chemical classification system is presented in **Table 3**.

Safety and Tolerability

Summary of adverse events

A total of 16 AEs was reported for 10 (11.6%) patients in Austria after 4 weeks of treatment and 15 AEs for 12 (23.1%) patients in Switzerland after 16 weeks of treatment (**Table 4**). The most common AE was diarrhoea, which occurred in 6 (7.0%) and 8 (15.4%) patients in Austria and

Switzerland, respectively. 'Drug ineffectiveness' was reported as an AE for 5 (5.8%) patients in Austria and 2 (3.9%) patients in Switzerland. AEs leading to treatment discontinuation occurred in 8 (9.3%) patients in Austria and 10 (19.2%) in Switzerland (**Table 2**). The majority of AEs were mild or moderate in intensity, while severe AEs were reported in 2 patients (2 events [1 abdominal distension and 1 rectal tenesmus]; 2.3%) in Austria and 4 patients (5 events [4 diarrhoea and 1 urge incontinence]; 7.7%) in Switzerland. An AE was considered severe if the intensity of the symptoms significantly interfered with the patient's daily activities. Of all 31 reported AEs, treatment causality was confirmed for 11 AEs reported by 8 patients in Austria (9.3%) and 14 AEs reported by 12 patients in Switzerland (23.1%). No serious AEs (i.e., AEs that were life-threatening) were reported in either country over the respective 4-week or 16-week treatment period.

Physician assessment of linaclotide tolerability

Treating physicians assessed the global tolerability of linaclotide treatment, and after 4 weeks of treatment, linaclotide tolerability was evaluated as "excellent" in 44 patients (51.2%), "good" in 28 patients (32.6%), "moderate" in 11 patients (12.8%), and "poor" in 3 patients (3.5%) in Austria. In Switzerland, physicians assessed linaclotide tolerability as "excellent" in 24 patients (49.0%), "good" in 13 patients (26.5%), "moderate" in 7 patients (14.3%), and "poor" in 5 patients (10.2%) after 16 weeks of treatment (**Fig. 5C**).

DISCUSSION

In this non-interventional study (NIS), the effectiveness, safety, and tolerability of linaclotide were evaluated in patients with moderate-to-severe IBS-C under real-life settings in Austria and Switzerland. We observed improvements in abdominal pain, bloating, and frequency of bowel movements following a 4-week treatment period in both countries, which were further sustained over 12 additional weeks in Switzerland. Significant improvements in abdominal pain and bloating were observed in both patients who received prior laxative treatment and in those who did not receive IBS-C pre-treatment. However, between patients who administered laxative concomitant with linaclotide treatment and those who did not administer concomitant therapy, the degree of reduction after 4 weeks of treatment in mean intensity score in IBS-C symptoms suggests that concomitant laxative use diminished linaclotide effect. Importantly, treating physicians rated both the effectiveness and tolerability of linaclotide as good or excellent for a majority of patients. Few AEs were reported in this study, none of which were SAEs, and no new safety signals were observed throughout the study.

IBS is characterized by multiple symptoms; however, abdominal pain, which is challenging to treat, is the major clinical manifestation. Moreover, abdominal pain is highly correlated with IBS disease severity and higher economic burden [16-18]. In the present study, >90% of all patients reported abdominal pain at baseline with mean intensity scores of 6.0 in Austria and 5.4 in Switzerland. Collectively, the mean intensity of abdominal pain decreased from a baseline NRS level of 5.8 to 2.7 after 4 weeks of linaclotide treatment, corresponding to a 53% reduction in abdominal pain in both countries. In Austria, the reduction in mean abdominal pain intensity score was 3.5-points (57%) at 4 weeks, while a reduction of 2.2-points (41%) at 4 weeks and 2.9-points (53%) after 16 weeks was observed in Switzerland. In a recent NIS conducted in Germany, linaclotide treatment resulted in a reduction in mean pain intensity score of 1.72-points (35%) at 4 weeks and 2.5-points (50%) at 12 months after treatment initiation [15]. Data

from these European real-world studies demonstrate that improvements in abdominal pain are observed in linaclotide-treated patients within the first month of treatment initiation and are sustained throughout the respective treatment periods. Mechanistically, as a GC-C receptor agonist, linaclotide is believed to increase extracellular cGMP levels, which in turn reduces the firing of pain-sensing visceral afferent fibres, resulting in an analgesic effect, thus reducing abdominal pain [19].

In addition to improvements in abdominal pain, significant improvements in bloating were also observed following 4 weeks treatment with linaclotide. At baseline, >94% of all patients reported bloating, and an overall reduction of 2.8-points (47%) was observed after 4-week treatment in both countries, which was sustained after 16 weeks of treatment in Switzerland. Moreover, linaclotide treatment increased the mean frequency of bowel movements to 4.5 times a week from a mean of 2.1 at baseline in both countries. These observations are in line with previous animal studies that showed that linaclotide increases GI transit and fluid secretion via accumulation of intracellular cGMP in a dose-dependent manner [20].

At study initiation, >84% of patients in this study had received IBS-C pre-treatment, mainly comprising laxatives or dietary fibres. We found that linaclotide was effective in managing symptoms of patients regardless of prior treatment or concomitant medication use. In fact, our data found that a greater degree of improvement was observed in patients who did not use concomitant IBS-C treatment as compared to those who used concomitant laxatives (mean reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9), suggesting that laxatives might interfere with the efficacy of linaclotide. Laxatives such as polyethylene glycol (PEG) are often used a first-line therapy for IBS-C patients; however, their effect on improvements in abdominal pain or bloating are inconsistent and may lead to exacerbation of bloating, gas, and loose stools [21]. A recent consensus report recommended against the co-administration of linaclotide with laxatives especially at the beginning of treatment due to

potential diarrheal side effects, and only suggested co-administration in cases of partial response to linaclotide [2]. How concomitant laxatives may impact the efficacy of linaclotide is currently unclear. Osmotic laxatives may improve the frequency and consistency of bowel movements, but have no impact on abdominal pain or bloating; moreover, some stimulant laxatives (for which there are no RCTs in IBS-C) may relieve chronic constipation, but result in abdominal pain and cramping [1]. In real-life settings, some patients may choose to add laxative treatment based on the severity of constipation or water-binding agents may be titrated with linaclotide to gradually improve stool consistency; however, both of these strategies may inadvertently lessen the efficacy of linaclotide by binding excess fluids. Nonetheless, the present data demonstrates that linaclotide can effectively manage IBS-C symptoms irrespective of treatment history and does not require co-administration with other IBS-C medications, specifically laxatives.

The results of this study support the findings of two randomized clinical trial (RCT) Phase III studies that evaluated the efficacy and safety of linaclotide, which used the FDA's responder criteria of improvement of ≥30% from baseline in average daily worst abdominal pain (WAP) score and an increase of ≥1 complete spontaneous bowel movement (CSBM) per week. In the first double-blind, placebo-controlled 26-week study of 804 participants, 49% of patients treated with linaclotide exhibited ≥30% improvement in abdominal pain (corresponding to 2.1-point decrease) and 48% experienced an ≥1 increase in weekly CSBM (corresponding to 2.2-point decrease) for at least 6 of 12 treatment weeks [8]. Moreover, linaclotide treatment resulted in increases in spontaneous bowel movements (SBM) per week by 3.8 and CSBM per week by 2.2. In the second pivotal multicenter, double-blind, placebo-controlled study with 800 IBS-C patients treated over 12 weeks, linaclotide resulted in significant improvements in abdominal pain (1.9-point WAP improvement), bloating (1.9-point improvement), SBM per week (+3.9 frequency), and CSBM/week (+2.3 frequency) [12]. In both the RCTs and in the current NIS

setting, improvements in IBS-C symptoms were demonstrated for linaclotide immediately following therapy initiation, and sustained throughout treatment duration. Therefore, we can deduce that the NIS results under routine clinical settings in Europe, including those in the current study, are in agreement with the RCT findings from the US.

Global tolerability of linaclotide treatment was assessed as good or excellent in >75% patients by their treating physicians in both countries in the current study. Moreover, physician satisfaction with linaclotide therapy was evaluated on a 0-10 scale (very satisfied to totally unsatisfied), with a 2.9 score (good satisfaction) after 4 weeks in Austria and a 4.6 score (moderate satisfaction) after 16 weeks in Switzerland. In comparison, 45% and 52% of patients treated with linaclotide noted satisfaction with linaclotide in the two RCTs, while 62% of treating physicians rated the effectiveness of linaclotide as good or excellent in Germany in a recent NIS [8, 12, 15]. Previously, an 18-month long term safety study demonstrated similar patient satisfaction between linaclotide-treated patients who experienced diarrhea as compared to those who did not, and >85% reported moderate satisfaction during the treatment period, indicating high degree of treatment satisfaction irrespective of AEs [22].

Diarrhoea has previously been reported as a potential consequence of linaclotide-mediated increase in GI transit and fluid secretion, and as such, diarrhea was the most common reported AE during this study (7% of patients in Austria and 15% of patients in Switzerland). All events were mild or moderate in severity. In the Phase III RCTs, diarrhoea was reported by 19.5% in the study by Chey *et al*., and 19.7% in the study by Rao *et al*. [8, 12]. The discrepancy in diarrhoea rates between this NIS and the previous RCTs may be due to the difference in reporting methods. In fact, all diarrhoea AEs regardless of treatment relatedness were reported in the two RCTs, while only adverse drug reactions (ADRs) were reported in this NIS. Additionally, the lower incidence in the ADR reported in this NIS may be due to underreporting

of AEs already described in the summary of product characteristics (SmPC) by physicians [23]. Finally, the impact of concomitant laxative use on diarrhoea cannot be discounted.

Treatment options for IBS-C are limited, with traditional therapies showing limited effectiveness in improving symptoms and quality of life, and only four pharmacologic agents approved for treatment. One such FDA-approved agent is lubiprostone, a chloride channel activator that was shown to improve IBS-C symptoms in two RCTs; however, lubiprostone is not approved for treatment in men due to limited efficacy [24]. Recently, plecanatide, a GC-C receptor agonist in the same drug class as linaclotide was approved for the treatment of IBS-C based on data from two RCTs with a comparable safety and efficacy profile as linaclotide RCTs; however, no evidence from real-life clinical settings currently exists for plecanatide [25, 26]. Another FDA-approved agent for IBS-C was tegaserod, a prokinetic agent that improved IBS symptoms but was later withdrawn from the market due to increased cardiovascular risks [27]. Overall, the present data confirms RCT findings in a real-world setting showing that linaclotide is an effective and satisfactory treatment for the management of IBS-C, a disease for which there are few effective therapeutic options.

Some limitations are associated with this study which necessitate caution in interpreting these findings. The main limitations are the sample size and differing study durations between the two countries, which only allowed compilation of 4 weeks of data. In addition, as this was a NIS without a placebo control, the statistical analyses are descriptive, explorative, and no statistical hypotheses were pre-specified. Nevertheless, to the best of our knowledge, no real-world studies have been conducted evaluating IBS-C treatments in the Alpine region, and observational studies were thus undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in various European countries, with data recently published from Germany. Our current findings suggest that linaclotide is safe and effective in reducing major symptoms of IBS-C in routine clinical practice in Austria and Switzerland. This data

confirms the previously reported results from two randomized Phase III clinical trials that collectively demonstrate the efficacy and safety of linaclotide treatment for the management of IBS-C patients with moderate-to-severe abdominal symptoms.

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TABLES

Table 1 Patient baseline demographics and characteristics

	Austria (N=86)	Switzerland (N=52)
Female, n (%)	71 (82.6)	40 (76.9)
Mean age, years	51.3	49.2
Mean BMI, kg/m²	24.0	23.4
Average time since diagnosis, years	2.1	5.2
Received pre-treatment, n (%)	73 (84.9)	49 (94.2)
Laxatives, n (%)	67 (77.9)	41 (78.9)
Dietary fibres, n (%)	55 (64.0)	36 (69.2)
Concomitant disease, n (%)	35 (40.7)	10 (19.2)
Hypertension, n (%)	9 (10.5)	5 (9.6)
Received concurrent IBS treatment, n (%)	33 (38.4)	16 (30.8)
Laxatives, n (%)	22 (25.6)	13 (25.0)
Patients experiencing abdominal pain at baseline, n (%)	85 (98.8)	46 (90.2)
Mean intensity of abdominal pain at baseline (SD)	6.0 (±2.1)	5.4 (±2.7)
Patients experiencing bloating at baseline, n (%)	81 (95.3)	48 (94.1)
Mean intensity of bloating at baseline (SD)	5.8 (±2.4)	5.6 (±2.7)
Mean number of bowel movements/week (SD)	2.1 (±1.3)	2.1 (±1.4)
Solid stool consistency, n (%)	55 (64.0)	22 (44.0)
'Morning' was most commonly advised time of intake, n (%)	68 (80.0)	26 (53.1)

% are calculated from total number of patients providing data for that outcome. Baseline IBS symptoms were assessed during the week before start of therapy; 0=no pain/bloating 10=worst pain/bloating
BMI, body mass index; SD, standard deviation

Table 2 Reasons for discontinuing linaclotide

	Austria (N=86)	Switzerland (N=52)
Discontinued patients, n (%)	20 (23.3)	17 (32.7)
Lack of effectiveness	13 (15.1)	5 (9.6)
Adverse events	8 (9.3)	10 (19.2)
Improvement of symptoms	5 (5.8)	5 (9.6)
Lack of compliance	1 (1.2)	0
Excessive drug effect	0	1 (1.9)

Austria: 7 patients reported 2 reasons each
Switzerland: 4 patients reported 2 reasons each

Table 3 Use of concomitant medications

	Austria (N=86)	Switzerland (N=52)
Patients receiving at least one concomitant medication, n (%)	31 (36.1)	13 (25.0)
Renin-angiotensin system agents	7 (8.1)	6 (11.5)
Psychoanaleptics	6 (7.0)	2 (3.9)
Beta blocking agents	4 (4.7)	4 (7.7)
Lipid modifying agents	4 (4.7)	4 (7.7)
Psycholeptics	3 (3.5)	0
Diabetes drugs	3 (3.5)	0
Analgesics	0	3 (5.8)
Drugs for acid-related disorders	0	2 (3.9)

Concomitant medications reported by anatomical main group

Table 4 Summary of safety

	Austria (N=86)	Switzerland (N=52)
Total AEs	16	15
Serious AEs	0	0
Patients with ≥1 AE, n (%)	10 (11.6)	12 (23.1)
Diarrhea	6 (7.0)	8 (15.4)
Drug ineffective	5 (5.8)	2 (3.9)
Abdominal distension	2 (2.3)*	0
Dizziness	0	1 (2.0)
Condition aggravated	1 (1.2)	0
Rectal tenesmus	1 (1.2)	0
Headache	0	1 (1.9)
Hot flush	0	1 (1.9)
Nausea	0	1 (1.9)
Urge incontinence	0	1 (1.9)

Adverse events recorded per preferred term using Medical Dictionary for Regulatory Activities v18.0 (Austria) and v18.1 (Switzerland). *Two abdominal distension events reported for one patient; AE, adverse event

FIGURE LEGENDS

Figure 1 Effect of linaclotide treatment on (A) abdominal pain (B) bloating and (C) frequency of bowel movements in all patients. Data shown as last observation carried forward. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 2 Effect of linaclotide treatment in patients with and without prior treatment for IBS C on (A) abdominal pain and (B) bloating. Data shown as last observation carried forward. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 3 Effect of linaclotide treatment in patients with and without concomitant treatment for IBS C on (A) abdominal pain and (B) bloating. Data shown as last observation carried forward. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 4 Proportion of patients reporting overall and individual improvement of IBS-C symptoms at the end-of-treatment periods (week 4 in Austria and week 16 in Switzerland). Proportions based on number of patients with available data at respective end-of-treatment visits (Austria, n=85; Switzerland, n=51).

Figure 5 Physicians' assessment of (A) satisfaction, and global assessment of (B) effectiveness and (C) tolerability of linaclotide

SUPPORTING INFORMATION

508 STROBE Statement—checklist of items that should be included in reports of observational studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	8
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
Outcome data	15*	Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	31

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Daniel Pohl, Michael Fried, and Heinz Hammer participated in the study design, trial conduct, and data collection. Dominic Lawrance and Elmar Beck participated in data collection and analysis. All authors interpreted the data and participated in writing the manuscript with medical writing services provided by the funder. All authors read the manuscript critically and approved the final version.

DISCLOSURES

Writing and editorial assistance was provided to the authors by Germaine D. Agollah, PhD of Allergan. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Daniel Pohl is a consultant and speaker for Allergan. Dominic Lawrance is an employee of Allergan. Elmar Beck is an employee of Anfomed GmbH, which was contracted by Allergan as a contract research organization (CRO) for the conduct of this study. Heinz Hammer is a consultant and speaker for Allergan.

DATA AVAILABILITY

Data reported in this manuscript are available within the article and its supplementary materials. Additional data from the linaclotide real-world evidence Alpine study may be requested at http://www.allerganclinicaltrials.com/PatientDataRequest.htm

Linaclotide in IBS-C: The Alpine Study

Efficacy and tolerability of linaclotide in the treatment of irritable bowel syndrome with constipation in a real-world setting: The Alpine study

Daniel Pohl, Michael Fried, Dominic Lawrance, Elmar Beck, Heinz F. Hammer

Figure 1: Effect of linaclotide treatment on (A) abdominal pain (B) bloating and (C) frequency of bowel movements on all patients. Data shown as last observation carried forward. **p<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

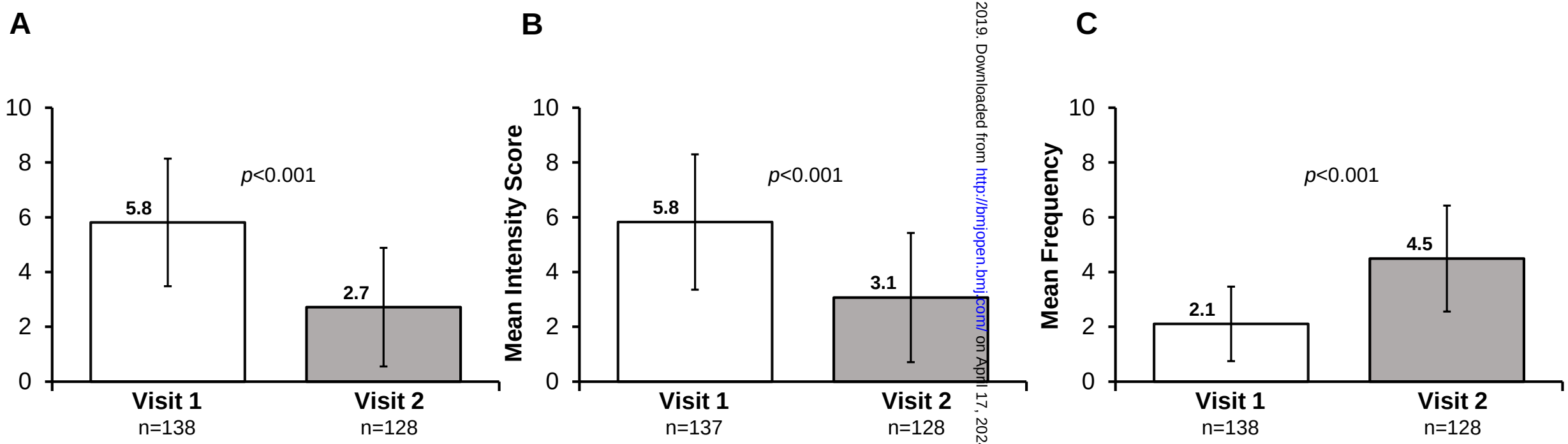


Figure 2: Effect of linaclotide treatment in patients with and without prior treatment for IBS C on (A) abdominal pain and (B) bloating. Data shown as last observation carried forward. **p<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

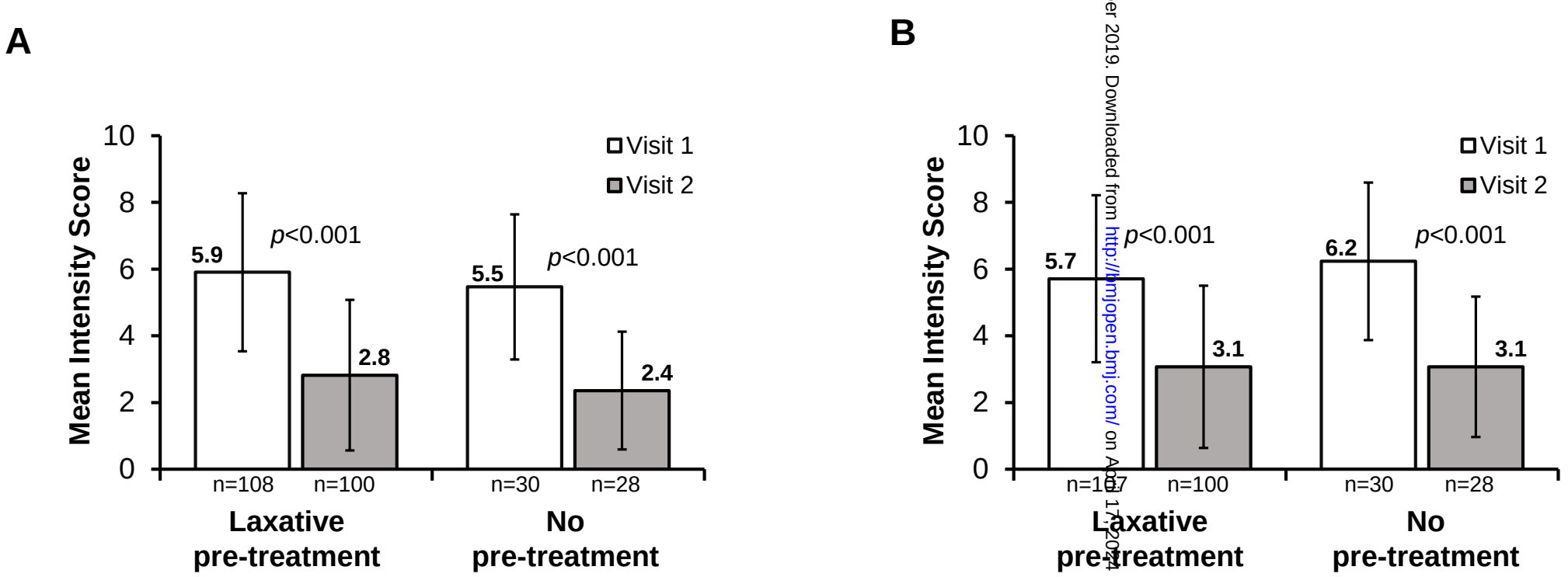


Figure 3: Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Data shown as last observation carried forward. **p<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

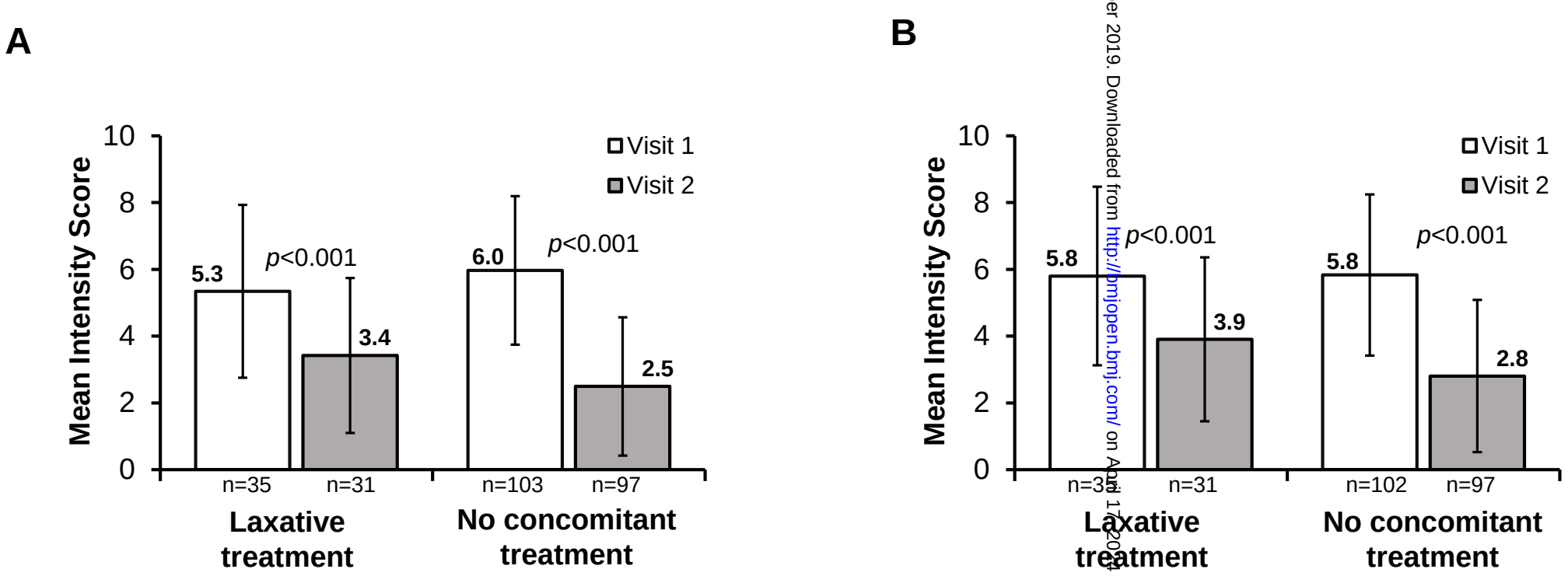


Figure 4: Proportion of patients reporting overall and individual improvement of IBS-C symptoms at the end-of-treatment periods (week 4 in Austria and week 16 in Switzerland). Proportions based on number of patients with available data at respective end-of-treatment visits (Austria, n=85; Switzerland, n=51).

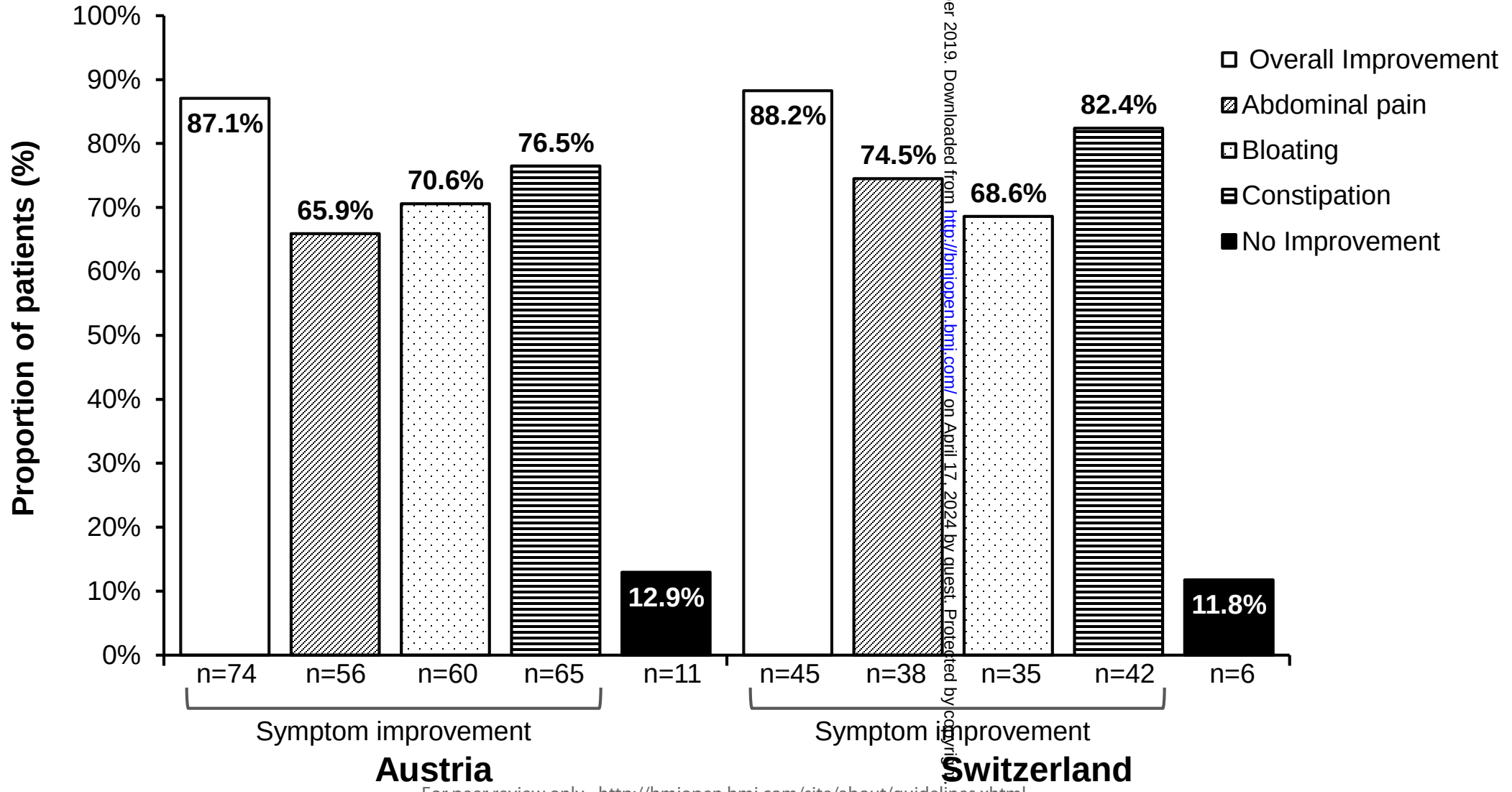
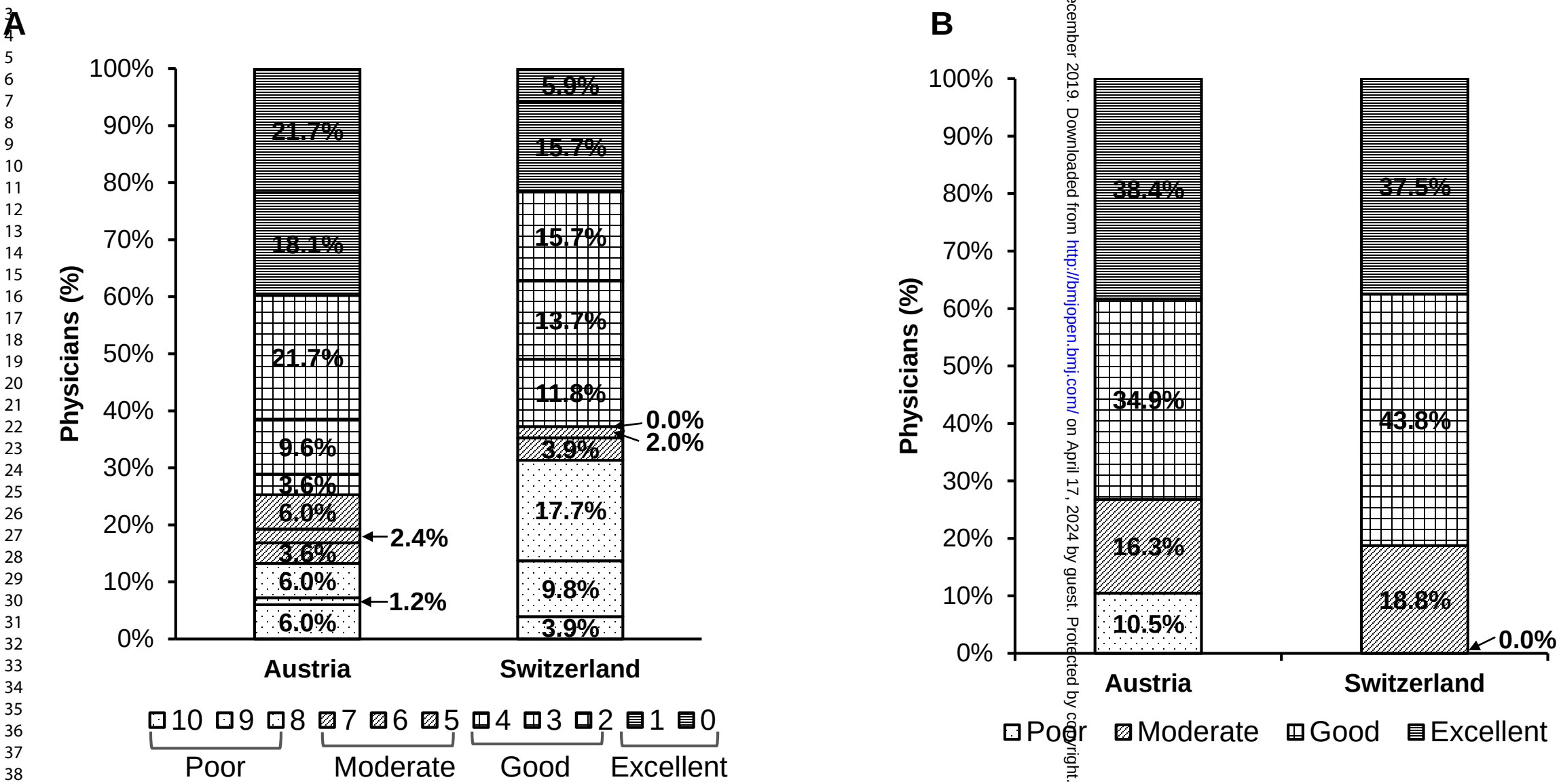
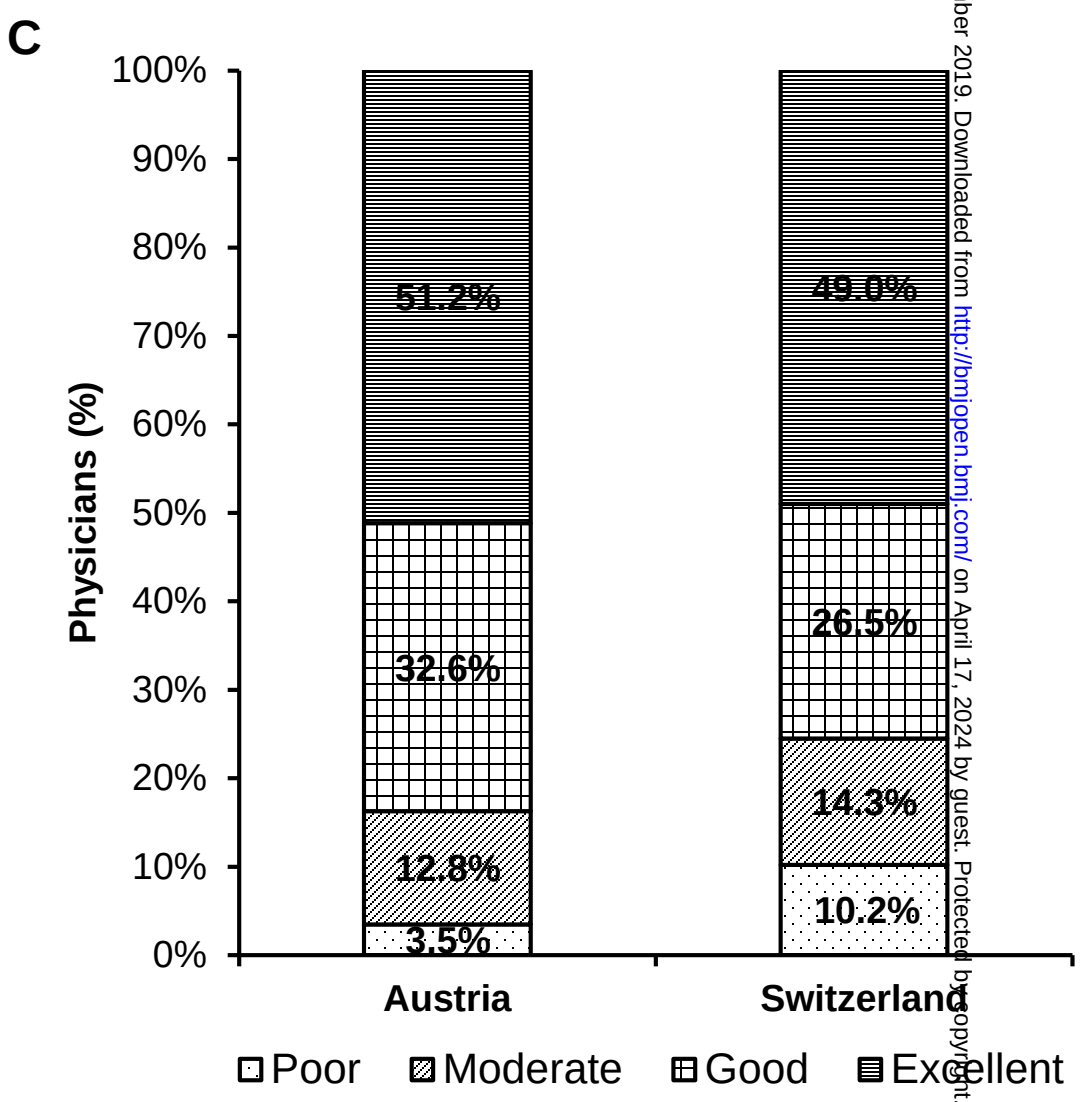


Figure 5: Physicians' assessment of (A) satisfaction, and global assessment of (B) effectiveness and (C) tolerability of linaclotide



Scale: 0 (very satisfied) to 10 (totally unsatisfied)
Austria: mean 2.9 ± 3.0 points (good satisfaction)
Switzerland: mean 4.6 ± 3.2 points (moderate satisfaction)

Figure 5: Physicians' assessment of (A) satisfaction, and global assessment of (B) effectiveness and (C) tolerability of linaclotide



Practical experience report Constella®

The new GC-C agonist in the treatment of IBS-C - efficacy and safety of linaclotide under real life conditions in Switzerland

Observational Plan

Title	Practical experience report Constella® - The new GC-C agonist in the treatment of IBS-C - efficacy and safety of linaclotide under real life conditions
Study drug	Constella® 290 micrograms capsule
Active substance	Linaclotide
Dosage	according to SmPC
Area of application	for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults
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The information contained in this document is confidential and must not be disclosed to third parties unless the written consent of Almirall AG has been obtained, with the exception of conditional distribution of information to persons directly involved in the practical experience report.

Table of contents

1. Synopsis

Aim of the study	The aim of the practical experience report is to document efficacy and safety of linaclotide therapy in the treatment of moderate-to-severe IBS-C under real life conditions.
Number of patients	200
Country	Switzerland
Clinical phase	Post marketing authorization
Centers	40 Gastroenterologists
Type of study	multicenter, non-interventional, prospective study (practical experience report)
Administration of Constella®	According to the usual therapeutic procedure of the attending physician and in accordance with the authorized indications and summary of product characteristics (SmPC).
Procedure of study	The physician selects suitable patients, i.e. patients intended for therapy with Constella®, who meet all the required criteria for data collection within the scope of the practical experience report and obtains their written consent. Data will be documented for following survey times: • Visit I: before start of treatment • Visit II: about 4 weeks after start of treatment (± 2 weeks) • Visit III: about 4 months after start of treatment (± 6 weeks)
End point of study	**Efficacy** of Constella® should be determined under real life conditions by following parameters: • Reduction of abdominal pain and bloating after 4 weeks and 4 months in comparison to the time before therapy start measured by 11-NSR (numeric rating scale) • Incomplete bowel evacuation as subjective sensation of patient • Change of predominant stool consistency • Physician evaluation of efficacy 4 months after therapy start **Tolerance** of Constella® should be determined under real life conditions by following parameters: • Number, intensity and severity of Adverse Events (AE) • Physician evaluation of tolerance 4 months after therapy start **Satisfaction** with therapy should be evaluated 4 weeks and 4 months after therapy start by 11-NSR.

Study duration per patient	An observational period per patient of about 4 months is intended.
Survey data	• Date of visits • Demographic data • Inclusion and exclusion criteria • Medical history • (Pre-) treatment of IBS-C • Concomitant diseases and medication • Treatment with Constella® • Adverse drug reaction • Symptoms of IBS-C • Assessment of Constella® therapy by the attending physician • Confirmation physician (Visit III)
Statistic aspects	According to study design, evaluation will be solely descriptive and explorative.
Study duration	The practical experience report will start on **April 1st 2014. Last center may be enrolled until May 31st 2014.** Last patient may be enrolled until **June 30th 2014**. Case report forms sent in later than **December 15th 2014** will not be compensated.
Adverse Drug Reactions	**Any adverse drug reaction** during the practical experience report, in which relation to Constella® therapy cannot be excluded, must be carefully documented on the **ADRform** and faxed **within 24 hours** to the **Drug safety department of ANFOMED GmbH,** fax number: 049-9133-7762-62, Ursula Burkard, Senior Data Manager, ANFOMED GmbH, Röttenbacher Straße 17, 91096 Möhrendorf. **Pregnancies** should also be documented on the ADR-form and faxed **within 24 hours** to ANFOMED.
Medical director Almirall AG	Dr. med. Elisabeth Schuller Medical Advisor Austria and Switzerland Almirall AG Alte Winterthurerstrasse 14 CH-8304 Wallisellen Tel.: +43 1 595 39 60 100 Fax: +43 1 595 39 60 111 Email: elisabeth.schuller@almirall.com
Principal investigator	Prof. Dr. med. Michael Fried

2. Introduction, study objectives and endpoint of study

2.1. Introduction

Irritable Bowel Syndrome (IBS) is characterized by chronic abdominal discomfort with irregular bowel movements without any apparent cause in routine diagnosis [1]. More than 10% of the European population is affected by IBS. The complaints of IBS can significantly impair quality of life [2]. Up to one-third of IBS patients have IBS-C, Irritable Bowel Syndrome with prevalent constipation. In addition to abdominal pain or discomfort and reduced stool frequency, IBS-C patients also report a number of other complaints including bloating, hard stools and a sensation of incomplete evacuation [3]. Constella® is the first and sole drug that has been approved by the European Commission for symptomatic treatment of moderate to severe IBS-C in female and male adults and eases abdominal pain/discomfort, bloating and constipation. The active ingredient of Constella®, Linaclotide, attaches to the intestinal Guanylate cyclase-C-receptor. The adhesion to the receptors provides pain relief and increases the intestinal fluid volume, whereby stool loosens up and intestinal transit is accelerated. [4]. Evidence of superior efficacy of Linaclotide compared to a placebo was shown in two randomized, double-blind, placebo-controlled phase 3 trials with more than 1600 patients [3, 5].

2.2. Study objectives

The aim of the practical experience report is to document efficacy and safety of linaclotide therapy in the treatment of moderate-to-severe IBS-C under real life conditions.

2.3. End point of study

Efficacy of Constella® should be determined under real life conditions by following parameters:

- Reduction of abdominal pain and bloating after 4 weeks and 4 months in comparison to the time before therapy start measured by 11-NSR (numeric rating scale)
- Incomplete bowel evacuation as subjective sensation of patient
- Change of predominant stool consistency
- Physician evaluation of efficacy 4 months after therapy start

Tolerance of Constella® should be determined under real life conditions by following parameters:

- Number, intensity and severity of Adverse Events (AE)
- Physician evaluation of tolerance 4 months after therapy start

Satisfaction with therapy should be evaluated 4 weeks and 4 months after therapy start by 11-NSR.

3. Methods

3.1. Type of study and selection reasons

This is a prospective, non-interventional, open observational study (practical experience report) in patients with irritable bowel syndrome with constipation (IBS-C). There are no treatment groups or actions to which patients could be randomly assigned. The aim of the study is to collect data on the use of Constella® under practical conditions. All decisions regarding therapy with Constella® are subject to the physician's discretion and should reflect the current treatment routine. However, the treatment should take into account marketing authorization information as specified in the Summary Product Characteristics (SmPC). Patients can be enrolled in the study at the initial visit if the physician had previously opted for treatment with Constella®. All treatment and diagnostic procedures are at the discretion of the participating physician and adhere to the medical assessment and the local standard of medical care.

3.2. Selection of physicians

Sales representatives select physicians of the department of gastroenterology. The distribution of the physicians extends throughout Switzerland. The total number of participating physicians is 40.

3.3. Sample size calculation

Enrollment of 200 patients is planned. A total of 200 patients, regarding feasibility of the practical experience report in terms of medical practice, is required in order to gain a representative clientele of patients within the termed indication.

Statistical significance based on 200 documented cases:

- in case of dichotomous variables for the underlying binominal probability, a 95%-confidence interval of in maximum 14.27 percentage points in length will be reached,
- 95%-confidence intervals on the underlying means of quantitative variables have a length of 0.279 standard deviations,
- rare events with an incidence down to 0.015 (1:67) are included at least once in the sample with a probability of 95%.

3.4. Selection of patients

The observation should be performed in patients:

- who suffer from moderate to severe Irritable Bowel Syndrome with Constipation (IBS-C)
- who are at least 18 years old
- who will be treated with Constella® based on the physicians therapeutic decision reached before including the patient into the study

The observation should **not be performed** in patients

- with a known hypersensitivity to the active substance or to any other ingredient of Constella® and/or
- a known or suspected mechanical gastrointestinal obstruction.

Pregnant women or nursing women as well as women willing to become pregnant during treatment with Constella® may not to be enrolled.

The physician may document data of 5 - 10 patients.

Requirement for participation is a signed informed consent by the patient.

4. Administration of Constella®

Constella® is indicated for symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults. Application of Constella® is made according to usual therapeutic procedure of the attending physician and in accordance with the authorized indications and summary of product characteristics (SmPC). According to the SmPC the recommended dose is one capsule (290 micrograms) once daily. Intake of capsule should be 30 minutes before a meal [7].

5. Observational period and total duration of the study

An observational period per patient of about 4 months is intended. The practical experience report will start on **Dezember 1st, 2014.** Last center may be enrolled until **April 30 2015**. Last patient may be enrolled until April **30th, 2015**. Case report forms sent in later than **October 15th 2015** will not be compensated.

6. Documentation during the practical experience report

6.1. Documentary components

The attending physician will receive a documentary folder containing all required documents for 5 patients, including:

- two contracts of participation including return envelopes
- a short summary of the survey
- the observational plan
- the SmPC of Constella®
- patient overview
- five CRFs
- five patient questionnaire forms each for five patients
- two patient information and consent forms each for five patients
- five forms for documenting adverse drug reactions (ADR forms),

6.2. Survey dates

Three survey dates are planned:

- Visit I: before start of treatment
- Visit II: about 4 weeks after start of treatment (± 2 weeks)
- Visit III: about 4 months after start of treatment (± 6 weeks)

The exact examination dates will be determined by the attending physician.

6.3. Collected data

Case report forms include documentation of following data:

6.3.1. Visit I (before start of treatment)

- Date of Visit I
- Demographic data
- Inclusion and exclusion criteria
- Medical history
- (Pre-) treatment of IBS-C
- Concomitant diseases and medication
- Treatment with Constella®

6.3.2. Visit II (about 4 weeks after start of treatment)

- Date of Visit II
- Treatment with Constella®
- Adverse drug reactions
- Symptoms of IBS-C
- Treatment of IBS-C
- Assessment of Constella® therapy by the attending physician

6.3.3. Visit III (about 4 months after start of treatment or at the end of therapy)

- Date of Visit III
- Treatment with Constella®
- Adverse drug reactions
- Symptoms of IBS-C
- Treatment of IBS-C
- Changes of concomitant diseases and medication
- Assessment of Constella® therapy by the attending physician
- Physician‘s affirmation

6.4. Conducting the practical experience report

Sales representatives of Almirall AG are responsible for distributing study documents and will

be at hand to answer administrative questions related to survey conduction. Distribution of documents will be executed according to the Swiss Pharma Code (Pharmakodex) [13] and will not be linked to any pharmaceutical advertising actions. Central coordination of the study will be conducted by the assigned clinical research organization ANFOMED GmbH.

The physician selects suitable patients, i.e. patients intended for therapy with Constella®, who meet all the required criteria for data collection within the scope of the practical experience report and obtains their written consent. It should be particularly noted that selection of patients who are to be included in the study is based solely on the assessment of medical sense and necessity by the attaining physician. Patients are only to be considered for enrollment after treatment with Constella® has been decided on. Treatment including diagnosis of IBS-C as well as determination of severity of IBS-C and supervision of patients will be conducted according to routine medical procedures.

Before therapy start, the physician carries out Visit I and results will be documented in the CRF. Visit II is planned about 4 weeks after baseline (according to the treatment algorithm of the Constella® SmPC). A final examination (Visit III) should be conducted about 4 months after baseline examination. Obtained results are documented in the CRF. If treatment with Constella® is discontinued prior to 4 months after starting therapy, Visit III should be filled in.

After Visit II (4 weeks after baseline) and Visit III (4 months after baseline or at the end of therapy) CRFs will be collected by the sales representatives and forwarded to the assigned clinical research organization ANFOMED GmbH for data entry, validation and evaluation. Case report forms sent in later than **December 15th 2014** will not be compensated.

All adverse drug reactions that occur in the course of the study, in which relation to Constella® therapy cannot be excluded, must be reported to the drug safety department of ANFOMED GmbH **within 24 hours**. Anfomed GmbH processes these messages (recording, translation into English, implementation into standard notification forms) and immediately forwards them to the drug safety of Almirall S.A. in Spain. The scientific assessment is the responsibility of Almirall S.A., Spain. Almirall is responsible for (electronic) reporting of all adverse events in accordance with the Swiss Federal Law on Medicinal Products and Medical Devices to the **Swiss Agency for Therapeutic Products, Swissmedic.**

7. Adverse drug reactions (ADR)

7.1. Definitions

7.1.1. Adverse events

Every adverse medical event that occurs after administration of a drug/medical product in a patient or clinical trial participants that is not necessarily related in a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory values), symptom, or disease, for which there is a temporal association with the use of a medicine/medical product, regardless of whether a connection with the drug/medical product is accepted or not.

7.1.2. Adverse drug reactions (ADRs)

A noxious and unintended response to a medicinal product, which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of a disease or the modification of physiological functions. "Response to a medicinal product" means that a causal relationship between the drug and the adverse event can reasonably exist .

7.1.3. Serious adverse events (SAEs)

Each adverse event, regardless of the dose, that either results in death, is life-threatening, requires hospitalization or prolongs hospitalization, leads to a lasting or significant disability, or is a congenital malformation/birth defect . A medically significant event that does not result in death, is life-threatening, or makes a hospital stay necessary, can however be classified as a serious adverse event if

after medical assessment it endangers the safety of patients and makes medical or surgical interventions necessary in order to prevent one of the above-mentioned effects .

7.1.4. Serious adverse drug reaction (SADR)

Each serious adverse event suspected to be caused by or related to the use of the drug.

Any adverse drug reaction during the practical experience report, in which relation to Constella® therapy cannot be excluded, must be carefully documented on the **ADR-form** and **faxed within 24 hours** to the **Drug safety department of ANFOMED GmbH, fax number: 049-9133-7762-62, Frau Ursula Burkard, Senior Data Manager, Röttenbacher Straße 17, 91096 Möhrendorf.** ANFOMED will forward these reports to the drug safety department of Almirall S.A. in Spain.

Reporting of pregnancy:

Occurring **pregnancies** should be documented in the **ADR-report form** and faxed **within 24 hours** to the **drug safety department of ANFOMED**. After that, physicians receive a special reporting form by mail, which must be forwarded to ANFOMED after completion (contact details see above).

8. Data Management, Quality control and statistical analysis

8.1. Data Management

Data management is based on the “Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP) [8]”. Prior to field phase, a database will be designed and a data management plan will be

created. The Data Management Plan will include a description of the plausibility and consistency tests that must be run during data processing as well as rules defining how to deal with any discrepancies. Returned CRFs containing data obtained by standardized forms will be immediately checked for adverse

drug reactions (ADRs) by the assigned clinical research organization ANFOMED GmbH. All data will be entered into a project-specific database which is the basis for statistical analysis and final report. Consistency of the ADR data shall be ensured by comparing the project database with the drug safety database of Almirall AG. Discrepancies will be resolved by joint consultation.

8.2. Quality control

Returned documentation will be checked on data validation, plausibility, and completeness and will be medically reviewed for quality control. Inconsistent and/or implausible data will be corrected as far as possible. In case of incomplete or incorrect data in returned CRFs, the physician concerned will be contacted in written form by ANFOMED GmbH in means of a query requesting clarification or completion of data.

8.3. Statistical analysis

Data processing and statistical analysis will be performed with the SAS™ program system. Tables will be created in MS Word format. Statistical analysis will be performed in a descriptive and explorative way. All collected variables will be listed and illustrated graphically and by frequency and parameter tables. Variables collected at the relevant examination dates during the observational period will be statistically analyzed to evaluate and measure changes [9]. All ADRs will be entered into the database separately and coded according to MedDRA (latest version at start of data return). All cases containing ADRs will be listed and presented sorted by system-organ-class (SOC). Incidences are calculated for each type of adverse drug reaction (95% probability of incidence in the population). Results will be presented in a final report in accordance with Almirall AG.

9. Responsibility

The practical experience report will be conducted by Almirall AG, Alte Winterthurerstrasse 14, CH-8304 Wallisellen. Medical director of the study is Dr. med. Elisabeth Schuller, Medical Advisor Austria and Switzerland, Almirall AG.

Person in charge of:

medical and scientific contents:	organization, procedure, pharmacovigilance:
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10. General regulations

Almirall AG and/or ANFOMED GmbH will, to the necessary extent, submit the practical experience report to the relevant ethics committees. Documentation of data will start after the approval of the practical experience report by the responsible ethics committee. Recognized standards for the implementation of practical experience reports are considered. According to the character of a practical experience report, the documentation is subject to the therapeutic responsibility of the treating physician. By signing the documents, each participating physician confirms that the data has been collected in accordance with the observational plan.

The expense allowance is based on the time required for the elucidation of the IBS-C patients about the meaning and purpose of this study and for study document management and documentation of data. The expense allowance and the payment terms are specified in the fees agreement.

The documentation will be retained by Almirall AG for 10 years.

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A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and Tertiary Centers: The Alpine study

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TITLE PAGE

A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and Tertiary Centers: The Alpine study

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Running Title: Linaclotide in IBS-C – The Alpine study

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Keywords: Irritable bowel syndrome-constipation; IBS-C; linaclotide; real world evidence; non-interventional study; abdominal pain; bloating

ABSTRACT

Objectives: We evaluated the effectiveness and tolerability of linaclotide, a minimally absorbed guanylate cyclase-C agonist, in patients with irritable bowel syndrome with constipation (IBS-C) in routine clinical practice.

Setting: A multicenter, non-interventional study conducted between December 2013 and November 2015 across 31 primary, secondary, and tertiary centers in Austria and Switzerland.

Participants: The study enrolled 138 patients aged ≥18 years with moderate-to-severe IBS-C. Treatment decision was at the physician's discretion. Patients with known hypersensitivity to the study drug or suspected mechanical obstruction were excluded. The mean age of participants was 50 years, >75% of whom were female. 128 patients completed the study.

Primary and secondary outcome measures: Data were collected at weeks 0 and 4 in Austria and weeks 0, 4, and 16 in Switzerland. The primary effectiveness endpoints included: severity of abdominal pain and bloating (11-point numeric rating scale [0=no pain/bloating to 10=worst possible pain/bloating]), frequency of bowel movements, and physicians' global effectiveness of linaclotide. Treatment-related adverse events were recorded.

Results: Following a 4-week treatment period, the mean intensity score of abdominal pain was reduced to 2.7 from 5.8 at baseline, while the bloating intensity score was reduced to 3.1 from 5.8 at baseline (both indices $p<0.001$). The frequency of mean weekly bowel movements increased from 2.1 at baseline to 4.5 at week 4 ($p<0.001$). Global effectiveness and tolerability of linaclotide were assessed as "good" or "excellent" in >70% of patients by the treating physicians. In total, 31 adverse events were reported in 22 patients, the most common being diarrhea, reported by six (7%) and eight (15.4%) patients in Austria and Switzerland, respectively.

Conclusions: Linaclotide was effective in treating moderate-to-severe symptoms in routine clinical practice of this IBS-C patient population. Linaclotide was safe and well tolerated and no new safety concerns were raised, confirming results from previous clinical trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first real-world study evaluating the effectiveness and tolerability of an IBS-C treatment in the Alpine region.
- This study sought to evaluate whether the efficacy and tolerability of linaclotide that was demonstrated in randomized clinical trials could be recapitulated in clinical practice in a real-world setting.
- Results from the physicians' global assessment of efficacy and tolerability will be useful in determining physician comfort level with prescribing linaclotide for their patients.
- This was a non-interventional study that lacked a placebo control; thus, the statistical analyses are descriptive and exploratory in nature.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain or discomfort and change in bowel habits.[1] IBS is a common GI ailment, with global prevalence ranging from 3-21%, depending on the diagnostic criteria.[2] The prevalence of IBS in Europe is estimated at 12-15%.[3] IBS is subtyped based on the predominant stool pattern, and includes IBS subtype with constipation (IBS-C), diarrhea (IBS-D), mixed stool (IBS-M), or unsubtyped (IBS-U) when stool consistency does not meet criteria for IBS-C, -D, or -M.[4] When defined by Rome III diagnostic criteria, IBS is prevalent in approximately 1-29% of the general population, with IBS-C present in 1-4%.[5] Of the IBS subtypes, IBS-C is the second most common subtype, comprising approximately 35% of all IBS cases.[3]

In addition to abdominal pain and discomfort, patients with IBS-C often experience hard or lumpy stools, straining, feeling of incomplete evacuation, and bloating. Moreover, IBS-C has an undue impact on quality of life, increases healthcare costs, and reduces work productivity.[6,7] Since IBS-C presents with a constellation of symptoms, therapy options have centered on symptom relief and have generally included dietary and lifestyle modifications, and over-the-counter medications such as fiber supplements and laxatives that aim to relieve constipation. However, these treatments are often ineffective and patients resort to additional therapies, which in turn, drive up healthcare costs and resources, thus underscoring the need to identify efficacious treatment options for IBS-C.[8]

Linaclotide is a minimally absorbed 14-amino acid guanylate cyclase-C (GC-C) receptor agonist structurally related to the guanylin peptide family.[9] Upon binding to GC-C receptors, linaclotide increases the intracellular production of cyclic guanosine monophosphate (cGMP), which in turn activates the cystic fibrosis transmembrane conductance regulator, resulting in secretion of chloride and bicarbonate into the intestinal lumen, ultimately accelerating intestinal transit.[10]

Linaclotide was demonstrated to increase colonic transit and reduce abdominal pain and constipation in patients with IBS-C in Phase II trials.[11,12] Subsequently, the efficacy and safety of linaclotide for the treatment of IBS-C was established in two placebo-controlled Phase III trials that showed improvements in IBS-C symptoms, including abdominal pain and bowel movements.[9,13]

Linaclotide was approved by the Food and Drug Administration (FDA) and European Medicines Agency in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C.[14,15] While the efficacy and safety of linaclotide has been established in clinical trial settings, these may not depict real-life experiences. To address this need, observational studies were undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in Europe. In routine clinical practice, linaclotide has recently been shown to be effective in improving IBS-C symptoms in a post-marketing authorization study conducted in Germany.[16] Herein, we aimed to document the effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C in adults under real-life conditions in the Alpine region of Austria and Switzerland.

METHODS

Study design

This was a multicenter, non-interventional study (NIS) evaluating the effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C, in adult patients under real-life routine clinical practice conditions in Austria and Switzerland. A total of 200 patients were planned for enrollment across 40 sites in each country. The study was conducted from December 2013 to March 2015 in Austria and from November 2014 to November 2015 in Switzerland.

The study comprised a 4-week treatment period commencing with visit 1 at treatment initiation and visit 2 occurring approximately 4 weeks after initiation in Austria. In Switzerland, data were

collected over the course of three visits, at 0, 4, and 16 weeks after treatment initiation. Linaclotide was administered per the usual therapeutic procedure of the attending physician and in accordance with the indication for the drug (290 µg once daily, taken at least 30 minutes before meals).[15]

The study protocols were approved by the local Institutional Review Board or Independent Ethics Committee of each center (study approval numbers: Austria, 26-279 ex 13/14; Switzerland, KEK-ZH-Nr.2014-0137). The study was conducted in accordance with the Declaration of Helsinki, applicable local laws and regulations, and International Conference on Harmonisation E6 Good Clinical Practice guidelines. All participants provided written informed consent prior to study initiation.

Participants

Eligible patients were aged ≥18 years with a diagnosis of moderate-to-severe IBS-C (diagnosed by the treating physician), characterized by clinical evidence of relevant interference of symptoms with well-being and/or daily routines at work or during leisure. The decision to treat a patient with linaclotide was made solely by the treating physician prior to inclusion in the study. Patients with known hypersensitivity to the active ingredient or any other component of linaclotide, suspected or known GI obstruction, or who were pregnant or planning to become pregnant were excluded from the study.

Study assessments

All relevant data collected during routine treatment with linaclotide were recorded in case report forms. Patient demographics and medical history were collected, including diagnosis, prior treatment, and symptoms of IBS-C, comorbidities, and concomitant medications.

The primary effectiveness endpoints included severity of abdominal pain and bloating, frequency of bowel movements during the week before each visit, general symptom improvement relative to pre-treatment, physicians' satisfaction with linaclotide therapy,

sensation of incomplete bowel evacuation, change in predominant stool consistency, and physicians' global assessment of the effectiveness of linaclotide. Changes in the severity of abdominal pain and bloating were measured using an 11-point numeric rating scale (NRS; 0=no pain/bloating to 10=worst possible pain/bloating). Physicians' satisfaction with linaclotide therapy was measured using a 10-point NRS (0=very satisfied to 10=totally unsatisfied). General symptom improvement and improvement in three individual symptoms – abdominal pain, bloating, and constipation – were measured by patient response to simple yes/no questions asked by the physician (e.g., "Have symptoms improved over the last week compared to the time prior to therapy start?"). Frequency of bowel movements during the week before each visit, sensation of incomplete bowel evacuation, and change in predominant stool consistency were patient-reported.

Adverse events (AEs) related to linaclotide treatment or whose relation to linaclotide treatment could not be excluded were documented. AEs assessed by the physician as not related to linaclotide treatment were not documented. Other safety measures included physicians' global assessment of the tolerability of linaclotide.

Statistical analyses

Statistical analysis was performed using SAS™ v9.4 software (SAS Institute, Cary, NC). Data were analyzed using descriptive statistics and no hypotheses were pre-specified. To determine whether the pre–post changes of symptoms were statistically significant, the Wilcoxon signed-rank test was applied. Reported *p*-values are two-tailed, using an alpha level of 0.05 to assess statistical significance. Missing data were imputed using the last observation carried forward method. Visit 1 and 2 efficacy data were compiled for both countries, where applicable.

Patient and public involvement

This was an observational study. Patients continued on existing medication at their own discretion. Study outcomes were scored by the patients and the data collected during this study were informed by the patients' experiences.

RESULTS

Patient characteristics

A total of 86 patients in 22 sites and 52 patients in nine sites were enrolled in Austria and Switzerland, respectively. Baseline characteristics were generally comparable between the two countries. Of the enrolled patients, 71 (82.6%) in Austria and 40 (76.9%) in Switzerland were female, and the mean age was 51 and 49 years, respectively (**table 1**). The mean body mass index was 24 kg/m^2 and 23 kg/m^2 in each country. The average time since IBS-C diagnosis was 2.1 years and 5.2 years for patients in Austria and Switzerland, respectively. At baseline, more than 90% of patients in both countries reported abdominal pain (mean intensity scores of 6.0 and 5.4, respectively) and bloating (mean intensity scores of 5.8 and 5.6, respectively). Patients in both countries reported a mean of 2.1 bowel movements per week. Prior treatment for IBS-C was reported by 73 (84.9%) patients in Austria and 49 (94.2%) patients in Switzerland, mainly consisting of laxatives and dietary fibers, while 33 (38.4%) patients in Austria and 16 (30.8%) patients in Switzerland received concurrent IBS treatment. Concomitant diseases were reported by 35 (40.7%) patients in Austria and 10 (19.2%) patients in Switzerland (**table 1**). Collectively, baseline characteristics of the patients with IBS-C in this study were reflective of the general IBS patient population (i.e., approximately 70% of IBS patients are typically female, with a high likelihood of the majority of patients being ≤50 years).

Throughout the course of the study, 20 (23.3%) patients in Austria and 17 (32.7%) patients in Switzerland discontinued linaclotide treatment, with the main reasons for discontinuation being lack of effectiveness for 13 (15.1%) patients in Austria and adverse events in Switzerland,

reported in 10 (19.2%) patients. Reasons for treatment discontinuation are summarized in **table 2**.

Effectiveness outcomes

Effect of linaclotide treatment on symptoms of IBS-C

Linaclotide was administered over 4 weeks in Austria and 16 weeks in Switzerland, and data from the initial 4-week treatment periods are compiled in this analysis. Of the 138 enrolled patients, data were available for 128 patients at week 4. Improvements in abdominal pain, bloating, and bowel movements were observed after 4 weeks of treatment with linaclotide. From a mean intensity score of 5.8 at baseline, abdominal pain was reduced to 2.7 after 4 weeks of treatment in both countries (**figure 1A**; $p<0.001$ vs. visit 1; 11-point NRS [0=no pain to 10=worst possible pain). In Switzerland, continued reduction in abdominal pain was observed at week 16, with a mean intensity score of 2.5 (standard deviation [SD]±2.0; n=51; $p<0.0001$ vs. visit 1). Improvements in bloating were also seen after 4 weeks of treatment in both countries; from a baseline mean intensity score of 5.8, the bloating score was reduced to 3.1 at week 4 (**figure 1B**; $p<0.001$ vs. visit 1; 11-point NRS [0=no bloating to 10=worst possible bloating]), with a mean intensity score of 3.0 (SD±2.2; n=51; $p<0.0001$ vs. visit 1) at week 16 in Switzerland. Furthermore, the frequency of bowel movements increased from a mean of 2.1 per week at baseline to 4.5 at week 4 (**figure 1C**; $p<0.001$ vs. visit 1) in both countries, and to 4.7 (SD±1.6; n=51; $p<0.0001$ vs. visit 1) at week 16 in Switzerland.

Data were stratified based on patients who received prior IBS-C treatment, and improvements in IBS-C symptoms were observed within the 4-week treatment period, regardless of prior IBS-C treatment. Significant reductions from week 1 to week 4 in mean abdominal pain intensity and mean bloating intensity were seen in patients who had received laxative pre-treatment and in those who did not receive prior IBS-C treatment (**figure 2A** and **figure 2B**, respectively; all $p<0.001$ vs. visit 1). Similar degrees of mean reduction in abdominal pain were seen in patients

who did not and those who received laxative pre-treatment (both 3.1). Furthermore, the effect of concomitant laxative use with linaclotide was evaluated. Our results showed that significant reduction was achieved after 4 weeks of treatment in mean abdominal pain intensity (**figure 3A**; all $p<0.001$ vs. visit 1) and mean bloating intensity (**figure 3B**; all $p<0.001$ vs. visit 1), both in patients who used laxative concomitantly with linaclotide and those who did not. Greater symptom improvement was observed in those who did not use concomitant treatment (mean reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9; **figure 3A** and **3B**; all differences $p<0.001$ vs. visit 1).

Patient assessment of improvement of IBS-C symptoms

At each respective end-of-treatment period, patients were asked to indicate their sense of general improvement of symptoms as compared to the pre-treatment period. In Austria, 74 patients (87.1%) reported overall improved symptoms, among which 56 (65.9%) patients experienced improvements in abdominal pain, 60 (70.6%) had improvements in bloating, and 65 (76.5%) reported improvements in constipation at visit 2 compared to baseline (**figure 4**). In Switzerland, 45 patients (88.2%) reported overall improved symptoms, consisting of 38 (74.5%) patients with improvements in abdominal pain, 35 (68.6%) with improvements in bloating, and 42 (82.4%) reporting improvements in constipation after 16 weeks of treatment compared to baseline (**figure 4**).

Physician assessment of satisfaction and effectiveness of linaclotide therapy

Physicians' satisfaction with linaclotide treatment was assessed on a scale from 0 (very satisfied) to 10 (totally unsatisfied). In Austria, mean satisfaction was 2.9 (SD±3.0; median 2.0) points after 4 weeks of treatment, indicative of "good satisfaction", with at least 60% of the 83 total patients rated a score of ≤2.0 by their treating physicians. In Switzerland, mean satisfaction was 4.6 (SD±3.2; median 3.0) points after 16 weeks of treatment, indicative of "moderate

satisfaction", with at least 50% of the 51 total patients rated a score of ≤3.0 by their treating physicians (**figure 5A**). Furthermore, physicians assessed the global effectiveness of linaclotide treatment at the end of the treatment periods, and at visit 2, linaclotide effectiveness was evaluated as "excellent" in 33 patients (38.4%), "good" in 30 patients (34.9%), "moderate" in 14 patients (16.3%), and "poor" in nine patients (10.5%) in Austria. In Switzerland, physicians assessed linaclotide effectiveness as "excellent" in 18 patients (37.5%), "good" in 21 patients (43.8%), and "moderate" in nine patients (18.8%), with the effectiveness not rated as "poor" in any patient after 16 weeks of treatment (**figure 5B**).

Physicians were also asked to indicate the rationale for initiating linaclotide treatment. In Austria, linaclotide was prescribed due to low efficacy of previous medication for 39 (45.4%) patients; for three (3.5%) patients, linaclotide was prescribed due to low tolerability of prior medication; and for 52 (60.5%) patients, linaclotide was a new prescription whose treatment rationale was not a consequence of any previous medication. In Switzerland, 31 (59.6%) patients were prescribed linaclotide due to low efficacy of previous medication, three (5.8%) patients were prescribed linaclotide due to low tolerability of prior medication, while 20 (38.5%) patients received linaclotide as a new IBS-C prescription and not due to any previous medication.

Use of concomitant medications

Concomitant medication use was reported in 31 (36.1%) and 13 (25.0%) patients in Austria and Switzerland, respectively, with the most common being antihypertensive renin-angiotensin system agents in both countries, used by seven (8.1%) patients in Austria and six (11.5%) patients in Switzerland. A summary of concomitant medication use by Anatomical Therapeutic Chemical classification system is presented in **table 3**.

Safety and tolerability

Summary of adverse events

Sixteen AEs were reported in 10 (11.6%) patients in Austria after 4 weeks of treatment and 15 AEs were reported in 12 (23.1%) patients in Switzerland after 16 weeks of treatment (**table 4**). The most common AE was diarrhea, which occurred in six (7.0%) and eight (15.4%) patients in Austria and Switzerland, respectively. Drug ineffectiveness was reported as an AE for five (5.8%) patients in Austria and two (3.9%) patients in Switzerland. AEs leading to treatment discontinuation occurred in eight (9.3%) patients in Austria and 10 (19.2%) in Switzerland (**table 2**). AEs leading to dose reduction occurred in two (2.3%) patients in Austria. The majority of AEs were mild or moderate in intensity, while severe AEs were reported in two patients (two events [one abdominal distension and one rectal tenesmus]; 2.3%) in Austria and four patients (five events [four diarrhea and one urge incontinence]; 7.7%) in Switzerland. An AE was considered severe if the intensity of the symptoms significantly interfered with the patient's daily activities. Of all 31 reported AEs, treatment causality was confirmed for 11 AEs reported by eight patients in Austria (9.3%) and 14 AEs reported by 12 patients in Switzerland (23.1%). No serious AEs (i.e., AEs that were life-threatening) were reported in either country over the respective 4-week or 16-week treatment periods.

Physician assessment of linaclotide tolerability

Treating physicians assessed the global tolerability of linaclotide treatment, and after 4 weeks of treatment, linaclotide tolerability was evaluated as "excellent" in 44 patients (51.2%), "good" in 28 patients (32.6%), "moderate" in 11 patients (12.8%), and "poor" in three patients (3.5%) in Austria. In Switzerland, physicians assessed linaclotide tolerability as "excellent" in 24 patients (49.0%), "good" in 13 patients (26.5%), "moderate" in seven patients (14.3%), and "poor" in five patients (10.2%) after 16 weeks of treatment (**figure 5C**).

DISCUSSION

In this NIS, the effectiveness, safety, and tolerability of linaclotide were evaluated in patients with moderate-to-severe IBS-C under real-life settings in Austria and Switzerland. We observed improvements in abdominal pain, bloating, and frequency of bowel movements following a 4-week treatment period in both countries, which were further sustained over 12 additional weeks in Switzerland. Significant improvements in abdominal pain and bloating were observed both in patients who received prior laxative treatment and in those who did not receive IBS-C pre-treatment. However, between patients who administered laxative concomitant with linaclotide treatment and those who did not administer concomitant therapy, the degree of reduction after 4 weeks of treatment in mean intensity score in IBS-C symptoms suggests that concomitant laxative use diminished linaclotide effect. Importantly, treating physicians rated both the effectiveness and tolerability of linaclotide as “good” or “excellent” for a majority of patients. Few AEs were reported in this study, none of which were serious AEs, and no new safety signals were observed throughout the study.

IBS is characterized by multiple symptoms; however, abdominal pain, which is challenging to treat, is the major clinical manifestation. Moreover, abdominal pain is highly correlated with IBS disease severity and higher economic burden.[17-19] In the present study, >90% of all patients reported abdominal pain at baseline, with mean intensity scores of 6.0 in Austria and 5.4 in Switzerland, measured using the 11-point NRS. Clinically relevant change in the 11-point NRS for pain intensity was previously evaluated using data from 10 placebo-controlled trials that included 2724 patients with chronic pain (postherpetic neuralgia, osteoarthritis, diabetic neuropathy, chronic low back pain, and fibromyalgia).[20] By relating the 11-point NRS to the 7-point Patient Global Impression of Change with categories of “much improved” and “very much improved” used to determine a clinically relevant difference, a reduction of two points or 30% in the 11-point NRS was deemed clinically relevant.[20] A 10-point NRS for pain intensity was

evaluated in a cohort of 277 patients with IBS from the PROOF cohort, where the minimal clinically important difference was determined as 2.2 points or a 29.5% reduction in the NRS.[19] Our findings showed that collectively, the mean intensity of abdominal pain decreased from a baseline NRS level of 5.8 to 2.7 after 4 weeks of linaclotide treatment, corresponding to a 53% reduction in abdominal pain in both countries. In Austria, the reduction in mean abdominal pain intensity score was 3.5 points (57%) at 4 weeks, while reductions of 2.2 points (41%) at 4 weeks and 2.9 points (53%) after 16 weeks were observed in Switzerland. These reductions are consistent with those previously validated as clinically relevant change in pain intensity.[19,20]

In a recent NIS conducted in Germany, linaclotide treatment resulted in a reduction in mean pain intensity score of 1.72 points (35%) at 4 weeks and 2.5 points (50%) at 12 months after treatment initiation.[16] Data from these European real-world studies demonstrate that improvements in abdominal pain are observed in linaclotide-treated patients within the first month of treatment initiation and are sustained throughout the respective treatment periods. Mechanistically, as a GC-C receptor agonist, linaclotide is believed to increase extracellular cGMP levels, which in turn reduces the firing of pain-sensing visceral afferent fibers, resulting in an analgesic effect, thus reducing abdominal pain.[21]

In addition to improvements in abdominal pain, significant improvements in bloating were also observed following 4 weeks of treatment with linaclotide. At baseline, >94% of all patients reported bloating, and an overall reduction of 2.8 points (47%) was observed after the 4-week treatment period in both countries, which was sustained after 16 weeks of treatment in Switzerland. Moreover, linaclotide treatment increased the mean frequency of bowel movements to 4.5 times a week from a mean of 2.1 times a week at baseline in both countries. These observations are in line with previous animal studies that showed that linaclotide increases GI transit and fluid secretion via accumulation of intracellular cGMP in a dose-dependent manner.[22]

At study initiation, >84% of patients in this study had received IBS-C pre-treatment, mainly comprising laxatives or dietary fibers. We found that linaclotide was effective in managing symptoms of patients, regardless of prior treatment or concomitant medication use. In fact, our data found that a greater degree of improvement was observed in patients who did not use concomitant IBS-C treatment as compared to those who used concomitant laxatives (mean reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9), suggesting that laxatives might interfere with the efficacy of linaclotide. Laxatives such as polyethylene glycol are often used as first-line therapy for patients with IBS-C; however, their effect on improvements in abdominal pain or bloating are inconsistent and may lead to exacerbation of bloating, gas, and loose stools.[1,23] A recent consensus report recommended against the co-administration of linaclotide with laxatives, especially at the beginning of treatment due to potential diarrheal side effects, and only suggested co-administration in cases of partial response to linaclotide.[2] How concomitant laxatives may impact the efficacy of linaclotide is currently unclear. Osmotic laxatives may improve the frequency and consistency of bowel movements, but have no impact on abdominal pain or bloating; moreover, some stimulant laxatives (for which there are no randomized controlled trials [RCTs] in IBS-C) may relieve chronic constipation but result in abdominal pain and cramping.[1] In real-life settings, some patients may choose to add laxative treatment based on the severity of constipation, or water-binding agents may be titrated with linaclotide to gradually improve stool consistency; however, both of these strategies may inadvertently lessen the efficacy of linaclotide by binding excess fluids. Nonetheless, the present data demonstrate that linaclotide can effectively manage IBS-C symptoms irrespective of treatment history, and it does not require co-administration with other IBS-C medications, specifically laxatives.

The results of this study support the findings from pivotal Phase III RCTs that evaluated the efficacy and safety of linaclotide in IBS-C [9,13,24,25]. Two of the RCTs used the FDA's

responder criteria of improvement of ≥30% from baseline in average daily worst abdominal pain score and an increase of ≥1 in complete spontaneous bowel movements (CSBMs) per week. In the first double-blind, placebo-controlled, 26-week study of 804 participants, 49% of patients treated with linaclotide exhibited ≥30% improvement in abdominal pain (corresponding to a 2.1-point decrease) and 48% experienced an increase of ≥1 in weekly CSBMs (corresponding to a 2.2-point decrease) for at least six of the 12 treatment weeks.[9] Moreover, linaclotide treatment resulted in increases in spontaneous bowel movements (SBMs) per week by 3.8 and CSBMs per week by 2.2. In the second pivotal multicenter, double-blind, placebo-controlled study with 800 patients with IBS-C treated over 12 weeks, linaclotide resulted in significant improvements in abdominal pain (1.9-point worst abdominal pain improvement), bloating (1.9-point improvement), SBMs per week (+3.9 frequency), and CSBMs per week (+2.3 frequency).[13] In both the RCTs and the current NIS setting, improvements in IBS-C symptoms were demonstrated for linaclotide immediately following therapy initiation, and were sustained throughout treatment duration. Therefore, we can deduce that the NIS results under routine clinical settings in Europe, including those in the current study, are in agreement with the RCT findings from the US.

Global tolerability of linaclotide treatment was assessed as “good” or “excellent” in >75% patients by their treating physicians in both countries in the current study. Moreover, physician satisfaction with linaclotide therapy was evaluated on a 0-10 scale (“very satisfied” to “totally unsatisfied”), with scores of 2.9 (“good” satisfaction) after 4 weeks in Austria and 4.6 (“moderate” satisfaction) after 16 weeks in Switzerland. In comparison, 45% and 52% of patients treated with linaclotide noted satisfaction with linaclotide in the two RCTs, while 62% of treating physicians rated the effectiveness of linaclotide as “good” or “excellent” in Germany in a recent NIS.[9,13,16] Previously, an 18-month long-term safety study demonstrated similar patient satisfaction between linaclotide-treated patients who experienced diarrhea as compared

to those who did not, and >85% reported moderate satisfaction during the treatment period, indicating a high degree of treatment satisfaction irrespective of AEs.[26]

Diarrhea has previously been reported as a potential consequence of linaclotide-mediated increase in GI transit and fluid secretion, and as such, was the most commonly reported AE during this study (7% of patients in Austria and 15% of patients in Switzerland). All events were mild or moderate in severity. In the Phase III RCTs, diarrhea was reported by 19.5% of patients in the study by Chey *et al*., and by 19.7% in the study by Rao *et al*.[9,13] The discrepancy in diarrhea rates between this NIS and the previous RCTs may be due to the difference in reporting methods. In fact, all diarrhea AEs, regardless of treatment relatedness, were reported in the two RCTs, while only adverse drug reactions were reported in this NIS. Additionally, the lower incidence of adverse drug reactions reported in this NIS may be due to underreporting of AEs already described in the summary of product characteristics by physicians.[27] Finally, the impact of concomitant laxative use on diarrhea cannot be discounted.

Treatment options for IBS-C are limited, with traditional therapies showing limited effectiveness in improving symptoms and quality of life, and only four pharmacologic agents are approved for use. One such FDA-approved agent is lubiprostone, a chloride channel activator that was shown to improve IBS-C symptoms in two RCTs; however, lubiprostone is not approved for treatment in men due to limited efficacy.[28] Recently, plecanatide, a GC-C receptor agonist in the same drug class as linaclotide, was approved for the treatment of IBS-C based on data from two RCTs, with a comparable safety and efficacy profile as linaclotide RCTs; however, no evidence from real-life clinical settings currently exists for plecanatide.[29,30] Another FDA-approved agent for IBS-C is tegaserod, a prokinetic agent that was approved in 2002 but was withdrawn from the market in 2007 due to increased cardiovascular risks.[31] The FDA recently approved its reintroduction for use in adult women <65 years of age with IBS-C.[32] Overall, the present data confirm RCT findings in a real-world setting, showing that linaclotide is an effective

and satisfactory treatment for the management of IBS-C, a disease for which there are few effective therapeutic options.

Some limitations are associated with this study, which necessitate caution when interpreting the findings. The main limitations are the sample size and differing study durations between the two countries, which only allowed compilation of 4 weeks of data. Another limitation is that satisfaction with linaclotide was a physician-measured outcome, as compared to a patient-measured outcome in the clinical trials, which may lead to potential bias. The FDA's composite primary endpoint for IBS-C (responder: improvement of ≥30% in average daily worst abdominal pain score and increase of ≥1 CSBMs from baseline, both in the same week for at least 50% of weeks assessed) was used in the two clinical trials of linaclotide to determine efficacy.[9,13] In the present study, the lack of a composite primary endpoint may have led to inflation in the efficacy of linaclotide when compared to the clinical trials. As the diagnosis of moderate-to-severe IBS-C was determined by the treating physician without strict diagnosis criteria, selection bias may have occurred. In addition, as this was an NIS without a placebo control, the statistical analyses are descriptive and explorative, and no statistical hypotheses were pre-specified. Nevertheless, to the best of our knowledge, no real-world studies have been conducted evaluating IBS-C treatments in the Alpine region, and observational studies were thus undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in various European countries, with data recently published from Sweden,[33] the UK,[34] and Germany.[16] Our current findings suggest that linaclotide is safe and effective in reducing major symptoms of IBS-C in routine clinical practice in Austria and Switzerland. These data confirm the previously reported results from two randomized Phase III clinical trials that collectively demonstrate the efficacy and safety of linaclotide treatment for the management of patients with IBS-C with moderate-to-severe abdominal symptoms.

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TABLES

Table 1 Patient baseline demographics and characteristics

	Austria (N=86)	Switzerland (N=52)
Female, n (%)	71 (82.6)	40 (76.9)
Mean age, years	51.3	49.2
Mean BMI, kg/m²	24.0	23.4
Average time since diagnosis, years	2.1	5.2
Received pre-treatment, n (%)	73 (84.9)	49 (94.2)
Laxatives, n (%)	67 (77.9)	41 (78.9)
Dietary fibers, n (%)	55 (64.0)	36 (69.2)
Concomitant disease, n (%)	35 (40.7)	10 (19.2)
Hypertension, n (%)	9 (10.5)	5 (9.6)
Received concurrent IBS treatment, n (%)	33 (38.4)	16 (30.8)
Laxatives, n (%)	22 (25.6)	13 (25.0)
Osmotic, n (%)	18 (20.9)	6 (11.5)
Macrogol, combinations	9 (10.5)	5 (9.6)
Lactulose	5 (5.8)	1 (1.9)
Magnesium citrate	3 (3.5)	0
Sodium phosphate	1 (1.2)	0
Magnesium hydroxide	0	2 (3.9)
Bulk-forming, n (%)	0	5 (9.6)
Sterculia	0	4 (7.7)
Ispaghula (psylla seeds)	0	1 (1.9)
Stimulant, n (%)	17 (19.8)	7 (13.5)
Bisacodyl	8 (9.3)	3 (5.8)
Sodium picosulfate	5 (5.8)	2 (3.9)
Senna glycosides, combinations	2 (2.3)	2 (3.9)
Carbon dioxide-producing drugs	2 (2.3)	0

Stimulant/stool softener, n (%)	0	2 (3.9)
Glycerol	0	2 (3.9)
Stool softener, n (%)	0	2 (3.9)
Liquid paraffin, combinations	0	2 (3.9)
Patients experiencing abdominal pain at baseline, n (%)	85 (98.8)	46 (90.2)
Mean intensity score of abdominal pain at baseline (SD)	6.0 (±2.1)	5.4 (±2.7)
Patients experiencing bloating at baseline, n (%)	81 (95.3)	48 (94.1)
Mean intensity score of bloating at baseline (SD)	5.8 (±2.4)	5.6 (±2.7)
Mean number of bowel movements/week (SD)	2.1 (±1.3)	2.1 (±1.4)
Solid stool consistency, n (%)	55 (64.0)	22 (44.0)
'Morning' was most commonly advised time of intake, n (%)	68 (80.0)	26 (53.1)

% are calculated from total number of patients providing data for that outcome. Laxatives reported by type and chemical substance.

Baseline IBS symptoms were assessed during the week before start of therapy; 0=no pain/bloating; 10=worst pain/bloating.

BMI, body mass index; IBS, irritable bowel syndrome; SD, standard deviation.

Table 2 Reasons for discontinuing linaclotide

	Austria (N=86)	Switzerland (N=52)
Discontinued patients, n (%)	20 (23.3)	17 (32.7)
Lack of effectiveness	13 (15.1)	5 (9.6)
Adverse events	8 (9.3)	10 (19.2)
Improvement of symptoms	5 (5.8)	5 (9.6)
Lack of compliance	1 (1.2)	0
Excessive drug effect	0	1 (1.9)

Austria: Seven patients reported two reasons each.

Switzerland: Four patients reported two reasons each.

Table 3 Use of concomitant medications

	Austria (N=86)	Switzerland (N=52)
Patients receiving at least one concomitant medication, n (%)	31 (36.1)	13 (25.0)
Renin-angiotensin system agents	7 (8.1)	6 (11.5)
Psychoanaleptics	6 (7.0)	2 (3.9)
Beta-blocking agents	4 (4.7)	4 (7.7)
Lipid-modifying agents	4 (4.7)	4 (7.7)
Psycholeptics	3 (3.5)	0
Diabetes drugs	3 (3.5)	0
Analgesics	0	3 (5.8)
Drugs for acid-related disorders	0	2 (3.9)

Concomitant medications reported by anatomical main group.

Table 4 Summary of safety

	Austria (N=86)	Switzerland (N=52)
Total AEs	16	15
Serious AEs	0	0
Patients with ≥1 AE, n (%)	10 (11.6)	12 (23.1)
Diarrhea	6 (7.0)	8 (15.4)
Drug ineffective	5 (5.8)	2 (3.9)
Abdominal distension	2 (2.3)*	0
Dizziness	0	1 (2.0)
Condition aggravated	1 (1.2)	0
Rectal tenesmus	1 (1.2)	0
Headache	0	1 (1.9)
Hot flush	0	1 (1.9)
Nausea	0	1 (1.9)
Urge incontinence	0	1 (1.9)

AEs recorded per preferred term using Medical Dictionary for Regulatory Activities v18.0 (Austria) and v18.1 (Switzerland).

*Two abdominal distension events reported for one patient.

AE, adverse event.

FIGURE LEGENDS

Figure 1 Effect of linaclotide treatment on (A) abdominal pain, (B) bloating, and (C) frequency of bowel movements in all patients. Visit 1 and visit 2 refer to baseline and week 4, respectively. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 2 Effect of linaclotide treatment in patients with and without prior treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 3 Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 4 Proportion of patients reporting overall and individual improvement of IBS-C symptoms at the end-of-treatment periods (week 4 in Austria and week 16 in Switzerland). Proportions are based on the number of patients with available data at respective end-of-treatment visits (Austria, n=85; Switzerland, n=51).

Figure 5 Physicians' assessment of (A) satisfaction, and global assessment of (B) effectiveness and (C) tolerability of linaclotide. Satisfaction data in (A) presented on a scale of 0 [very satisfied] to 10 [totally unsatisfied]; Austria, mean 2.9 ± 3.0 points ["good" satisfaction]; Switzerland, mean 4.6 ± 3.2 points ["moderate" satisfaction].

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AUTHOR CONTRIBUTIONS

Daniel Pohl, Michael Fried, and Heinz Hammer participated in the study design, trial conduct, and data collection. Dominic Lawrance and Elmar Beck participated in data collection and analysis. All authors interpreted the data and participated in writing the manuscript with medical writing services provided by the funder. All authors read the manuscript critically and approved the final version.

DISCLOSURES

Writing and editorial assistance was provided to the authors by Germaine D. Agollah, PhD of Allergan. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Daniel Pohl is a consultant and speaker for Allergan. Dominic Lawrance is an employee of Allergan. Elmar Beck is an employee of Anfomed GmbH, which was contracted by Allergan as a contract research organization for the conduct of this study. Heinz Hammer is a consultant and speaker for Allergan.

DATA AVAILABILITY

Data reported in this manuscript are available within the article. Allergan will share de-identified patient-level and/or study-level data, including protocols and clinical study reports, for Phase II–IV trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The indication studied in the trial must have regulatory approval in the United States and/or

European Union and the primary manuscript from the trial must be published prior to data sharing. To request access to the data, the researcher must sign a data use agreement. All shared data are to be used for non-commercial purposes only. More information can be found on http://www.allerganclinicaltrials.com/.

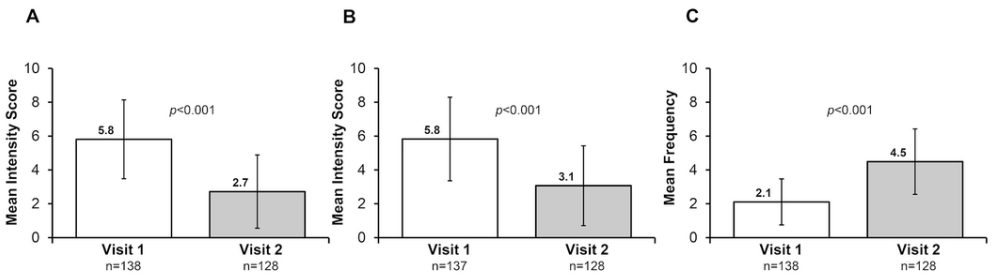

Figure 1 Effect of linaclotide treatment on (A) abdominal pain, (B) bloating, and (C) frequency of bowel movements in all patients. Visit 1 and visit 2 refer to baseline and week 4, respectively. **$p<0.001$ versus visit 1, assessed by Wilcoxon signed-rank test.

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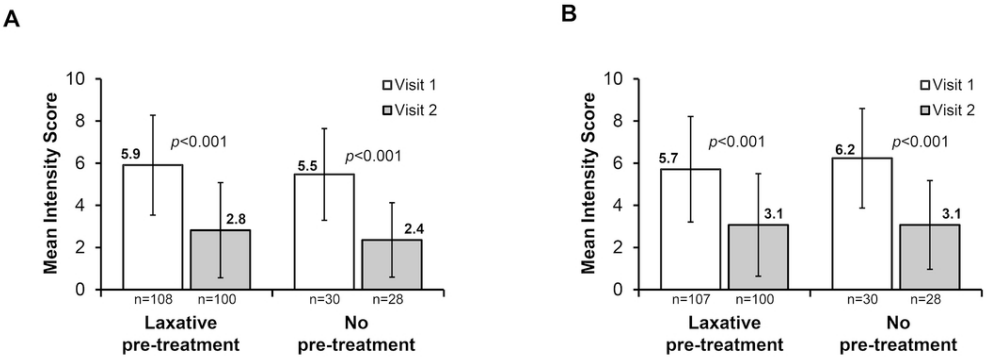

Figure 2 Effect of linaclotide treatment in patients with and without prior treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. $^{**}p<0.001$ versus visit 1, assessed by Wilcoxon signed-rank test.

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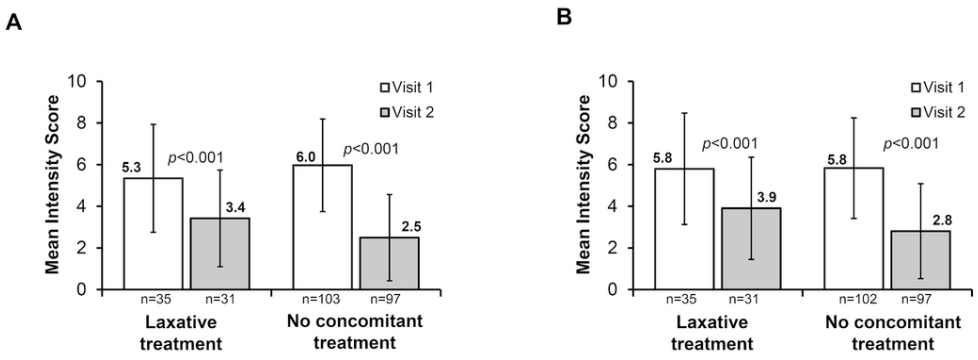

Figure 3 Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. **$p<0.001$ versus visit 1, assessed by Wilcoxon signed-rank test.

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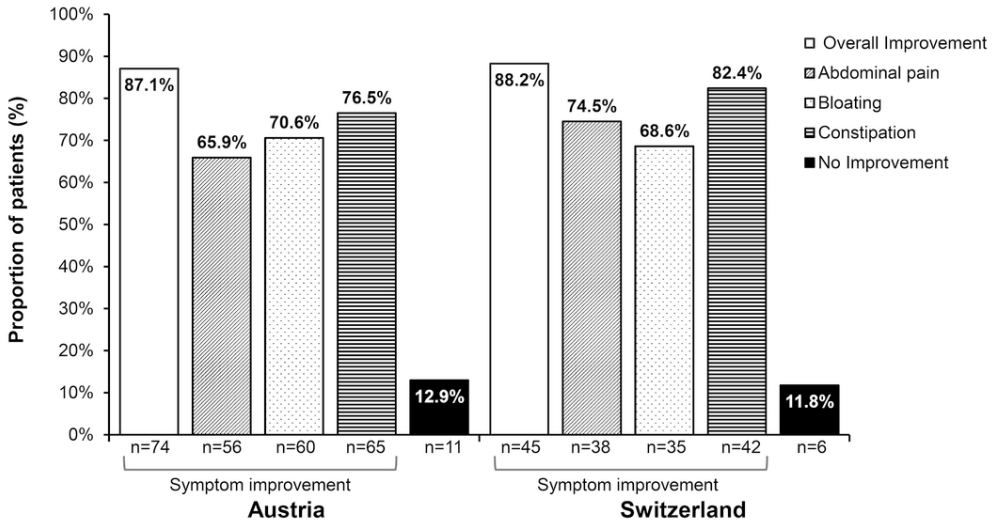

Figure 4 Proportion of patients reporting overall and individual improvement of IBS-C symptoms at the end-of-treatment periods (week 4 in Austria and week 16 in Switzerland). Proportions are based on the number of patients with available data at respective end-of-treatment visits (Austria, n=85; Switzerland, n=51).

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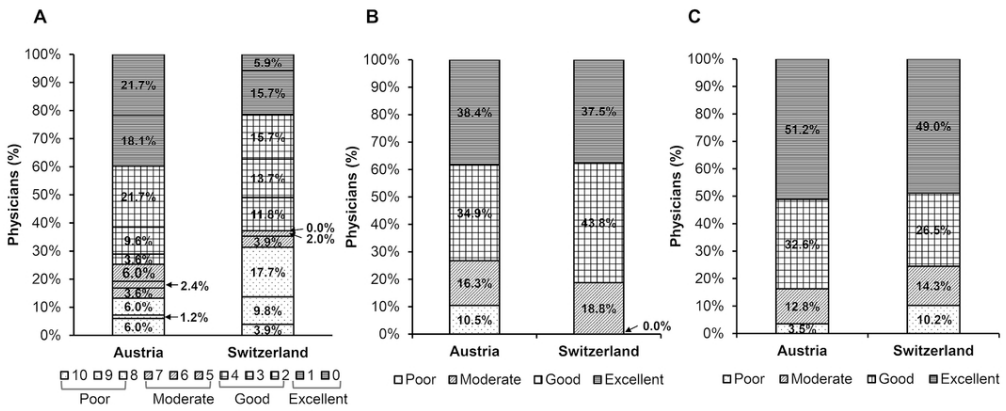

Figure 5 Physicians' assessment of (A) satisfaction, and global assessment of (B) effectiveness and (C) tolerability of linaclotide. Satisfaction data in (A) presented on a scale of 0 [very satisfied] to 10 [totally unsatisfied]; Austria, mean 2.9 ± 3.0 points ["good" satisfaction]; Switzerland, mean 4.6 ± 3.2 points ["moderate" satisfaction].

90x37mm (300 x 300 DPI)

RESEARCH CHECKLIST

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7

Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	N/A

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	33

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and Tertiary Centers: The Alpine study

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TITLE PAGE

A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and Tertiary Centers: The Alpine study

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Running Title: Linaclotide in IBS-C – The Alpine study

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Keywords: Irritable bowel syndrome-constipation; IBS-C; linaclotide; real world evidence; non-interventional study; abdominal pain; bloating

ABSTRACT

Objectives: We evaluated the effectiveness and tolerability of linaclotide, a minimally absorbed guanylate cyclase-C agonist, in patients with irritable bowel syndrome with constipation (IBS-C) in routine clinical practice.

Setting: A multicenter, non-interventional study conducted between December 2013 and November 2015 across 31 primary, secondary, and tertiary centers in Austria and Switzerland.

Participants: The study enrolled 138 patients aged ≥18 years with moderate-to-severe IBS-C. Treatment decision was at the physician's discretion. Patients with known hypersensitivity to the study drug or suspected mechanical obstruction were excluded. The mean age of participants was 50 years, >75% of whom were female. 128 patients completed the study.

Primary and secondary outcome measures: Data were collected at weeks 0 and 4 in Austria and weeks 0, 4, and 16 in Switzerland. The primary effectiveness endpoints included: severity of abdominal pain and bloating (11-point numeric rating scale [0=no pain/bloating to 10=worst possible pain/bloating]), frequency of bowel movements, and physicians' global effectiveness of linaclotide. Treatment-related adverse events were recorded.

Results: Following a 4-week treatment period, the mean intensity score of abdominal pain was reduced to 2.7 from 5.8 at baseline, while the bloating intensity score was reduced to 3.1 from 5.8 at baseline (both indices $p<0.001$). The frequency of mean weekly bowel movements increased from 2.1 at baseline to 4.5 at week 4 ($p<0.001$). Global effectiveness and tolerability of linaclotide were assessed as "good" or "excellent" in >70% of patients by the treating physicians. In total, 31 adverse events were reported in 22 patients, the most common being diarrhea, reported by six (7%) and eight (15.4%) patients in Austria and Switzerland, respectively.

Conclusions: Patients with IBS-C receiving linaclotide experienced effective treatment of moderate-to-severe symptoms in routine clinical practice. Linaclotide was safe and well tolerated and no new safety concerns were raised, supporting results from previous clinical trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first real-world study evaluating the effectiveness and tolerability of an IBS-C treatment in the Alpine region.
- This study sought to evaluate whether the efficacy and tolerability of linaclotide that was demonstrated in randomized clinical trials could be recapitulated in clinical practice in a real-world setting.
- Results from the physicians' global assessment of efficacy and tolerability will be useful in determining physician comfort level with prescribing linaclotide for their patients.
- This was a non-interventional study that lacked a placebo control; thus, the statistical analyses are descriptive and exploratory in nature.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurrent abdominal pain or discomfort and change in bowel habits.[1] IBS is a common GI ailment, with global prevalence ranging from 3-21%, depending on the diagnostic criteria.[2] The prevalence of IBS in Europe is estimated at 12-15%.[3] IBS is subtyped based on the predominant stool pattern, and includes IBS subtype with constipation (IBS-C), diarrhea (IBS-D), mixed stool (IBS-M), or unsubtyped (IBS-U) when stool consistency does not meet criteria for IBS-C, -D, or -M.[4] When defined by Rome III diagnostic criteria, IBS is prevalent in approximately 1-29% of the general population, with IBS-C present in 1-4%.[5] Of the IBS subtypes, IBS-C is the second most common subtype, comprising approximately 35% of all IBS cases.[3]

In addition to abdominal pain and discomfort, patients with IBS-C often experience hard or lumpy stools, straining, feeling of incomplete evacuation, and bloating. Moreover, IBS-C has an undue impact on quality of life, increases healthcare costs, and reduces work productivity.[6,7] Since IBS-C presents with a constellation of symptoms, therapy options have centered on symptom relief and have generally included dietary and lifestyle modifications, and over-the-counter medications such as fiber supplements and laxatives that aim to relieve constipation. However, these treatments are often ineffective and patients resort to additional therapies, which in turn, drive up healthcare costs and resources, thus underscoring the need to identify efficacious treatment options for IBS-C.[8]

Linaclotide is a minimally absorbed 14-amino acid guanylate cyclase-C (GC-C) receptor agonist structurally related to the guanylin peptide family.[9] Upon binding to GC-C receptors, linaclotide increases the intracellular production of cyclic guanosine monophosphate (cGMP), which in turn activates the cystic fibrosis transmembrane conductance regulator, resulting in secretion of chloride and bicarbonate into the intestinal lumen, ultimately accelerating intestinal transit.[10]

Linaclotide was demonstrated to increase colonic transit and reduce abdominal pain and constipation in patients with IBS-C in Phase II trials.[11,12] Subsequently, the efficacy and safety of linaclotide for the treatment of IBS-C was established in two placebo-controlled Phase III trials that showed improvements in IBS-C symptoms, including abdominal pain and bowel movements.[9,13]

Linaclotide was approved by the Food and Drug Administration (FDA) and European Medicines Agency in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C.[14,15] While the efficacy and safety of linaclotide has been established in clinical trial settings, these may not depict real-life experiences. To address this need, observational studies were undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in Europe. In routine clinical practice, linaclotide has recently been shown to be effective in improving IBS-C symptoms in a post-marketing authorization study conducted in Germany.[16] Herein, we aimed to document the effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C in adults under real-life conditions in the Alpine region of Austria and Switzerland.

METHODS

Study design

This was a multicenter, open, observational, non-interventional study (NIS) evaluating the effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C, in adult patients under real-life routine clinical practice conditions in Austria and Switzerland. There were no treatment groups or actions to which patients were randomly assigned. A total of 200 patients were planned for enrollment across 40 sites in each country. The study was conducted from December 2013 to March 2015 in Austria and from November 2014 to November 2015 in Switzerland.

The study comprised a 4-week treatment period commencing with visit 1 at treatment initiation and visit 2 occurring approximately 4 weeks after initiation in Austria. In Switzerland, data were collected over the course of three visits, at 0, 4, and 16 weeks after treatment initiation. Linaclotide was administered per the usual therapeutic procedure of the attending physician and in accordance with the indication for the drug (290 µg once daily, taken at least 30 minutes before meals).[15]

The study protocols were approved by the local Institutional Review Board or Independent Ethics Committee of each center (study approval numbers: Austria, 26-279 ex 13/14; Switzerland, KEK-ZH-Nr.2014-0137). The study was conducted in accordance with the Declaration of Helsinki, applicable local laws and regulations, and International Conference on Harmonisation E6 Good Clinical Practice guidelines. All participants provided written informed consent prior to study initiation.

Participants

Eligible patients were aged ≥18 years with a diagnosis of moderate-to-severe IBS-C (diagnosed by the treating physician), characterized by clinical evidence of relevant interference of symptoms with well-being and/or daily routines at work or during leisure. The decision to treat a patient with linaclotide was made solely by the treating physician prior to inclusion in the study. Patients with known hypersensitivity to the active ingredient or any other component of linaclotide, suspected or known GI obstruction, or who were pregnant or planning to become pregnant were excluded from the study.

Study assessments

All relevant data collected during routine treatment with linaclotide were recorded in case report forms. Patient demographics and medical history were collected, including diagnosis, prior treatment, and symptoms of IBS-C, comorbidities, and concomitant medications.

The primary effectiveness endpoints included severity of abdominal pain and bloating, frequency of bowel movements during the week before each visit, general symptom improvement relative to pre-treatment, physicians' satisfaction with linaclotide therapy, sensation of incomplete bowel evacuation, change in predominant stool consistency, and physicians' global assessment of the effectiveness of linaclotide. Changes in the severity of abdominal pain and bloating were measured using an 11-point numeric rating scale (NRS; 0=no pain/bloating to 10=worst possible pain/bloating). Physicians' satisfaction with linaclotide therapy was measured using a 10-point NRS (0=very satisfied to 10=totally unsatisfied). General symptom improvement and improvement in three individual symptoms – abdominal pain, bloating, and constipation – were measured by patient response to simple yes/no questions asked by the physician (e.g., "Have symptoms improved over the last week compared to the time prior to therapy start?"). Frequency of bowel movements during the week before each visit, sensation of incomplete bowel evacuation, and change in predominant stool consistency were patient-reported.

Adverse events (AEs) related to linaclotide treatment or whose relation to linaclotide treatment could not be excluded were documented. AEs assessed by the physician as not related to linaclotide treatment were not documented. Other safety measures included physicians' global assessment of the tolerability of linaclotide.

Statistical analyses

Statistical analysis was performed using SAS™ v9.4 software (SAS Institute, Cary, NC). Data were analyzed using descriptive statistics and no hypotheses were pre-specified. To determine whether the pre–post changes of symptoms were statistically significant, the Wilcoxon signed-rank test was applied. Reported *p*-values are two-tailed, using an alpha level of 0.05 to assess statistical significance. Missing data were imputed using the last observation carried forward method. Visit 1 and 2 efficacy data were compiled for both countries, where applicable.

Patient and public involvement

This was an observational study. Patients continued on existing medication at their own discretion. Study outcomes were scored by the patients and the data collected during this study were informed by the patients' experiences.

RESULTS

Patient characteristics

A total of 86 patients in 22 sites and 52 patients in nine sites were enrolled in Austria and Switzerland, respectively. Baseline characteristics were generally comparable between the two countries. Of the enrolled patients, 71 (82.6%) in Austria and 40 (76.9%) in Switzerland were female, and the mean age was 51 and 49 years, respectively (**table 1**). The mean body mass index was 24 kg/m^2 and 23 kg/m^2 in each country. The average time since IBS-C diagnosis was 2.1 years and 5.2 years for patients in Austria and Switzerland, respectively. At baseline, more than 90% of patients in both countries reported abdominal pain (mean intensity scores of 6.0 and 5.4, respectively) and bloating (mean intensity scores of 5.8 and 5.6, respectively). Patients in both countries reported a mean of 2.1 bowel movements per week. Prior treatment for IBS-C was reported by 73 (84.9%) patients in Austria and 49 (94.2%) patients in Switzerland, mainly consisting of laxatives and dietary fibers, while 33 (38.4%) patients in Austria and 16 (30.8%) patients in Switzerland received concurrent IBS treatment. Concomitant diseases were reported by 35 (40.7%) patients in Austria and 10 (19.2%) patients in Switzerland (**table 1**). Collectively, baseline characteristics of the patients with IBS-C in this study were reflective of the general IBS patient population (i.e., approximately 70% of IBS patients are typically female, with a high likelihood of the majority of patients being ≤50 years).

Throughout the course of the study, 20 (23.3%) patients in Austria and 17 (32.7%) patients in Switzerland discontinued linaclotide treatment, with the main reasons for discontinuation being

lack of effectiveness for 13 (15.1%) patients in Austria and adverse events in Switzerland, reported in 10 (19.2%) patients. Reasons for treatment discontinuation are summarized in **table 2**.

Effectiveness outcomes

Effect of linaclotide treatment on symptoms of IBS-C

Linaclotide was administered over 4 weeks in Austria and 16 weeks in Switzerland, and data from the initial 4-week treatment periods are compiled in this analysis. Of the 138 enrolled patients, data were available for 128 patients at week 4. Improvements in abdominal pain, bloating, and bowel movements were observed after 4 weeks of treatment with linaclotide. From a mean intensity score of 5.8 at baseline, abdominal pain was reduced to 2.7 after 4 weeks of treatment in both countries (**figure 1A**; $p<0.001$ vs. visit 1; 11-point NRS [0=no pain to 10=worst possible pain). In Switzerland, continued reduction in abdominal pain was observed at week 16, with a mean intensity score of 2.5 (standard deviation [SD]±2.0; n=51; $p<0.0001$ vs. visit 1). Improvements in bloating were also seen after 4 weeks of treatment in both countries; from a baseline mean intensity score of 5.8, the bloating score was reduced to 3.1 at week 4 (**figure 1B**; $p<0.001$ vs. visit 1; 11-point NRS [0=no bloating to 10=worst possible bloating]), with a mean intensity score of 3.0 (SD±2.2; n=51; $p<0.0001$ vs. visit 1) at week 16 in Switzerland. Furthermore, the frequency of bowel movements increased from a mean of 2.1 per week at baseline to 4.5 at week 4 (**figure 1C**; $p<0.001$ vs. visit 1) in both countries, and to 4.7 (SD±1.6; n=51; $p<0.0001$ vs. visit 1) at week 16 in Switzerland.

Data were stratified based on patients who received prior IBS-C treatment, and improvements in IBS-C symptoms were observed within the 4-week treatment period, regardless of prior IBS-C treatment. Significant reductions from week 1 to week 4 in mean abdominal pain intensity and mean bloating intensity were seen in patients who had received laxative pre-treatment and in those who did not receive prior IBS-C treatment (**figure 2A** and **figure 2B**, respectively; all

p<0.001 vs. visit 1). Similar degrees of mean reduction in abdominal pain were seen in patients who did not and those who received laxative pre-treatment (both 3.1). Furthermore, the effect of concomitant laxative use with linaclotide was evaluated. Our results showed that significant reduction was achieved after 4 weeks of treatment in mean abdominal pain intensity (**figure 3A**; all *p*<0.001 vs. visit 1) and mean bloating intensity (**figure 3B**; all *p*<0.001 vs. visit 1), both in patients who used laxative concomitantly with linaclotide and those who did not. Greater symptom improvement was observed in those who did not use concomitant treatment (mean reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9; **figure 3A** and **3B**; all differences *p*<0.001 vs. visit 1).

Patient assessment of improvement of IBS-C symptoms

At each respective end-of-treatment period, patients were asked to indicate their sense of general improvement of symptoms as compared to the pre-treatment period. In Austria, 74 patients (87.1%) reported overall improved symptoms, among which 56 (65.9%) patients experienced improvements in abdominal pain, 60 (70.6%) had improvements in bloating, and 65 (76.5%) reported improvements in constipation at visit 2 compared to baseline (**figure 4**). In Switzerland, 45 patients (88.2%) reported overall improved symptoms, consisting of 38 (74.5%) patients with improvements in abdominal pain, 35 (68.6%) with improvements in bloating, and 42 (82.4%) reporting improvements in constipation after 16 weeks of treatment compared to baseline (**figure 4**).

Physician assessment of satisfaction and effectiveness of linaclotide therapy

Physicians' satisfaction with linaclotide treatment was assessed on a scale from 0 (very satisfied) to 10 (totally unsatisfied). In Austria, mean satisfaction was 2.9 (SD±3.0; median 2.0) points after 4 weeks of treatment, indicative of "good satisfaction", with at least 60% of the 83 total patients rated a score of ≤2.0 by their treating physicians. In Switzerland, mean satisfaction

was 4.6 (SD±3.2; median 3.0) points after 16 weeks of treatment, indicative of "moderate satisfaction", with at least 50% of the 51 total patients rated a score of ≤3.0 by their treating physicians (**figure 5A**). Furthermore, physicians assessed the global effectiveness of linaclotide treatment at the end of the treatment periods, and at visit 2, linaclotide effectiveness was evaluated as "excellent" in 33 patients (38.4%), "good" in 30 patients (34.9%), "moderate" in 14 patients (16.3%), and "poor" in nine patients (10.5%) in Austria. In Switzerland, physicians assessed linaclotide effectiveness as "excellent" in 18 patients (37.5%), "good" in 21 patients (43.8%), and "moderate" in nine patients (18.8%), with the effectiveness not rated as "poor" in any patient after 16 weeks of treatment (**figure 5B**).

Physicians were also asked to indicate the rationale for initiating linaclotide treatment. In Austria, linaclotide was prescribed due to low efficacy of previous medication for 39 (45.4%) patients; for three (3.5%) patients, linaclotide was prescribed due to low tolerability of prior medication; and for 52 (60.5%) patients, linaclotide was a new prescription whose treatment rationale was not a consequence of any previous medication. In Switzerland, 31 (59.6%) patients were prescribed linaclotide due to low efficacy of previous medication, three (5.8%) patients were prescribed linaclotide due to low tolerability of prior medication, while 20 (38.5%) patients received linaclotide as a new IBS-C prescription and not due to any previous medication.

Use of concomitant medications

Concomitant medication use was reported in 31 (36.1%) and 13 (25.0%) patients in Austria and Switzerland, respectively, with the most common being antihypertensive renin-angiotensin system agents in both countries, used by seven (8.1%) patients in Austria and six (11.5%) patients in Switzerland. A summary of concomitant medication use by Anatomical Therapeutic Chemical classification system is presented in **table 3**.

Safety and tolerability

Summary of adverse events

Sixteen AEs were reported in 10 (11.6%) patients in Austria after 4 weeks of treatment and 15 AEs were reported in 12 (23.1%) patients in Switzerland after 16 weeks of treatment (**table 4**). The most common AE was diarrhea, which occurred in six (7.0%) and eight (15.4%) patients in Austria and Switzerland, respectively. Drug ineffectiveness was reported as an AE for five (5.8%) patients in Austria and two (3.9%) patients in Switzerland. AEs leading to treatment discontinuation occurred in eight (9.3%) patients in Austria and 10 (19.2%) in Switzerland (**table 2**). AEs leading to dose reduction occurred in two (2.3%) patients in Austria. The majority of AEs were mild or moderate in intensity, while severe AEs were reported in two patients (two events [one abdominal distension and one rectal tenesmus]; 2.3%) in Austria and four patients (five events [four diarrhea and one urge incontinence]; 7.7%) in Switzerland. An AE was considered severe if the intensity of the symptoms significantly interfered with the patient's daily activities. Of all 31 reported AEs, treatment causality was confirmed for 11 AEs reported by eight patients in Austria (9.3%) and 14 AEs reported by 12 patients in Switzerland (23.1%). No serious AEs (i.e., AEs that were life-threatening) were reported in either country over the respective 4-week or 16-week treatment periods.

Physician assessment of linaclotide tolerability

Treating physicians assessed the global tolerability of linaclotide treatment, and after 4 weeks of treatment, linaclotide tolerability was evaluated as "excellent" in 44 patients (51.2%), "good" in 28 patients (32.6%), "moderate" in 11 patients (12.8%), and "poor" in three patients (3.5%) in Austria. In Switzerland, physicians assessed linaclotide tolerability as "excellent" in 24 patients (49.0%), "good" in 13 patients (26.5%), "moderate" in seven patients (14.3%), and "poor" in five patients (10.2%) after 16 weeks of treatment (**figure 5C**).

DISCUSSION

In this NIS, the effectiveness, safety, and tolerability of linaclotide were evaluated in patients with moderate-to-severe IBS-C under real-life settings in Austria and Switzerland. We observed improvements in abdominal pain, bloating, and frequency of bowel movements following a 4-week treatment period in both countries, which were further sustained over 12 additional weeks in Switzerland. Significant improvements in abdominal pain and bloating were observed both in patients who received prior laxative treatment and in those who did not receive IBS-C pre-treatment. However, between patients who administered laxative concomitant with linaclotide treatment and those who did not administer concomitant therapy, the degree of reduction after 4 weeks of treatment in mean intensity score in IBS-C symptoms suggests that concomitant laxative use diminished linaclotide effect. Importantly, treating physicians rated both the effectiveness and tolerability of linaclotide as “good” or “excellent” for a majority of patients. Few AEs were reported in this study, none of which were serious AEs, and no new safety signals were observed throughout the study.

Abdominal pain is the major clinical manifestation of IBS and is challenging to treat. Moreover, abdominal pain is highly correlated with IBS disease severity and higher economic burden.[17-19] In the present study, >90% of all patients reported abdominal pain at baseline, with mean intensity scores of 6.0 in Austria and 5.4 in Switzerland, measured using the 11-point NRS. Clinically relevant change in the 11-point NRS for pain intensity was previously evaluated using data from 10 placebo-controlled trials that included 2724 patients with chronic pain (postherpetic neuralgia, osteoarthritis, diabetic neuropathy, chronic low back pain, and fibromyalgia).[20] By relating the 11-point NRS to the 7-point Patient Global Impression of Change with categories of “much improved” and “very much improved” used to determine a clinically relevant difference, a reduction of two points or 30% in the 11-point NRS was deemed clinically relevant.[20] A 10-point NRS for pain intensity was evaluated in a cohort of 277 patients with IBS from the PROOF

cohort, where the minimal clinically important difference was determined as 2.2 points or a 29.5% reduction in the NRS.[19] Our findings showed that collectively, the mean intensity of abdominal pain decreased from a baseline NRS level of 5.8 to 2.7 after 4 weeks of linaclotide treatment, corresponding to a 53% reduction in abdominal pain in both countries. In Austria, the reduction in mean abdominal pain intensity score was 3.5 points (57%) at 4 weeks, while reductions of 2.2 points (41%) at 4 weeks and 2.9 points (53%) after 16 weeks were observed in Switzerland. These reductions are consistent with those previously validated as clinically relevant change in pain intensity.[19,20]

In a recent NIS conducted in Germany, linaclotide treatment resulted in a reduction in mean pain intensity score of 1.72 points (35%) at 4 weeks and 2.5 points (50%) at 12 months after treatment initiation.[16] Data from these European real-world studies demonstrate that improvements in abdominal pain are observed in linaclotide-treated patients within the first month of treatment initiation and are sustained throughout the respective treatment periods. Mechanistically, as a GC-C receptor agonist, linaclotide is believed to increase extracellular cGMP levels, which in turn reduces the firing of pain-sensing visceral afferent fibers, resulting in an analgesic effect, thus reducing abdominal pain.[21]

In addition to improvements in abdominal pain, significant improvements in bloating were also observed following 4 weeks of treatment with linaclotide. At baseline, >94% of all patients reported bloating, and an overall reduction of 2.8 points (47%) was observed after the 4-week treatment period in both countries, which was sustained after 16 weeks of treatment in Switzerland. Moreover, linaclotide treatment increased the mean frequency of bowel movements to 4.5 times a week from a mean of 2.1 times a week at baseline in both countries. These observations are in line with previous animal studies that showed that linaclotide increases GI transit and fluid secretion via accumulation of intracellular cGMP in a dose-dependent manner.[22]

At study initiation, >84% of patients in this study had received IBS-C pre-treatment, mainly comprising laxatives or dietary fibers. We found that linaclotide was effective in managing symptoms of patients, regardless of prior treatment or concomitant medication use. In fact, our data found that a greater degree of improvement was observed in patients who did not use concomitant IBS-C treatment as compared to those who used concomitant laxatives (mean reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9), suggesting that laxatives might interfere with the efficacy of linaclotide. Laxatives such as polyethylene glycol are often used as first-line therapy for patients with IBS-C; however, their effect on improvements in abdominal pain or bloating are inconsistent.[1,23] A recent consensus report recommended against the co-administration of linaclotide with laxatives, especially at the beginning of treatment due to potential diarrheal side effects, and only suggested co-administration in cases of partial response to linaclotide.[2] How concomitant laxatives may impact the efficacy of linaclotide is currently unclear. Osmotic laxatives may improve the frequency and consistency of bowel movements, but have no impact on abdominal pain or bloating; moreover, some stimulant laxatives (for which there are no randomized controlled trials [RCTs] in IBS-C) may relieve chronic constipation but result in abdominal pain and cramping.[1] In real-life settings, some patients may choose to add laxative treatment based on the severity of constipation, or water-binding agents may be titrated with linaclotide to gradually improve stool consistency; however, both of these strategies may inadvertently lessen the efficacy of linaclotide by binding excess fluids. Nonetheless, the present data demonstrate that linaclotide can effectively manage IBS-C symptoms irrespective of treatment history, and it does not require co-administration with other IBS-C medications, specifically laxatives.

The results of this study support the findings from pivotal Phase III RCTs that evaluated the efficacy and safety of linaclotide in IBS-C [9,13,24,25]. Two of the RCTs used the FDA's responder criteria of improvement of ≥30% from baseline in average daily worst abdominal pain

score and an increase of ≥1 in complete spontaneous bowel movements (CSBMs) per week. In the first double-blind, placebo-controlled, 26-week study of 804 participants, 49% of patients treated with linaclotide exhibited ≥30% improvement in abdominal pain (corresponding to a 2.1-point decrease) and 48% experienced an increase of ≥1 in weekly CSBMs (corresponding to a 2.2-point decrease) for at least six of the 12 treatment weeks.[9] Moreover, linaclotide treatment resulted in increases in spontaneous bowel movements (SBMs) per week by 3.8 and CSBMs per week by 2.2. In the second pivotal multicenter, double-blind, placebo-controlled study with 800 patients with IBS-C treated over 12 weeks, linaclotide resulted in significant improvements in abdominal pain (1.9-point worst abdominal pain improvement), bloating (1.9-point improvement), SBMs per week (+3.9 frequency), and CSBMs per week (+2.3 frequency).[13]

Global tolerability of linaclotide treatment was assessed as “good” or “excellent” in >75% patients by their treating physicians in both countries in the current study. Moreover, physician satisfaction with linaclotide therapy was evaluated on a 0-10 scale (“very satisfied” to “totally unsatisfied”), with scores of 2.9 (“good” satisfaction) after 4 weeks in Austria and 4.6 (“moderate” satisfaction) after 16 weeks in Switzerland. In comparison, 45% and 52% of patients treated with linaclotide noted satisfaction with linaclotide in the two RCTs, while 62% of treating physicians rated the effectiveness of linaclotide as “good” or “excellent” in Germany in a recent NIS.[9,13,16] Previously, an 18-month long-term safety study demonstrated similar patient satisfaction between linaclotide-treated patients who experienced diarrhea as compared to those who did not, and >85% reported moderate satisfaction during the treatment period, indicating a high degree of treatment satisfaction irrespective of AEs.[26]

Diarrhea has previously been reported as a potential consequence of linaclotide-mediated increase in GI transit and fluid secretion, and as such, was the most commonly reported AE during this study (7% of patients in Austria and 15% of patients in Switzerland). All events were mild or moderate in severity. In the Phase III RCTs, diarrhea was reported by 19.5% of patients

in the study by Chey *et al*., and by 19.7% in the study by Rao *et al*.[9,13] The discrepancy in diarrhea rates between this NIS and the previous RCTs may be due to the difference in reporting methods. Additionally, the lower incidence of adverse drug reactions reported in this NIS may be due to underreporting of AEs already described in the summary of product characteristics by physicians.[27] Finally, the impact of concomitant laxative use on diarrhea cannot be discounted.

Treatment options for IBS-C are limited, with traditional therapies showing limited effectiveness in improving symptoms and quality of life, and only four pharmacologic agents are approved for use. One such FDA-approved agent is lubiprostone, a chloride channel activator that was shown to improve IBS-C symptoms in two RCTs; however, lubiprostone is not approved for treatment in men due to limited efficacy.[28] Recently, plecanatide, a GC-C receptor agonist in the same drug class as linaclotide, was approved for the treatment of IBS-C based on data from two RCTs, with a comparable safety and efficacy profile as linaclotide RCTs; however, no evidence from real-life clinical settings currently exists for plecanatide.[29,30] Another FDA-approved agent for IBS-C is tegaserod, a prokinetic agent that was approved in 2002 but was withdrawn from the market in 2007 due to increased cardiovascular risks.[31] The FDA recently approved its reintroduction for use in adult women <65 years of age with IBS-C.[32]

Some limitations are associated with this study, which necessitate caution when interpreting the findings. The main limitations are the sample size and differing study durations between the two countries, which only allowed compilation of 4 weeks of data. Another limitation is that satisfaction with linaclotide was a physician-measured outcome, as compared to a patient-measured outcome in the clinical trials, which may lead to potential bias. The FDA's composite primary endpoint for IBS-C (responder: improvement of ≥30% in average daily worst abdominal pain score and increase of ≥1 CSBMs from baseline, both in the same week for at least 50% of weeks assessed) was used in the two clinical trials of linaclotide to determine efficacy.[9,13] In

the present study, the lack of a composite primary endpoint may have led to inflation in the efficacy of linaclotide when compared to the clinical trials. As the diagnosis of moderate-to-severe IBS-C was determined by the treating physician without strict diagnosis criteria, selection bias may have occurred. In addition, as this was an NIS without a placebo control, the statistical analyses are descriptive and explorative, and no statistical hypotheses were pre-specified. Nevertheless, to the best of our knowledge, no real-world studies have been conducted evaluating IBS-C treatments in the Alpine region, and observational studies were thus undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in various European countries, with data recently published from Sweden,[33] the UK,[34] and Germany.[16] Our current findings suggest that linaclotide is safe and effective in reducing major symptoms of IBS-C in routine clinical practice in Austria and Switzerland. These data support the previously reported results from two randomized Phase III clinical trials that collectively demonstrate the efficacy and safety of linaclotide treatment for the management of patients with IBS-C with moderate-to-severe abdominal symptoms.

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TABLES

Table 1 Patient baseline demographics and characteristics

	Austria (N=86)	Switzerland (N=52)
Female, n (%)	71 (82.6)	40 (76.9)
Mean age, years	51.3	49.2
Mean BMI, kg/m²	24.0	23.4
Average time since diagnosis, years	2.1	5.2
Received pre-treatment, n (%)	73 (84.9)	49 (94.2)
Laxatives, n (%)	67 (77.9)	41 (78.9)
Dietary fibers, n (%)	55 (64.0)	36 (69.2)
Concomitant disease, n (%)	35 (40.7)	10 (19.2)
Hypertension, n (%)	9 (10.5)	5 (9.6)
Received concurrent IBS treatment, n (%)	33 (38.4)	16 (30.8)
Laxatives, n (%)	22 (25.6)	13 (25.0)
Osmotic, n (%)	18 (20.9)	6 (11.5)
Macrogol, combinations	9 (10.5)	5 (9.6)
Lactulose	5 (5.8)	1 (1.9)
Magnesium citrate	3 (3.5)	0
Sodium phosphate	1 (1.2)	0
Magnesium hydroxide	0	2 (3.9)
Bulk-forming, n (%)	0	5 (9.6)
Sterculia	0	4 (7.7)
Ispaghula (psylla seeds)	0	1 (1.9)
Stimulant, n (%)	17 (19.8)	7 (13.5)
Bisacodyl	8 (9.3)	3 (5.8)
Sodium picosulfate	5 (5.8)	2 (3.9)
Senna glycosides, combinations	2 (2.3)	2 (3.9)
Carbon dioxide-producing drugs	2 (2.3)	0

Stimulant/stool softener, n (%)	0	2 (3.9)
Glycerol	0	2 (3.9)
Stool softener, n (%)	0	2 (3.9)
Liquid paraffin, combinations	0	2 (3.9)
Patients experiencing abdominal pain at baseline, n (%)	85 (98.8)	46 (90.2)
Mean intensity score of abdominal pain at baseline (SD)	6.0 (±2.1)	5.4 (±2.7)
Patients experiencing bloating at baseline, n (%)	81 (95.3)	48 (94.1)
Mean intensity score of bloating at baseline (SD)	5.8 (±2.4)	5.6 (±2.7)
Mean number of bowel movements/week (SD)	2.1 (±1.3)	2.1 (±1.4)
Solid stool consistency, n (%)	55 (64.0)	22 (44.0)
'Morning' was most commonly advised time of intake, n (%)	68 (80.0)	26 (53.1)

% are calculated from total number of patients providing data for that outcome. Laxatives reported by type and chemical substance.

Baseline IBS symptoms were assessed during the week before start of therapy; 0=no pain/bloating; 10=worst pain/bloating.

BMI, body mass index; IBS, irritable bowel syndrome; SD, standard deviation.

Table 2 Reasons for discontinuing linaclotide

	Austria (N=86)	Switzerland (N=52)
Discontinued patients, n (%)	20 (23.3)	17 (32.7)
Lack of effectiveness	13 (15.1)	5 (9.6)
Adverse events	8 (9.3)	10 (19.2)
Improvement of symptoms	5 (5.8)	5 (9.6)
Lack of compliance	1 (1.2)	0
Excessive drug effect	0	1 (1.9)

Austria: Seven patients reported two reasons each.

Switzerland: Four patients reported two reasons each.

Table 3 Use of concomitant medications

	Austria (N=86)	Switzerland (N=52)
Patients receiving at least one concomitant medication, n (%)	31 (36.1)	13 (25.0)
Renin-angiotensin system agents	7 (8.1)	6 (11.5)
Psychoanaleptics	6 (7.0)	2 (3.9)
Beta-blocking agents	4 (4.7)	4 (7.7)
Lipid-modifying agents	4 (4.7)	4 (7.7)
Psycholeptics	3 (3.5)	0
Diabetes drugs	3 (3.5)	0
Analgesics	0	3 (5.8)
Drugs for acid-related disorders	0	2 (3.9)

Concomitant medications reported by anatomical main group.

Table 4 Summary of safety

	Austria (N=86)	Switzerland (N=52)
Total AEs	16	15
Serious AEs	0	0
Patients with ≥1 AE, n (%)	10 (11.6)	12 (23.1)
Diarrhea	6 (7.0)	8 (15.4)
Drug ineffective	5 (5.8)	2 (3.9)
Abdominal distension	2 (2.3)*	0
Dizziness	0	1 (2.0)
Condition aggravated	1 (1.2)	0
Rectal tenesmus	1 (1.2)	0
Headache	0	1 (1.9)
Hot flush	0	1 (1.9)
Nausea	0	1 (1.9)
Urge incontinence	0	1 (1.9)

AEs recorded per preferred term using Medical Dictionary for Regulatory Activities v18.0 (Austria) and v18.1 (Switzerland).

*Two abdominal distension events reported for one patient.

AE, adverse event.

FIGURE LEGENDS

Figure 1 Effect of linaclotide treatment on (A) abdominal pain, (B) bloating, and (C) frequency of bowel movements in all patients. Visit 1 and visit 2 refer to baseline and week 4, respectively. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 2 Effect of linaclotide treatment in patients with and without prior treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 3 Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. ***p*<0.001 versus visit 1, assessed by Wilcoxon signed-rank test.

Figure 4 Proportion of patients reporting overall and individual improvement of IBS-C symptoms at the end-of-treatment periods (week 4 in Austria and week 16 in Switzerland). Proportions are based on the number of patients with available data at respective end-of-treatment visits (Austria, n=85; Switzerland, n=51).

Figure 5 Physicians' assessment of (A) satisfaction, and global assessment of (B) effectiveness and (C) tolerability of linaclotide. Satisfaction data in (A) presented on a scale of 0 [very satisfied] to 10 [totally unsatisfied]; Austria, mean 2.9 ± 3.0 points ["good" satisfaction]; Switzerland, mean 4.6 ± 3.2 points ["moderate" satisfaction].

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AUTHOR CONTRIBUTIONS

Daniel Pohl, Michael Fried, and Heinz Hammer participated in the study design, trial conduct, and data collection. Dominic Lawrance and Elmar Beck participated in data collection and analysis. All authors interpreted the data and participated in writing the manuscript with medical writing services provided by the funder. All authors read the manuscript critically and approved the final version.

DISCLOSURES

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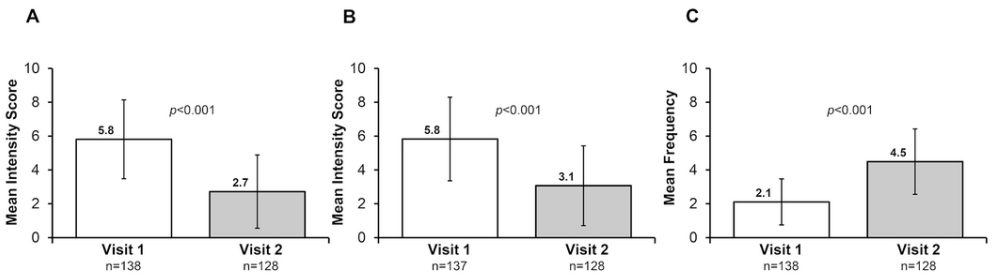
Competing interest statement

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors. Daniel Pohl is a consultant and speaker for Allergan. Dominic Lawrance is an employee of Allergan. Elmar Beck is an employee of Anfomed GmbH, which was contracted by Allergan as a contract research organization for the conduct of this study. Heinz Hammer is a consultant and speaker for Allergan.

DATA AVAILABILITY

Data reported in this manuscript are available within the article. Allergan will share de-identified patient-level and/or study-level data, including protocols and clinical study reports, for Phase II–IV trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The indication studied in the trial must have regulatory approval in the United States and/or European Union and the primary manuscript from the trial must be published prior to data sharing. To request access to the data, the researcher must sign a data use agreement. All shared data are to be used for non-commercial purposes only. More information can be found on http://www.allerganclinicaltrials.com/.



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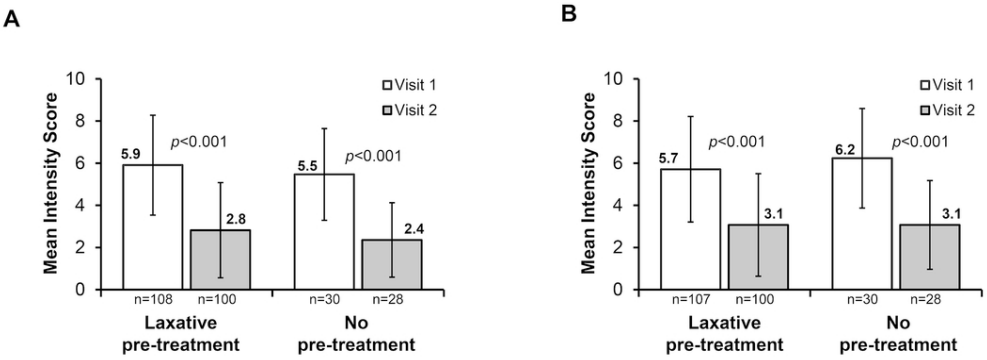

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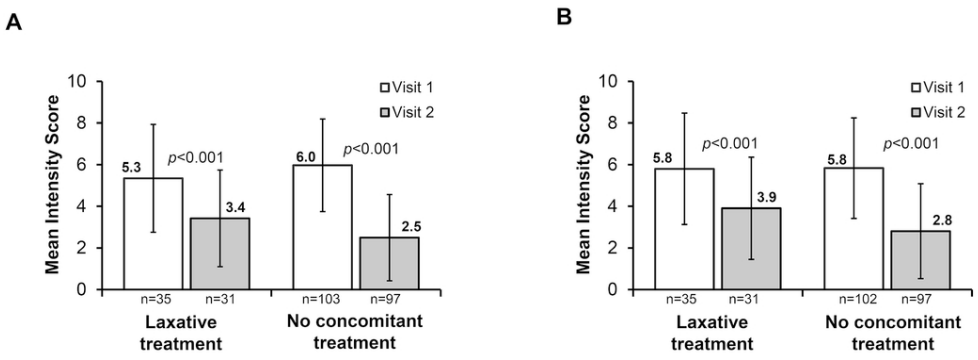

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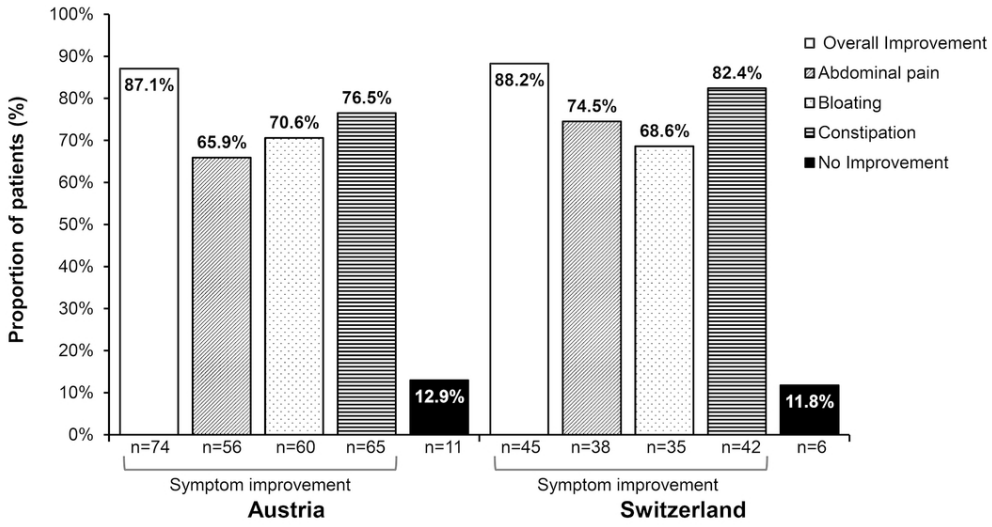

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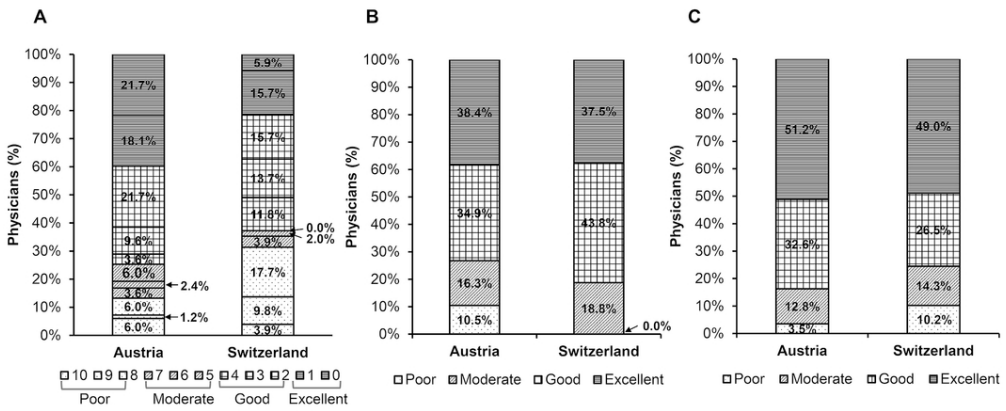

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RESEARCH CHECKLIST

STROBE Statement—checklist of items that should be included in reports of observational studies

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7

Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	N/A

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-12
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	33

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.