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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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Manuscripts

1 **COVER PAGE**2 **LINACLOTIDE ALPINE RWE: MANUSCRIPT**

Title	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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4 **TITLE PAGE**5 **Efficacy and Tolerability of Linaclotide in the Treatment of Irritable Bowel Syndrome with**  
6 **Constipation in a Real-World Setting: The Alpine study**  
7 -----  
88 **Running Title:** Linaclotide in IBS-C – The Alpine study9 Daniel Pohl<sup>1</sup>, Michael Fried<sup>1</sup>, Dominic Lawrance<sup>2</sup>, Elmar Beck<sup>3</sup>, Heinz F. Hammer<sup>4</sup>10 **Affiliations:**11 <sup>1</sup>University Hospital Zurich, Department of Gastroenterology, Switzerland12 <sup>2</sup>Allergan plc, Marlow, UK13 <sup>3</sup>ANFOMED GmbH, Möhrendorf, Germany14 <sup>4</sup>Medical University Graz, Dept. of Gastroenterology and Hepatology, Graz, Austria16 **Corresponding Author Information:**

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

**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  $\geq 18$  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

Pohl *et al.*, Linaclotide in IBS-C – The Alpine Study

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3 45 increased from 2.1 at baseline to 4.5 at week 4 ( $p < 0.001$ ). Global effectiveness and tolerability  
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6 46 of linaclotide were assessed as good or excellent in  $> 70\%$  patients by the treating physicians.  
7  
8 47 In total, 31 adverse events were reported in 22 patients, the most common being diarrhoea,  
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11 48 reported by 6 (7%) and 8 (15.4%) patients in Austria and Switzerland, respectively.

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13  
14 49 **Conclusions:** Linaclotide was effective in treating moderate-to-severe symptoms in routine  
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17 50 clinical practice of this IBS-C patient population. Linaclotide was safe and well tolerated and no  
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20 51 new safety concerns were raised, confirming results from previous clinical trials.  
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### 25 26 27 53 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 28  
29  
30 54 • This is the first real-world study evaluating the effectiveness and tolerability of an IBS-C  
31  
32 55 treatment in the Alpine region  
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34 56 • This study sought to evaluate whether the efficacy and tolerability of linaclotide that was  
35  
36 57 demonstrated in randomized clinical trials could be recapitulated in clinical practice in a real-  
37  
38 58 world setting  
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40 59 • Results from the physicians' global assessment of efficacy and tolerability will be useful in  
41  
42 60 determining physician comfort level with prescribing linaclotide for their patients  
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44 61 • This was a non-interventional study that lacked a placebo control; thus, the statistical  
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46 62 analyses are descriptive and exploratory in nature  
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## 63 INTRODUCTION

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

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

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

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3 88 Subsequently, the efficacy and safety of linaclotide for the treatment of IBS-C was established in  
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5 89 two placebo-controlled Phase 3 trials that showed improvements in IBS-C symptoms, including  
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7 90 abdominal pain and bowel movements [8, 12].  
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9

10 91 Linaclotide was approved by the Food and Drug Administration (FDA) and European Medicines  
11  
12 92 Agency (EMA) in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C  
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14 93 [13, 14]. While the efficacy and safety of linaclotide has been established in clinical trial settings,  
15  
16 94 these may not depict real-life experiences. To address this need, observational studies were  
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18 95 undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in  
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20 96 Europe. In routine clinical practice, linaclotide has recently been shown to be effective in  
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22 97 improving IBS-C symptoms in a post-marketing authorization study conducted in Germany [15].  
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24 98 Herein, we aimed to document the effectiveness and safety of linaclotide for the treatment of  
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26 99 moderate-to-severe IBS-C in adults under real-life conditions in the Alpine region of Austria and  
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29 100 Switzerland.  
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## 101 **METHODS**

### 102 ***Study Design***

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

108 The study comprised a 4-week treatment period commencing with visit 1 at treatment initiation  
109 and visit 2 occurring approximately 4 weeks after initiation in Austria. In Switzerland, data were  
110 collected over the course of three visits, at 0, 4, and 16 weeks after treatment initiation.

111 Linaclotide was administered per the usual therapeutic procedure of the attending physician and  
112 in accordance with the indication for the drug (290 µg once daily, taken at least 30 minutes  
113 before meals) [14].

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

### 120 ***Participants***

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

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

### 128 **Study Assessments**

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

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

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

### 141 **Statistical Analyses**

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

## 148 RESULTS

### 149 *Patient characteristics*

150 A total of 86 patients in 22 sites and 52 patients in 9 sites were respectively enrolled in Austria  
151 and Switzerland. Baseline characteristics were generally comparable between the two  
152 countries. Of the enrolled patients, 71 (82.6%) in Austria and 40 (76.9%) were female, and the  
153 mean age was 51 and 49 years, respectively (**Table 1**). The mean BMI was 24 kg/m<sup>2</sup> and  
154 23 kg/m<sup>2</sup> in each country. The average time since IBS-C diagnosis for patients in Austria was  
155 2.1 years and 5.2 years for patients in Switzerland. At baseline, more than 90% of patients in  
156 both countries reported abdominal pain (mean intensity 6 and 5.4, respectively) and bloating  
157 (mean intensity 5.8 and 5.6, respectively). Patients in both countries reported a mean of 2.1  
158 number of bowel movements per week. Prior treatment for IBS-C was reported by 73 (84.9%)  
159 patients in Austria and 49 (94.2%) patients in Switzerland, mainly consisting of laxatives and  
160 dietary fibres, while 33 (38.4%) patients in Austria and 16 (30.8%) patients in Switzerland  
161 received concurrent IBS-treatment. Concomitant diseases were reported by 35 (40.7%) patients  
162 in Austria and 10 (19.2%) patients in Switzerland (**Table 1**). Collectively, baseline characteristics  
163 of the IBS-C patients in this study were reflective of the general IBS patient population (i.e.,  
164 approximately 70% of IBS patients are typically female, with high likelihood of majority of  
165 patients being 50 years of age or younger).

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

### 170 **Table 2.**

### 171 *Effectiveness outcomes*

### 172 *Effect of linaclotide treatment on symptoms of IBS-C*

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3 173 Linaclotide was administered over 4 weeks in Austria and 16 weeks in Switzerland, and data  
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5 174 from the initial 4-week treatment periods is compiled in this analysis. Improvements in  
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7 175 abdominal pain, bloating, and bowel movement were observed after 4 weeks of treatment with  
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9 176 linaclotide. From a mean intensity score of 5.8 at baseline, abdominal pain reduced to 2.7 after  
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11 177 4 weeks of treatment in both countries (**Fig. 1A**;  $p < 0.001$  vs. visit 1; 11-point NRS, [0=no pain to  
12  
13 178 10=worst possible pain]). In Switzerland, continued reduction in abdominal pain was observed at  
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15 179 week 16 with a mean intensity score of 2.5 (SD  $\pm 2.0$ ;  $n=51$ ;  $p < 0.0001$  vs. visit 1). Improvements  
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17 180 in bloating were seen after 4 weeks of treatment in both countries; from a baseline mean  
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19 181 intensity score of 5.8, the score reduced to 3.1 at week 4 (**Fig. 1B**;  $p < 0.001$  vs. visit 1; 11-point  
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21 182 NRS [0=no bloating to 10=worst possible bloating]), with a mean intensity score of 3.0 (SD  $\pm 2.2$ ;  
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23 183  $n=51$ ;  $p < 0.0001$  vs. visit 1) at week 16 in Switzerland. Furthermore, the frequency of bowel  
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25 184 movements increased from a mean of 2.1 bowel movements per week at baseline to 4.5 at  
26  
27 185 week 4 (**Fig. 1C**;  $p < 0.001$  vs. visit 1) in both countries, and to 4.7 (SD  $\pm 1.6$ ;  $n=51$ ;  $p < 0.0001$  vs.  
28  
29 186 visit 1) at week 16 in Switzerland.

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33 187 Data was stratified based on patients who received prior IBS-C treatment, and improvements in  
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35 188 IBS-C symptoms were observed within the 4-week treatment period regardless of prior IBS-C  
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37 189 treatment. Significant reductions from week 1 to week 4 in mean abdominal pain intensity and  
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39 190 mean bloating intensity were seen in patients who had received laxative pre-treatment and in  
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41 191 those who did not receive prior IBS-C treatment (**Fig. 2A** and **Fig. 2B**, respectively; all  $p < 0.001$   
42  
43 192 vs. visit 1). Similar degrees of mean reduction in abdominal pain were seen in patients who did  
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45 193 not and those who received laxative pre-treatment (both 3.1), while a slightly greater mean  
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47 194 reduction in bloating was seen in those who did not receive IBS-C pre-treatment compared to  
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49 195 those who received laxative pre-treatment (2.6 and 3.1). Furthermore, the effect of concomitant  
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51 196 laxative use with linaclotide was evaluated. Our results showed that significant reduction was  
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53 197 achieved after 4 weeks of treatment in mean abdominal pain intensity (**Fig. 3A**; all  $p < 0.001$  vs.

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3 198 visit 1) and mean bloating intensity (**Fig. 3B**; all  $p < 0.001$  vs. visit 1) both in patients who used  
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5 199 laxative concomitantly with linaclotide and those who did not. A greater symptom improvement  
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7 200 was observed in those who did not use concomitant treatment (mean reduction in abdominal  
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9 201 pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9; **Fig. 3A** and **3B**; all differences  
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11 202  $p < 0.001$  vs. visit 1).

### 14 203 *Patient assessment of improvement of IBS-C symptoms*

17 204 At each respective end-of-treatment period, patients were asked to indicate their sense of  
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19 205 general improvement of symptoms as compared to the pre-treatment period. In Austria, 74  
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21 206 patients (87.1%) reported overall improved symptoms, among which 56 (65.9%) patients  
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23 207 experienced improvements in abdominal pain, 60 (70.6%) had improvements in bloating, and 65  
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25 208 (76.5%) reported improvements in constipation at visit 2 compared to baseline (**Fig. 4**). In  
26  
27 209 Switzerland, 45 patients (88.2%) reported overall improved symptoms, consisting of 38 (74.5%)  
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29 210 patients with improvements in abdominal pain, 35 (68.6%) with improvements in bloating, and  
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31 211 42 (82.4%) reporting improvements in constipation after 16 weeks of treatment compared to  
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33 212 baseline (**Fig. 4**).

### 37 213 *Physician assessment of satisfaction and effectiveness of linaclotide therapy*

39 214 Physicians' satisfaction with linaclotide treatment was assessed on a scale from 0 (very  
40  
41 215 satisfied) to 10 (totally unsatisfied). In Austria, mean satisfaction was 2.9 (SD±3.0; median 2.0)  
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43 216 points after 4 weeks of treatment, indicative of "good satisfaction", with at least 60% of the 83  
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45 217 total patients rated by a score of  $\leq 2.0$  by their treating physicians. In Switzerland, mean  
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47 218 satisfaction was 4.6 (SD±3.2; median 3.0) points after 16 weeks of treatment, indicative of  
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49 219 "moderate satisfaction", with at least 50% of the 51 total patients rated with a score of  $\leq 3.0$  by  
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51 220 their treating physicians (**Fig. 5A**). Furthermore, physicians assessed the global effectiveness  
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53 221 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

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3 246 Switzerland, respectively. ‘Drug ineffectiveness’ was reported as an AE for 5 (5.8%) patients in  
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5 247 Austria and 2 (3.9%) patients in Switzerland. AEs leading to treatment discontinuation occurred  
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7 248 in 8 (9.3%) patients in Austria and 10 (19.2%) in Switzerland (**Table 2**). The majority of AEs  
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9 249 were mild or moderate in intensity, while severe AEs were reported in 2 patients (2 events [1  
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11 250 abdominal distension and 1 rectal tenesmus]; 2.3%) in Austria and 4 patients (5 events [4  
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13 251 diarrhoea and 1 urge incontinence]; 7.7%) in Switzerland. An AE was considered severe if the  
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15 252 intensity of the symptoms significantly interfered with the patient’s daily activities. Of all 31  
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17 253 reported AEs, treatment causality was confirmed for 11 AEs reported by 8 patients in Austria  
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19 254 (9.3%) and 14 AEs reported by 12 patients in Switzerland (23.1%). No serious AEs (i.e., AEs  
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21 255 that were life-threatening) were reported in either country over the respective 4-week or 16-  
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23 256 week treatment period.

### 27 257 *Physician assessment of linaclotide tolerability*

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30 258 Treating physicians assessed the global tolerability of linaclotide treatment, and after 4 weeks of  
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32 259 treatment, linaclotide tolerability was evaluated as “excellent” in 44 patients (51.2%), “good” in  
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34 260 28 patients (32.6%), “moderate” in 11 patients (12.8%), and “poor” in 3 patients (3.5%) in  
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36 261 Austria. In Switzerland, physicians assessed linaclotide tolerability as “excellent” in 24 patients  
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38 262 (49.0%), “good” in 13 patients (26.5%), “moderate” in 7 patients (14.3%), and “poor” in 5  
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40 263 patients (10.2%) after 16 weeks of treatment (**Fig. 5C**).

## 264 DISCUSSION

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

278 IBS is characterized by multiple symptoms; however, abdominal pain, which is challenging to  
279 treat, is the major clinical manifestation. Moreover, abdominal pain is highly correlated with IBS  
280 disease severity and higher economic burden [16-18]. In the present study, >90% of all patients  
281 reported abdominal pain at baseline with mean intensity scores of 6.0 in Austria and 5.4 in  
282 Switzerland. Collectively, the mean intensity of abdominal pain decreased from a baseline NRS  
283 level of 5.8 to 2.7 after 4 weeks of linaclotide treatment, corresponding to a 53% reduction in  
284 abdominal pain in both countries. In Austria, the reduction in mean abdominal pain intensity  
285 score was 3.5-points (57%) at 4 weeks, while a reduction of 2.2-points (41%) at 4 weeks and  
286 2.9-points (53%) after 16 weeks was observed in Switzerland. In a recent NIS conducted in  
287 Germany, linaclotide treatment resulted in a reduction in mean pain intensity score of 1.72-  
288 points (35%) at 4 weeks and 2.5-points (50%) at 12 months after treatment initiation [15]. Data



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3 289 from these European real-world studies demonstrate that improvements in abdominal pain are  
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5 290 observed in linaclotide-treated patients within the first month of treatment initiation and are  
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7 291 sustained throughout the respective treatment periods. Mechanistically, as a GC-C receptor  
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9 292 agonist, linaclotide is believed to increase extracellular cGMP levels, which in turn reduces the  
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11 293 firing of pain-sensing visceral afferent fibres, resulting in an analgesic effect, thus reducing  
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13 294 abdominal pain [19].

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16 295 In addition to improvements in abdominal pain, significant improvements in bloating were also  
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18 296 observed following 4 weeks treatment with linaclotide. At baseline, >94% of all patients reported  
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20 297 bloating, and an overall reduction of 2.8-points (47%) was observed after 4-week treatment in  
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22 298 both countries, which was sustained after 16 weeks of treatment in Switzerland. Moreover,  
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24 299 linaclotide treatment increased the mean frequency of bowel movements to 4.5 times a week  
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26 300 from a mean of 2.1 at baseline in both countries. These observations are in line with previous  
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28 301 animal studies that showed that linaclotide increases GI transit and fluid secretion via  
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30 302 accumulation of intracellular cGMP in a dose-dependent manner [20].

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34 303 At study initiation, >84% of patients in this study had received IBS-C pre-treatment, mainly  
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36 304 comprising laxatives or dietary fibres. We found that linaclotide was effective in managing  
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38 305 symptoms of patients regardless of prior treatment or concomitant medication use. In fact, our  
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40 306 data found that a greater degree of improvement was observed in patients who did not use  
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42 307 concomitant IBS-C treatment as compared to those who used concomitant laxatives (mean  
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44 308 reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9), suggesting that  
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46 309 laxatives might interfere with the efficacy of linaclotide. Laxatives such as polyethylene glycol  
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48 310 (PEG) are often used a first-line therapy for IBS-C patients; however, their effect on  
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50 311 improvements in abdominal pain or bloating are inconsistent and may lead to exacerbation of  
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52 312 bloating, gas, and loose stools [21]. A recent consensus report recommended against the co-  
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54 313 administration of linaclotide with laxatives especially at the beginning of treatment due to

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3 314 potential diarrheal side effects, and only suggested co-administration in cases of partial  
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5 315 response to linaclotide [2]. How concomitant laxatives may impact the efficacy of linaclotide is  
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7 316 currently unclear. Osmotic laxatives may improve the frequency and consistency of bowel  
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9 317 movements, but have no impact on abdominal pain or bloating; moreover, some stimulant  
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11 318 laxatives (for which there are no RCTs in IBS-C) may relieve chronic constipation, but result in  
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13 319 abdominal pain and cramping [1]. In real-life settings, some patients may choose to add laxative  
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15 320 treatment based on the severity of constipation or water-binding agents may be titrated with  
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17 321 linaclotide to gradually improve stool consistency; however, both of these strategies may  
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19 322 inadvertently lessen the efficacy of linaclotide by binding excess fluids. Nonetheless, the present  
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21 323 data demonstrates that linaclotide can effectively manage IBS-C symptoms irrespective of  
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23 324 treatment history and does not require co-administration with other IBS-C medications,  
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25 325 specifically laxatives.

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29 326 The results of this study support the findings of two randomized clinical trial (RCT) Phase III  
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31 327 studies that evaluated the efficacy and safety of linaclotide, which used the FDA's responder  
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33 328 criteria of improvement of  $\geq 30\%$  from baseline in average daily worst abdominal pain (WAP)  
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35 329 score and an increase of  $\geq 1$  complete spontaneous bowel movement (CSBM) per week. In the  
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37 330 first double-blind, placebo-controlled 26-week study of 804 participants, 49% of patients treated  
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39 331 with linaclotide exhibited  $\geq 30\%$  improvement in abdominal pain (corresponding to 2.1-point  
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41 332 decrease) and 48% experienced an  $\geq 1$  increase in weekly CSBM (corresponding to 2.2-point  
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43 333 decrease) for at least 6 of 12 treatment weeks [8]. Moreover, linaclotide treatment resulted in  
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45 334 increases in spontaneous bowel movements (SBM) per week by 3.8 and CSBM per week by  
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47 335 2.2. In the second pivotal multicenter, double-blind, placebo-controlled study with 800 IBS-C  
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49 336 patients treated over 12 weeks, linaclotide resulted in significant improvements in abdominal  
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51 337 pain (1.9-point WAP improvement), bloating (1.9-point improvement), SBM per week (+3.9  
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53 338 frequency), and CSBM/week (+2.3 frequency) [12]. In both the RCTs and in the current NIS  
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3 339 setting, improvements in IBS-C symptoms were demonstrated for linaclotide immediately  
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5 340 following therapy initiation, and sustained throughout treatment duration. Therefore, we can  
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7 341 deduce that the NIS results under routine clinical settings in Europe, including those in the  
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9 342 current study, are in agreement with the RCT findings from the US.  
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12 343 Global tolerability of linaclotide treatment was assessed as good or excellent in >75% patients  
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14 344 by their treating physicians in both countries in the current study. Moreover, physician  
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16 345 satisfaction with linaclotide therapy was evaluated on a 0-10 scale (very satisfied to totally  
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18 346 unsatisfied), with a 2.9 score (good satisfaction) after 4 weeks in Austria and a 4.6 score  
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20 347 (moderate satisfaction) after 16 weeks in Switzerland. In comparison, 45% and 52% of patients  
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22 348 treated with linaclotide noted satisfaction with linaclotide in the two RCTs, while 62% of treating  
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24 349 physicians rated the effectiveness of linaclotide as good or excellent in Germany in a recent NIS  
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26 350 [8, 12, 15]. Previously, an 18-month long term safety study demonstrated similar patient  
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28 351 satisfaction between linaclotide-treated patients who experienced diarrhea as compared to  
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30 352 those who did not, and >85% reported moderate satisfaction during the treatment period,  
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32 353 indicating high degree of treatment satisfaction irrespective of AEs [22].  
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35 354 Diarrhoea has previously been reported as a potential consequence of linaclotide-mediated  
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37 355 increase in GI transit and fluid secretion, and as such, diarrhea was the most common reported  
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39 356 AE during this study (7% of patients in Austria and 15% of patients in Switzerland). All events  
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41 357 were mild or moderate in severity. In the Phase III RCTs, diarrhoea was reported by 19.5% in  
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43 358 the study by Chey *et al.*, and 19.7% in the study by Rao *et al.* [8, 12]. The discrepancy in  
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45 359 diarrhoea rates between this NIS and the previous RCTs may be due to the difference in  
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47 360 reporting methods. In fact, all diarrhoea AEs regardless of treatment relatedness were reported  
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49 361 in the two RCTs, while only adverse drug reactions (ADRs) were reported in this NIS.  
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51 362 Additionally, the lower incidence in the ADR reported in this NIS may be due to underreporting  
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3 363 of AEs already described in the summary of product characteristics (SmPC) by physicians [23].

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5 364 Finally, the impact of concomitant laxative use on diarrhoea cannot be discounted.

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8 365 Treatment options for IBS-C are limited, with traditional therapies showing limited effectiveness

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10 366 in improving symptoms and quality of life, and only four pharmacologic agents approved for

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12 367 treatment. One such FDA-approved agent is lubiprostone, a chloride channel activator that was

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14 368 shown to improve IBS-C symptoms in two RCTs; however, lubiprostone is not approved for

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16 369 treatment in men due to limited efficacy [24]. Recently, plecanatide, a GC-C receptor agonist in

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18 370 the same drug class as linaclotide was approved for the treatment of IBS-C based on data from

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20 371 two RCTs with a comparable safety and efficacy profile as linaclotide RCTs; however, no

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22 372 evidence from real-life clinical settings currently exists for plecanatide [25, 26]. Another FDA-

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24 373 approved agent for IBS-C was tegaserod, a prokinetic agent that improved IBS symptoms but

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26 374 was later withdrawn from the market due to increased cardiovascular risks [27]. Overall, the

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28 375 present data confirms RCT findings in a real-world setting showing that linaclotide is an effective

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30 376 and satisfactory treatment for the management of IBS-C, a disease for which there are few

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32 377 effective therapeutic options.

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35 378 Some limitations are associated with this study which necessitate caution in interpreting these

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37 379 findings. The main limitations are the sample size and differing study durations between the two

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39 380 countries, which only allowed compilation of 4 weeks of data. In addition, as this was a NIS

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41 381 without a placebo control, the statistical analyses are descriptive, explorative, and no statistical

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43 382 hypotheses were pre-specified. Nevertheless, to the best of our knowledge, no real-world

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45 383 studies have been conducted evaluating IBS-C treatments in the Alpine region, and

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47 384 observational studies were thus undertaken to evaluate the effectiveness and safety of

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49 385 linaclotide in real-world settings in various European countries, with data recently published

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51 386 from Germany. Our current findings suggest that linaclotide is safe and effective in reducing

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53 387 major symptoms of IBS-C in routine clinical practice in Austria and Switzerland. This data

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3 388 confirms the previously reported results from two randomized Phase III clinical trials that  
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5 389 collectively demonstrate the efficacy and safety of linaclotide treatment for the management of  
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7 390 IBS-C patients with moderate-to-severe abdominal symptoms.  
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471 **TABLES**472 **Table 1** Patient baseline demographics and characteristics

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
Female, n (%)	71 (82.6)	40 (76.9)
Mean age, years	51.3	49.2
Mean BMI, kg/m <sup>2</sup>	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)

473 % are calculated from total number of patients providing data for that outcome. Baseline IBS symptoms were assessed during the  
474 week before start of therapy; 0=no pain/bloating 10=worst pain/bloating  
475 BMI, body mass index; SD, standard deviation  
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478 **Table 2** Reasons for discontinuing linaclotide

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
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)

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

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483 **Table 3** Use of concomitant medications

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
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)

484 Concomitant medications reported by anatomical main group  
485

486 **Table 4** Summary of safety

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
Total AEs	16	15
Serious AEs	0	0
Patients with $\geq 1$ 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)

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

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507 **SUPPORTING INFORMATION**

For peer review only

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## 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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).



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## 518 **AUTHOR CONTRIBUTIONS**

519 Daniel Pohl, Michael Fried, and Heinz Hammer participated in the study design, trial conduct,  
520 and data collection. Dominic Lawrance and Elmar Beck participated in data collection and  
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523 the final version.

## 524 **DISCLOSURES**

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

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

## 534 **DATA AVAILABILITY**

535 Data reported in this manuscript are available within the article and its supplementary materials.

536 Additional data from the linaclotide real-world evidence Alpine study may be requested at

537 <http://www.allerganclinicaltrials.com/PatientDataRequest.htm>

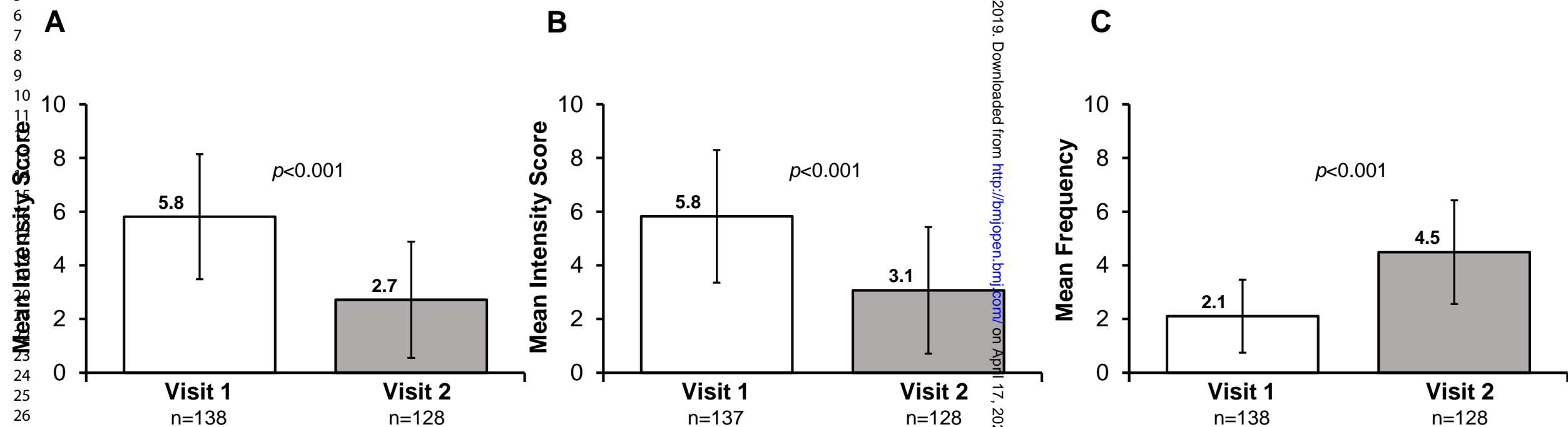
# Linaclootide in IBS-C: The Alpine Study

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

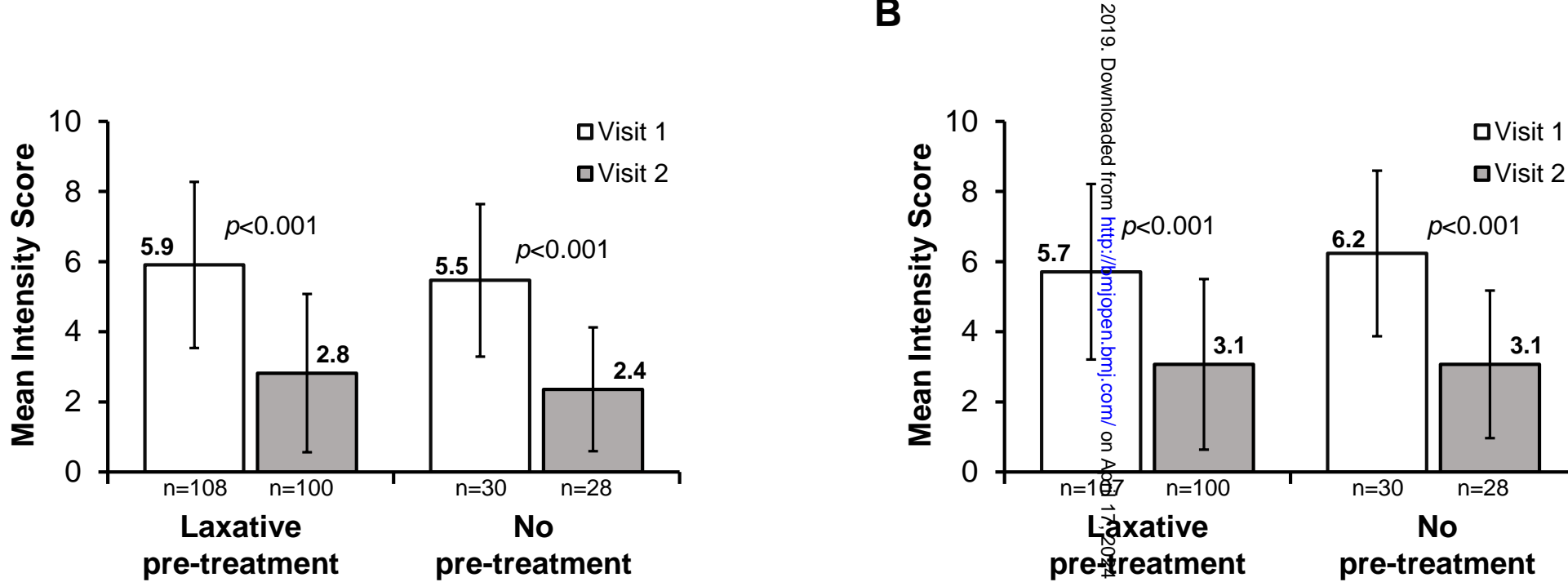
*Daniel Pohl, Michael Fried, Dominic Lawrance, Elmar Beck, Heinz F. Hammer*

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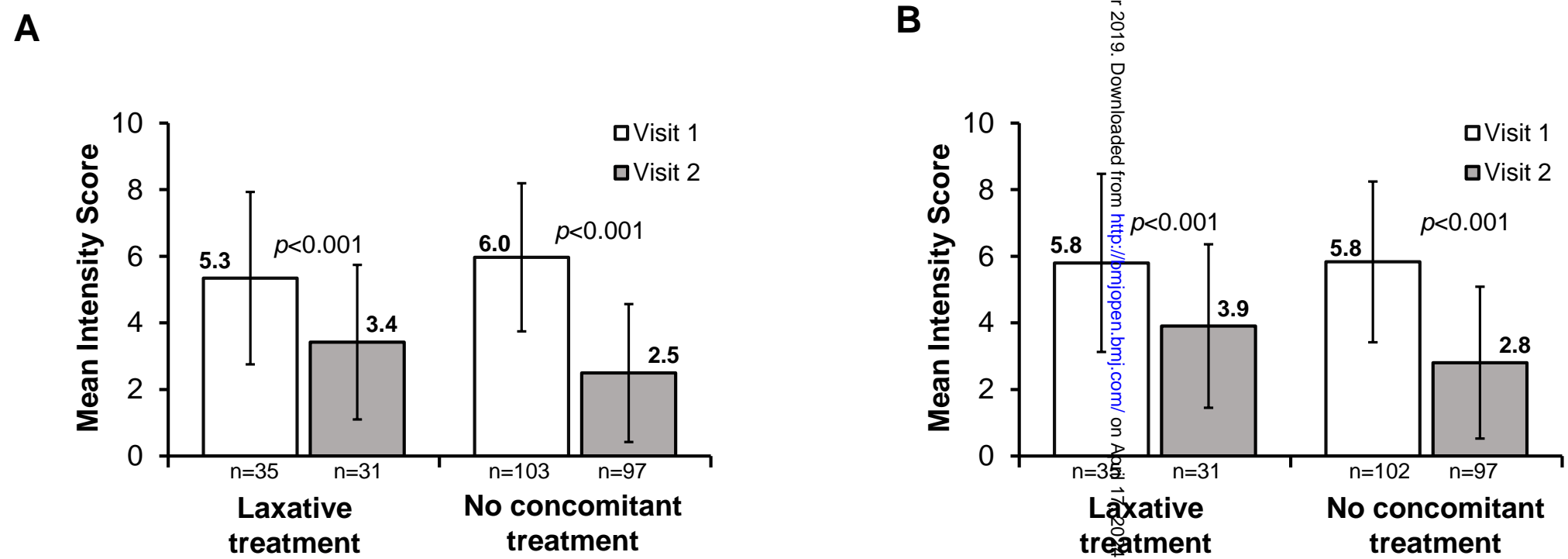
**Figure 1:** Effect of linaclotide treatment on (A) abdominal pain (B) bloating and (C) frequency of bowel movements on all patients. Data shown as last observation carried forward. \*\* $p < 0.001$  versus visit 1, assessed by Wilcoxon signed-rank test.



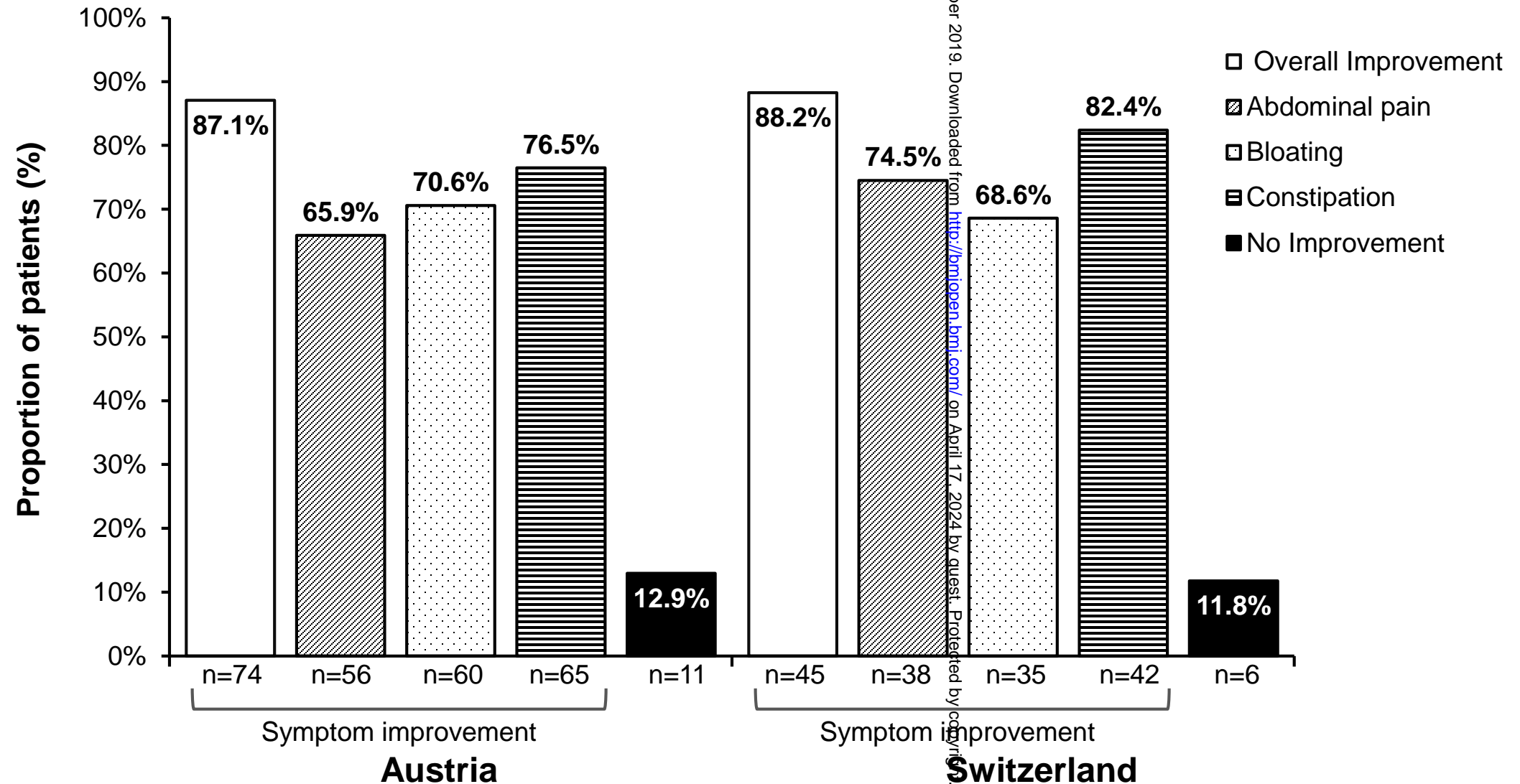
**Figure 2:** Effect of linaclotide treatment in patients with and without prior treatment for IBS C on (A) abdominal pain and (B) bloating. Data shown as last observation carried forward. \*\* $p < 0.001$  versus visit 1, assessed by Wilcoxon signed-rank test.



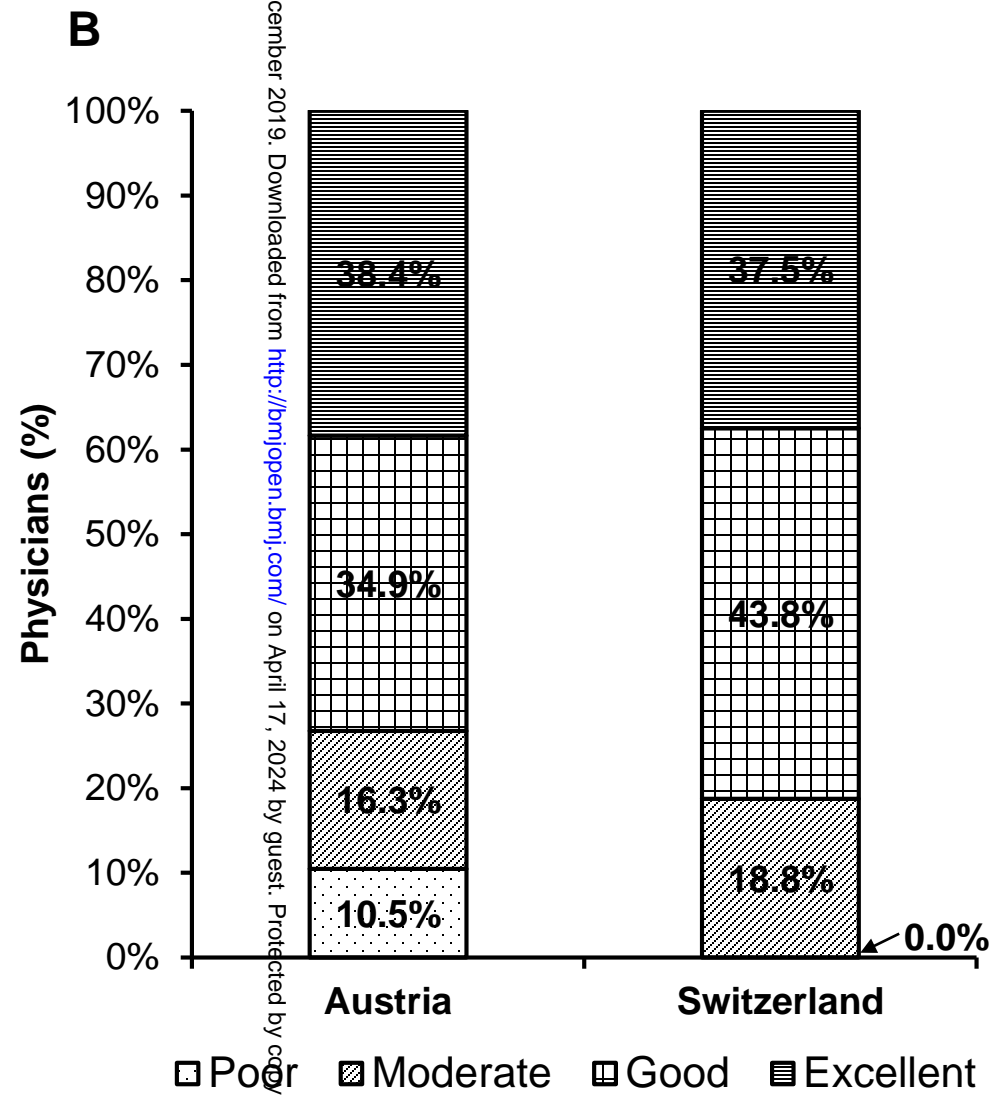
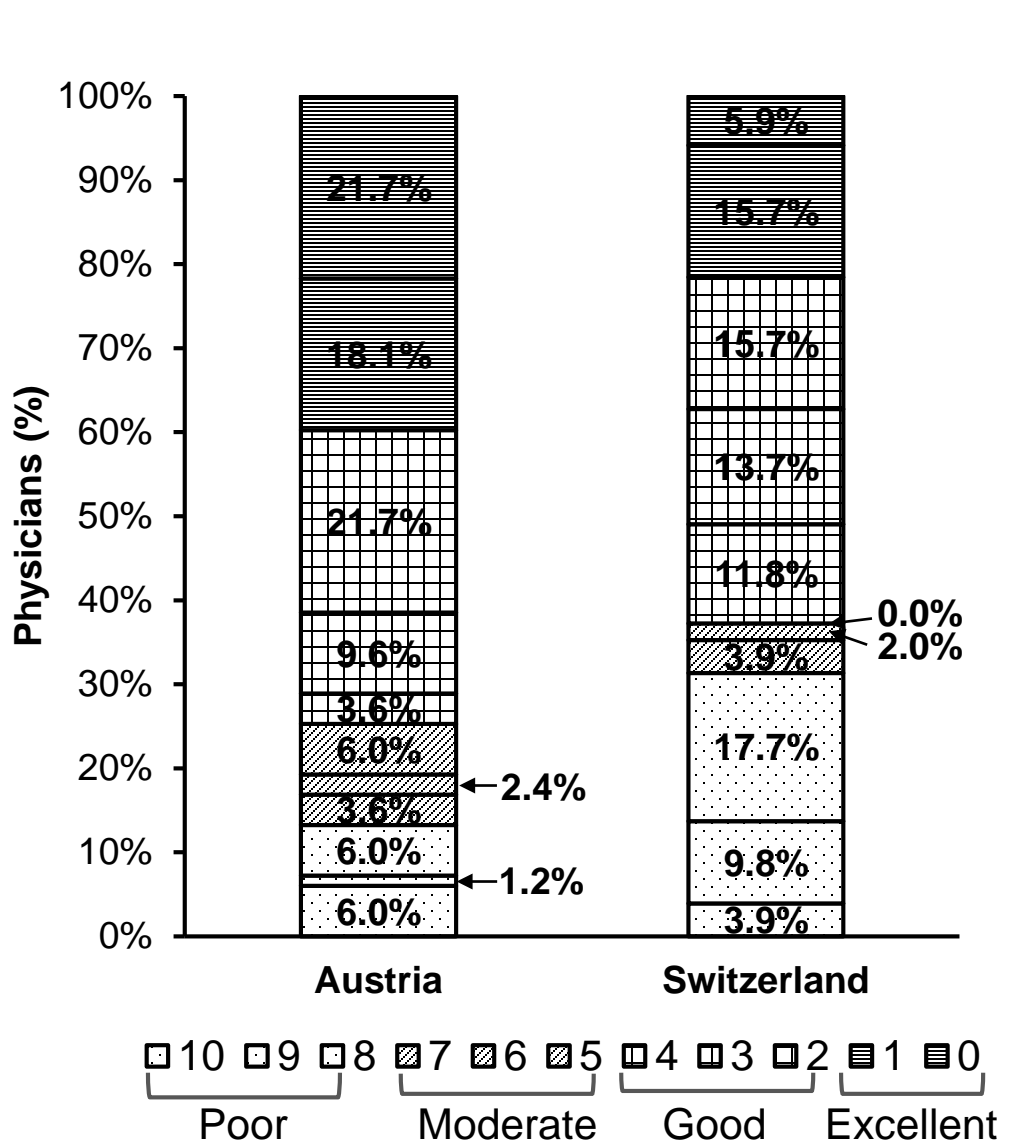
**Figure 3:** Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Data shown as last observation carried forward. \*\* $p < 0.001$  versus visit 1, assessed by Wilcoxon signed-rank test.



**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



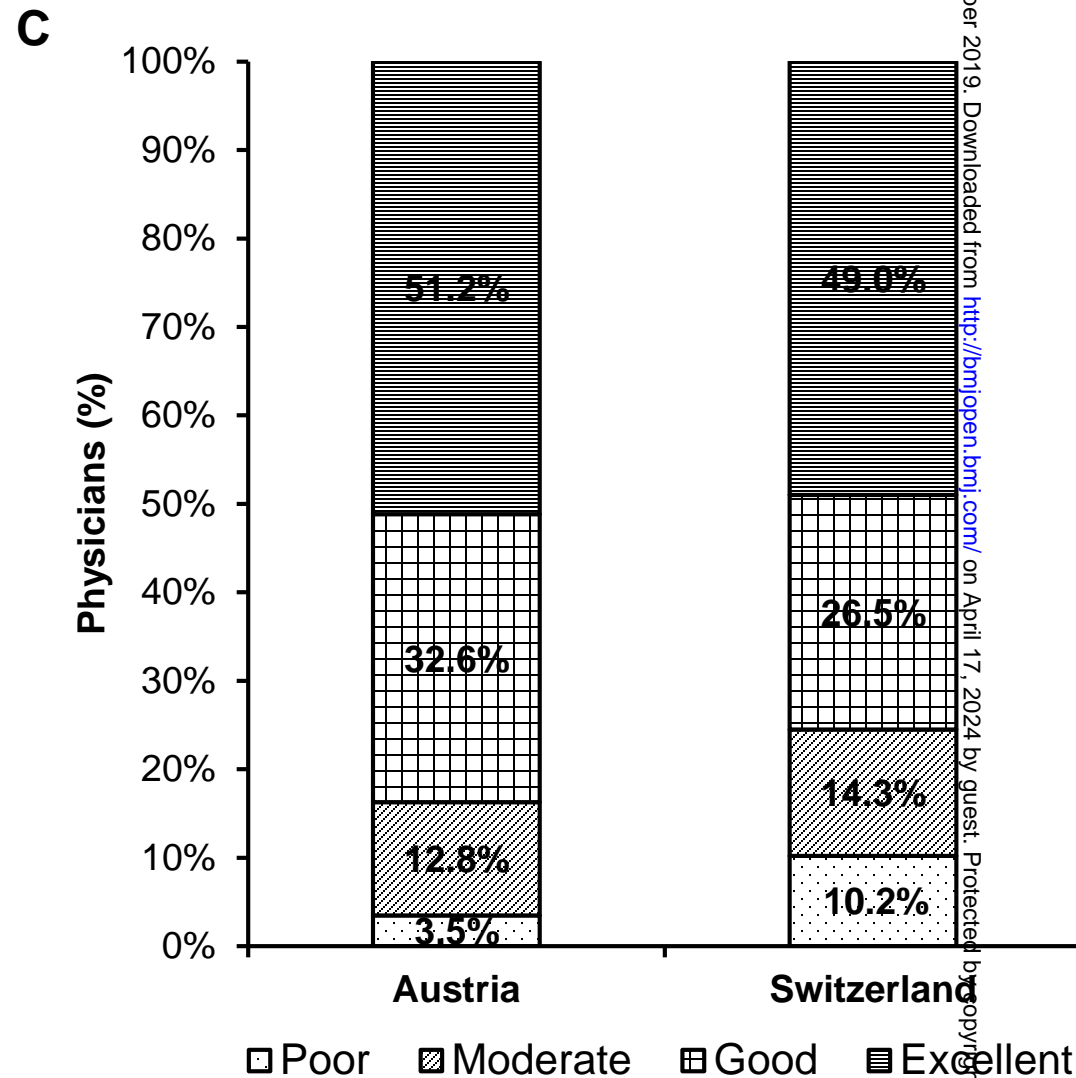
Scale: 0 (very satisfied) to 10 (totally unsatisfied) For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

Austria: mean 2.9 ± 3.0 points (good satisfaction)

Switzerland: mean 4.6 ± 3.2 points (moderate satisfaction)

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





# 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

<b>Title</b>	Practical experience report Constella® - The new GC-C agonist in the treatment of IBS-C - efficacy and safety of linaclotide under real life conditions
<b>Study drug</b>	Constella® 290 micrograms capsule
<b>Active substance</b>	Linaclotide
<b>Dosage</b>	according to SmPC
<b>Area of application</b>	for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults
<b>Medical director Almirall AG</b>	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: <a href="mailto:elisabeth.schuller@almirall.com">elisabeth.schuller@almirall.com</a>
<b>Principal investigator</b>	Prof. Dr. med. Michael Fried
<b>Responsible for project management</b>	<b>Michèle Kunz</b> Medical Liaison Manager Switzerland & Austria  T. +41 44 834 90 00   M. +41 78 817 75 17   <a href="mailto:michele.kunz@almirall.com">michele.kunz@almirall.com</a> Almirall, AG.   Alte Winterthurerstrasse 14  8034 Wallisellen  Schweiz
<b>Responsible for project coordination and drug safety (CRO)</b>	Sandra Grubmüller ANFOMED GmbH Röttenbacher Straße 17 D-91096 Möhrendorf Tel.: + 49-09133-7762-19 Fax:+ 49-09133-7762-62 Email: <a href="mailto:Sandra.grubmueller@anfomed.de">Sandra.grubmueller@anfomed.de</a>

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.....	4
2.	Introduction, study objectives and endpoint of study.....	6
2.1.	Introduction .....	6
2.2.	Study objectives .....	6
2.3.	End point of study .....	6
3.	Methods.....	7
3.1.	Type of study and selection reasons.....	7
3.2.	Selection of physicians.....	7
3.3.	Sample size calculation .....	7
3.4.	Selection of patients .....	7
4.	Administration of Constella® .....	8
5.	Observational period and total duration of the study.....	8
6.	Documentation during the practical experience report.....	8
6.1.	Documentary components .....	8
6.2.	Survey dates.....	9
6.3.	Collected data .....	9
6.3.1.	Visit I (before start of treatment) .....	9
6.3.2.	Visit II (about 4 weeks after start of treatment).....	9
6.3.3.	Visit III (about 4 months after start of treatment or at the end of therapy) .....	9
6.4.	Conducting the practical experience report .....	9
7.	Adverse drug reactions (ADR).....	10
7.1.	Definitions .....	10

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
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7.1.1. Adverse events..... 10

7.1.2. Adverse drug reactions (ADRs) ..... 11

7.1.3. Serious adverse events (SAEs) ..... 11

7.1.4. Serious adverse drug reaction (SADR) ..... 11

8. Data Management, Quality control and statistical analysis ..... 11

8.1. Data Management ..... 11

8.2. Quality control ..... 12

8.3. Statistical analysis ..... 12

9. Responsibility ..... 12

10. General regulations..... 13

11. References ..... 13

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## 1. Synopsis

<b>Aim of the study</b>	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.
<b>Number of patients</b>	200
<b>Country</b>	Switzerland
<b>Clinical phase</b>	Post marketing authorization
<b>Centers</b>	40 Gastroenterologists
<b>Type of study</b>	multicenter, non-interventional, prospective study (practical experience report)
<b>Administration of Constella®</b>	According to the usual therapeutic procedure of the attending physician and in accordance with the authorized indications and summary of product characteristics (SmPC).
<b>Procedure of study</b>	<p>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:</p> <ul style="list-style-type: none"> <li>• Visit I: before start of treatment</li> <li>• Visit II: about 4 weeks after start of treatment (<math>\pm</math> 2 weeks)</li> <li>• Visit III: about 4 months after start of treatment (<math>\pm</math> 6 weeks)</li> </ul>
<b>End point of study</b>	<p><b>Efficacy</b> of Constella® should be determined under real life conditions by following parameters:</p> <ul style="list-style-type: none"> <li>• 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)</li> <li>• Incomplete bowel evacuation as subjective sensation of patient</li> <li>• Change of predominant stool consistency</li> <li>• Physician evaluation of efficacy 4 months after therapy start</li> </ul> <p><b>Tolerance</b> of Constella® should be determined under real life conditions by following parameters:</p> <ul style="list-style-type: none"> <li>• Number, intensity and severity of Adverse Events (AE)</li> <li>• Physician evaluation of tolerance 4 months after therapy start</li> </ul> <p><b>Satisfaction</b> with therapy should be evaluated 4 weeks and 4 months after therapy start by 11-NSR.</p>

<b>Study duration per patient</b>	An observational period per patient of about 4 months is intended.
<b>Survey data</b>	<ul style="list-style-type: none"> <li>• Date of visits</li> <li>• Demographic data</li> <li>• Inclusion and exclusion criteria</li> <li>• Medical history</li> <li>• (Pre-) treatment of IBS-C</li> <li>• Concomitant diseases and medication</li> <li>• Treatment with Constella®</li> <li>• Adverse drug reaction</li> <li>• Symptoms of IBS-C</li> <li>• Assessment of Constella® therapy by the attending physician</li> <li>• Confirmation physician (Visit III)</li> </ul>
<b>Statistic aspects</b>	According to study design, evaluation will be solely descriptive and explorative.
<b>Study duration</b>	The practical experience report will start on <b>April 1<sup>st</sup> 2014</b> . <b>Last center may be enrolled until May 31<sup>st</sup> 2014</b> . Last patient may be enrolled until <b>June 30<sup>th</sup> 2014</b> . Case report forms sent in later than <b>December 15<sup>th</sup> 2014</b> will not be compensated.
<b>Adverse Drug Reactions</b>	<p><b>Any adverse drug reaction</b> during the practical experience report, in which relation to Constella® therapy cannot be excluded, must be carefully documented on the <b>ADRform</b> and faxed <b>within 24 hours</b> to the <b>Drug safety department of ANFOMED GmbH</b>, fax number: 049-9133-7762-62, Ursula Burkard, Senior Data Manager, ANFOMED GmbH, Röttenbacher Straße 17, 91096 Möhrendorf.</p> <p><b>Pregnancies</b> should also be documented on the ADR-form and faxed <b>within 24 hours</b> to ANFOMED.</p>
<b>Medical director Almirall AG</b>	<p>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: <a href="mailto:elisabeth.schuller@almirall.com">elisabeth.schuller@almirall.com</a></p>
<b>Principal investigator</b>	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 1<sup>st</sup>, 2014**. Last center may be enrolled until **April 30 2015**. Last patient may be enrolled until April **30<sup>th</sup>, 2015**. Case report forms sent in later than **October 15<sup>th</sup> 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 ( $\pm$  2 weeks)
- Visit III: about 4 months after start of treatment ( $\pm$  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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 15<sup>th</sup> 2014** will not be compensated.

All adverse drug reactions that occur in the course of the study, in which relation to Constella<sup>®</sup> 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

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

6  
7 database of Almirall AG. Discrepancies will be resolved by joint consultation.

### 8 9 10 **8.2. Quality control**

11 Returned documentation will be checked on data validation, plausibility, and completeness and will be  
12 medically reviewed for quality control. Inconsistent and/or implausible data will be corrected as far as  
13 possible. In case of incomplete or incorrect data in returned CRFs, the physician concerned will be  
14 contacted in written form by ANFOMED GmbH in means of a query requesting clarification or  
15 completion of data.  
16  
17

### 18 19 **8.3. Statistical analysis**

20 Data processing and statistical analysis will be performed with the SAS™ program system. Tables will be  
21 created in MS Word format. Statistical analysis will be performed in a descriptive and explorative way.  
22 All collected variables will be listed and illustrated graphically and by frequency and parameter tables.  
23 Variables collected at the relevant examination dates during the observational period will be statistically  
24 analyzed to evaluate and measure changes [9]. All ADRs will be entered into the database separately  
25 and coded according to MedDRA (latest version at start of data return). All cases containing ADRs will be  
26 listed and presented sorted by system-organ-class (SOC). Incidences are calculated for each type of  
27 adverse drug reaction (95% probability of incidence in the population). Results will be presented in a  
28 final report in accordance with Almirall AG.  
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## 33 34 **9. Responsibility**

35 The practical experience report will be conducted by Almirall AG, Alte Winterthurerstrasse 14, CH-8304  
36 Wallisellen. Medical director of the study is Dr. med. Elisabeth Schuller, Medical Advisor Austria and  
37 Switzerland, Almirall AG.  
38

### 39 40 **Person in charge of:**

<b>medical and scientific contents:</b>	<b>organization, procedure, pharmacovigilance:</b>
<p>41 42 <b>Michèle Kunz</b> 43 <b>Medical Liaison Manager</b> 44 <b>Switzerland &amp; Austria</b> 45 46 T. +41 44 834 90 00   M. +41 78 817 75 17   47 <a href="mailto:michele.kunz@almirall.com">michele.kunz@almirall.com</a> Almirall, AG.   Alte 48 Winterthurerstrasse 14   8034 Wallisellen   Schweiz 49 50 51 52</p>	<p>Sandra Grubmüller ANFOMED GmbH, Röttenbacher Straße 17 D-91096 Möhrendorf Tel.: + 49-09133-7762-19 Fax: + 49-09133-7762-62 Email: <a href="mailto:sandra.grubmueller@anfomed.de">sandra.grubmueller@anfomed.de</a></p>

## 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.

## 11. References

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# 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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4 1 **TITLE PAGE**5  
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7 2 **A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in**  
8 3 **the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and**  
9 4 **Tertiary Centers: The Alpine study**  
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11 5 -----12  
13 6 **Running Title:** Linaclotide in IBS-C – The Alpine study14  
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46 23 **Keywords:** Irritable bowel syndrome-constipation; IBS-C; linaclotide; real world evidence; non-47  
48 24 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  $\geq 18$  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.

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3 48 **Conclusions:** Linaclotide was effective in treating moderate-to-severe symptoms in routine  
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5 49 clinical practice of this IBS-C patient population. Linaclotide was safe and well tolerated and no  
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7 50 new safety concerns were raised, confirming results from previous clinical trials.  
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11 51 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 13 52 • This is the first real-world study evaluating the effectiveness and tolerability of an IBS-C  
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15 53 treatment in the Alpine region.  
16  
17 54 • This study sought to evaluate whether the efficacy and tolerability of linaclotide that was  
18  
19 55 demonstrated in randomized clinical trials could be recapitulated in clinical practice in a real-  
20  
21 56 world setting.  
22  
23 57 • Results from the physicians' global assessment of efficacy and tolerability will be useful in  
24  
25 58 determining physician comfort level with prescribing linaclotide for their patients.  
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28 59 • This was a non-interventional study that lacked a placebo control; thus, the statistical  
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30 60 analyses are descriptive and exploratory in nature.  
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## 61 INTRODUCTION

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

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

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

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3 86 Linaclotide was demonstrated to increase colonic transit and reduce abdominal pain and  
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5 87 constipation in patients with IBS-C in Phase II trials.[11,12] Subsequently, the efficacy and  
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7 88 safety of linaclotide for the treatment of IBS-C was established in two placebo-controlled Phase  
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9 89 III trials that showed improvements in IBS-C symptoms, including abdominal pain and bowel  
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11 90 movements.[9,13]  
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14 91 Linaclotide was approved by the Food and Drug Administration (FDA) and European Medicines  
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16 92 Agency in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C.[14,15]  
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18 93 While the efficacy and safety of linaclotide has been established in clinical trial settings, these  
19  
20 94 may not depict real-life experiences. To address this need, observational studies were  
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22 95 undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in  
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24 96 Europe. In routine clinical practice, linaclotide has recently been shown to be effective in  
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26 97 improving IBS-C symptoms in a post-marketing authorization study conducted in Germany.[16]  
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28 98 Herein, we aimed to document the effectiveness and safety of linaclotide for the treatment of  
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30 99 moderate-to-severe IBS-C in adults under real-life conditions in the Alpine region of Austria and  
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32 100 Switzerland.  
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## 36 101 **METHODS**

### 37 102 ***Study design***

38  
39 103 This was a multicenter, non-interventional study (NIS) evaluating the effectiveness and safety of  
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41 104 linaclotide for the treatment of moderate-to-severe IBS-C, in adult patients under real-life routine  
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43 105 clinical practice conditions in Austria and Switzerland. A total of 200 patients were planned for  
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45 106 enrollment across 40 sites in each country. The study was conducted from December 2013 to  
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47 107 March 2015 in Austria and from November 2014 to November 2015 in Switzerland.  
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52 108 The study comprised a 4-week treatment period commencing with visit 1 at treatment initiation  
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54 109 and visit 2 occurring approximately 4 weeks after initiation in Austria. In Switzerland, data were  
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3 110 collected over the course of three visits, at 0, 4, and 16 weeks after treatment initiation.  
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5 111 Linaclotide was administered per the usual therapeutic procedure of the attending physician and  
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7 112 in accordance with the indication for the drug (290 µg once daily, taken at least 30 minutes  
8  
9 113 before meals).[15]  
10  
11  
12 114 The study protocols were approved by the local Institutional Review Board or Independent  
13  
14 115 Ethics Committee of each center (study approval numbers: Austria, 26-279 ex 13/14;  
15  
16 116 Switzerland, KEK-ZH-Nr.2014-0137). The study was conducted in accordance with the  
17  
18 117 Declaration of Helsinki, applicable local laws and regulations, and International Conference on  
19  
20 118 Harmonisation E6 Good Clinical Practice guidelines. All participants provided written informed  
21  
22 119 consent prior to study initiation.  
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24

### 25 120 **Participants**

26 121 Eligible patients were aged  $\geq 18$  years with a diagnosis of moderate-to-severe IBS-C (diagnosed  
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28 122 by the treating physician), characterized by clinical evidence of relevant interference of  
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30 123 symptoms with well-being and/or daily routines at work or during leisure. The decision to treat a  
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32 124 patient with linaclotide was made solely by the treating physician prior to inclusion in the study.  
33  
34 125 Patients with known hypersensitivity to the active ingredient or any other component of  
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36 126 linaclotide, suspected or known GI obstruction, or who were pregnant or planning to become  
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38 127 pregnant were excluded from the study.  
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### 42 128 **Study assessments**

43 129 All relevant data collected during routine treatment with linaclotide were recorded in case report  
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45 130 forms. Patient demographics and medical history were collected, including diagnosis, prior  
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47 131 treatment, and symptoms of IBS-C, comorbidities, and concomitant medications.  
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51 132 The primary effectiveness endpoints included severity of abdominal pain and bloating,  
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53 133 frequency of bowel movements during the week before each visit, general symptom  
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55 134 improvement relative to pre-treatment, physicians' satisfaction with linaclotide therapy,  
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3 135 sensation of incomplete bowel evacuation, change in predominant stool consistency, and  
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5 136 physicians' global assessment of the effectiveness of linaclotide. Changes in the severity of  
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7 137 abdominal pain and bloating were measured using an 11-point numeric rating scale (NRS; 0=no  
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9 138 pain/bloating to 10=worst possible pain/bloating). Physicians' satisfaction with linaclotide  
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11 139 therapy was measured using a 10-point NRS (0=very satisfied to 10=totally unsatisfied).  
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13 140 General symptom improvement and improvement in three individual symptoms – abdominal  
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15 141 pain, bloating, and constipation – were measured by patient response to simple yes/no  
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17 142 questions asked by the physician (e.g., "Have symptoms improved over the last week compared  
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19 143 to the time prior to therapy start?"). Frequency of bowel movements during the week before  
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21 144 each visit, sensation of incomplete bowel evacuation, and change in predominant stool  
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23 145 consistency were patient-reported.

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25  
26 146 Adverse events (AEs) related to linaclotide treatment or whose relation to linaclotide treatment  
27  
28 147 could not be excluded were documented. AEs assessed by the physician as not related to  
29  
30 148 linaclotide treatment were not documented. Other safety measures included physicians' global  
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32 149 assessment of the tolerability of linaclotide.

### 33 34 35 36 150 **Statistical analyses**

37  
38 151 Statistical analysis was performed using SAS™ v9.4 software (SAS Institute, Cary, NC). Data  
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40 152 were analyzed using descriptive statistics and no hypotheses were pre-specified. To determine  
41  
42 153 whether the pre–post changes of symptoms were statistically significant, the Wilcoxon signed-  
43  
44 154 rank test was applied. Reported *p*-values are two-tailed, using an alpha level of 0.05 to assess  
45  
46 155 statistical significance. Missing data were imputed using the last observation carried forward  
47  
48 156 method. Visit 1 and 2 efficacy data were compiled for both countries, where applicable.

### 157 **Patient and public involvement**

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

## 161 **RESULTS**

### 162 **Patient characteristics**

163 A total of 86 patients in 22 sites and 52 patients in nine sites were enrolled in Austria and  
164 Switzerland, respectively. Baseline characteristics were generally comparable between the two  
165 countries. Of the enrolled patients, 71 (82.6%) in Austria and 40 (76.9%) in Switzerland were  
166 female, and the mean age was 51 and 49 years, respectively (**table 1**). The mean body mass  
167 index was 24 kg/m<sup>2</sup> and 23 kg/m<sup>2</sup> in each country. The average time since IBS-C diagnosis was  
168 2.1 years and 5.2 years for patients in Austria and Switzerland, respectively. At baseline, more  
169 than 90% of patients in both countries reported abdominal pain (mean intensity scores of 6.0  
170 and 5.4, respectively) and bloating (mean intensity scores of 5.8 and 5.6, respectively). Patients  
171 in both countries reported a mean of 2.1 bowel movements per week. Prior treatment for IBS-C  
172 was reported by 73 (84.9%) patients in Austria and 49 (94.2%) patients in Switzerland, mainly  
173 consisting of laxatives and dietary fibers, while 33 (38.4%) patients in Austria and 16 (30.8%)  
174 patients in Switzerland received concurrent IBS treatment. Concomitant diseases were reported  
175 by 35 (40.7%) patients in Austria and 10 (19.2%) patients in Switzerland (**table 1**). Collectively,  
176 baseline characteristics of the patients with IBS-C in this study were reflective of the general IBS  
177 patient population (i.e., approximately 70% of IBS patients are typically female, with a high  
178 likelihood of the majority of patients being ≤50 years).

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

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

### 184 ***Effectiveness outcomes***

#### 185 *Effect of linaclotide treatment on symptoms of IBS-C*

186 Linaclotide was administered over 4 weeks in Austria and 16 weeks in Switzerland, and data  
187 from the initial 4-week treatment periods are compiled in this analysis. Of the 138 enrolled  
188 patients, data were available for 128 patients at week 4. Improvements in abdominal pain,  
189 bloating, and bowel movements were observed after 4 weeks of treatment with linaclotide. From  
190 a mean intensity score of 5.8 at baseline, abdominal pain was reduced to 2.7 after 4 weeks of  
191 treatment in both countries (**figure 1A**;  $p < 0.001$  vs. visit 1; 11-point NRS [0=no pain to 10=worst  
192 possible pain]). In Switzerland, continued reduction in abdominal pain was observed at week 16,  
193 with a mean intensity score of 2.5 (standard deviation [SD] $\pm 2.0$ ;  $n = 51$ ;  $p < 0.0001$  vs. visit 1).  
194 Improvements in bloating were also seen after 4 weeks of treatment in both countries; from a  
195 baseline mean intensity score of 5.8, the bloating score was reduced to 3.1 at week 4 (**figure**  
196 **1B**;  $p < 0.001$  vs. visit 1; 11-point NRS [0=no bloating to 10=worst possible bloating]), with a  
197 mean intensity score of 3.0 (SD $\pm 2.2$ ;  $n = 51$ ;  $p < 0.0001$  vs. visit 1) at week 16 in Switzerland.  
198 Furthermore, the frequency of bowel movements increased from a mean of 2.1 per week at  
199 baseline to 4.5 at week 4 (**figure 1C**;  $p < 0.001$  vs. visit 1) in both countries, and to 4.7 (SD $\pm 1.6$ ;  
200  $n = 51$ ;  $p < 0.0001$  vs. visit 1) at week 16 in Switzerland.

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



207 who did not and those who received laxative pre-treatment (both 3.1). Furthermore, the effect of  
208 concomitant laxative use with linaclotide was evaluated. Our results showed that significant  
209 reduction was achieved after 4 weeks of treatment in mean abdominal pain intensity (**figure 3A**;  
210 all  $p < 0.001$  vs. visit 1) and mean bloating intensity (**figure 3B**; all  $p < 0.001$  vs. visit 1), both in  
211 patients who used laxative concomitantly with linaclotide and those who did not. Greater  
212 symptom improvement was observed in those who did not use concomitant treatment (mean  
213 reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9; **figure 3A** and  
214 **3B**; all differences  $p < 0.001$  vs. visit 1).

#### 215 *Patient assessment of improvement of IBS-C symptoms*

216 At each respective end-of-treatment period, patients were asked to indicate their sense of  
217 general improvement of symptoms as compared to the pre-treatment period. In Austria, 74  
218 patients (87.1%) reported overall improved symptoms, among which 56 (65.9%) patients  
219 experienced improvements in abdominal pain, 60 (70.6%) had improvements in bloating, and 65  
220 (76.5%) reported improvements in constipation at visit 2 compared to baseline (**figure 4**). In  
221 Switzerland, 45 patients (88.2%) reported overall improved symptoms, consisting of 38 (74.5%)  
222 patients with improvements in abdominal pain, 35 (68.6%) with improvements in bloating, and  
223 42 (82.4%) reporting improvements in constipation after 16 weeks of treatment compared to  
224 baseline (**figure 4**).

#### 225 *Physician assessment of satisfaction and effectiveness of linaclotide therapy*

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

231 satisfaction”, with at least 50% of the 51 total patients rated a score of  $\leq 3.0$  by their treating  
232 physicians (**figure 5A**). Furthermore, physicians assessed the global effectiveness of linaclotide  
233 treatment at the end of the treatment periods, and at visit 2, linaclotide effectiveness was  
234 evaluated as “excellent” in 33 patients (38.4%), “good” in 30 patients (34.9%), “moderate” in  
235 14 patients (16.3%), and “poor” in nine patients (10.5%) in Austria. In Switzerland, physicians  
236 assessed linaclotide effectiveness as “excellent” in 18 patients (37.5%), “good” in 21 patients  
237 (43.8%), and “moderate” in nine patients (18.8%), with the effectiveness not rated as “poor” in  
238 any patient after 16 weeks of treatment (**figure 5B**).

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

#### 248 *Use of concomitant medications*

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

## 254 **Safety and tolerability**

### 255 *Summary of adverse events*

256 Sixteen AEs were reported in 10 (11.6%) patients in Austria after 4 weeks of treatment and 15  
257 AEs were reported in 12 (23.1%) patients in Switzerland after 16 weeks of treatment (**table 4**).  
258 The most common AE was diarrhea, which occurred in six (7.0%) and eight (15.4%) patients in  
259 Austria and Switzerland, respectively. Drug ineffectiveness was reported as an AE for five  
260 (5.8%) patients in Austria and two (3.9%) patients in Switzerland. AEs leading to treatment  
261 discontinuation occurred in eight (9.3%) patients in Austria and 10 (19.2%) in Switzerland (**table**  
262 **2**). AEs leading to dose reduction occurred in two (2.3%) patients in Austria. The majority of AEs  
263 were mild or moderate in intensity, while severe AEs were reported in two patients (two events  
264 [one abdominal distension and one rectal tenesmus]; 2.3%) in Austria and four patients (five  
265 events [four diarrhea and one urge incontinence]; 7.7%) in Switzerland. An AE was considered  
266 severe if the intensity of the symptoms significantly interfered with the patient's daily activities.  
267 Of all 31 reported AEs, treatment causality was confirmed for 11 AEs reported by eight patients  
268 in Austria (9.3%) and 14 AEs reported by 12 patients in Switzerland (23.1%). No serious AEs  
269 (i.e., AEs that were life-threatening) were reported in either country over the respective 4-week  
270 or 16-week treatment periods.

### 271 *Physician assessment of linaclotide tolerability*

272 Treating physicians assessed the global tolerability of linaclotide treatment, and after 4 weeks of  
273 treatment, linaclotide tolerability was evaluated as “excellent” in 44 patients (51.2%), “good” in  
274 28 patients (32.6%), “moderate” in 11 patients (12.8%), and “poor” in three patients (3.5%) in  
275 Austria. In Switzerland, physicians assessed linaclotide tolerability as “excellent” in 24 patients  
276 (49.0%), “good” in 13 patients (26.5%), “moderate” in seven patients (14.3%), and “poor” in five  
277 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

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3 303 evaluated in a cohort of 277 patients with IBS from the PROOF cohort, where the minimal  
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5 304 clinically important difference was determined as 2.2 points or a 29.5% reduction in the  
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7 305 NRS.[19] Our findings showed that collectively, the mean intensity of abdominal pain decreased  
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9 306 from a baseline NRS level of 5.8 to 2.7 after 4 weeks of linaclotide treatment, corresponding to a  
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11 307 53% reduction in abdominal pain in both countries. In Austria, the reduction in mean abdominal  
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13 308 pain intensity score was 3.5 points (57%) at 4 weeks, while reductions of 2.2 points (41%) at 4  
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15 309 weeks and 2.9 points (53%) after 16 weeks were observed in Switzerland. These reductions are  
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17 310 consistent with those previously validated as clinically relevant change in pain intensity.[19,20]  
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21 311 In a recent NIS conducted in Germany, linaclotide treatment resulted in a reduction in mean  
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23 312 pain intensity score of 1.72 points (35%) at 4 weeks and 2.5 points (50%) at 12 months after  
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25 313 treatment initiation.[16] Data from these European real-world studies demonstrate that  
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27 314 improvements in abdominal pain are observed in linaclotide-treated patients within the first  
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29 315 month of treatment initiation and are sustained throughout the respective treatment periods.  
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31 316 Mechanistically, as a GC-C receptor agonist, linaclotide is believed to increase extracellular  
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33 317 cGMP levels, which in turn reduces the firing of pain-sensing visceral afferent fibers, resulting in  
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35 318 an analgesic effect, thus reducing abdominal pain.[21]  
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38 319 In addition to improvements in abdominal pain, significant improvements in bloating were also  
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40 320 observed following 4 weeks of treatment with linaclotide. At baseline, >94% of all patients  
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42 321 reported bloating, and an overall reduction of 2.8 points (47%) was observed after the 4-week  
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44 322 treatment period in both countries, which was sustained after 16 weeks of treatment in  
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46 323 Switzerland. Moreover, linaclotide treatment increased the mean frequency of bowel  
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48 324 movements to 4.5 times a week from a mean of 2.1 times a week at baseline in both countries.  
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50 325 These observations are in line with previous animal studies that showed that linaclotide  
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52 326 increases GI transit and fluid secretion via accumulation of intracellular cGMP in a dose-  
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54 327 dependent manner.[22]  
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3 328 At study initiation, >84% of patients in this study had received IBS-C pre-treatment, mainly  
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5 329 comprising laxatives or dietary fibers. We found that linaclotide was effective in managing  
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7 330 symptoms of patients, regardless of prior treatment or concomitant medication use. In fact, our  
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9 331 data found that a greater degree of improvement was observed in patients who did not use  
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11 332 concomitant IBS-C treatment as compared to those who used concomitant laxatives (mean  
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13 333 reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9), suggesting that  
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15 334 laxatives might interfere with the efficacy of linaclotide. Laxatives such as polyethylene glycol  
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17 335 are often used as first-line therapy for patients with IBS-C; however, their effect on  
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19 336 improvements in abdominal pain or bloating are inconsistent and may lead to exacerbation of  
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21 337 bloating, gas, and loose stools.[1,23] A recent consensus report recommended against the co-  
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23 338 administration of linaclotide with laxatives, especially at the beginning of treatment due to  
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25 339 potential diarrheal side effects, and only suggested co-administration in cases of partial  
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27 340 response to linaclotide.[2] How concomitant laxatives may impact the efficacy of linaclotide is  
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29 341 currently unclear. Osmotic laxatives may improve the frequency and consistency of bowel  
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31 342 movements, but have no impact on abdominal pain or bloating; moreover, some stimulant  
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33 343 laxatives (for which there are no randomized controlled trials [RCTs] in IBS-C) may relieve  
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35 344 chronic constipation but result in abdominal pain and cramping.[1] In real-life settings, some  
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37 345 patients may choose to add laxative treatment based on the severity of constipation, or water-  
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39 346 binding agents may be titrated with linaclotide to gradually improve stool consistency; however,  
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41 347 both of these strategies may inadvertently lessen the efficacy of linaclotide by binding excess  
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43 348 fluids. Nonetheless, the present data demonstrate that linaclotide can effectively manage IBS-C  
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45 349 symptoms irrespective of treatment history, and it does not require co-administration with other  
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47 350 IBS-C medications, specifically laxatives.  
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52 351 The results of this study support the findings from pivotal Phase III RCTs that evaluated the  
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54 352 efficacy and safety of linaclotide in IBS-C [9,13,24,25]. Two of the RCTs used the FDA's

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3 353 responder criteria of improvement of  $\geq 30\%$  from baseline in average daily worst abdominal pain  
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5 354 score and an increase of  $\geq 1$  in complete spontaneous bowel movements (CSBMs) per week. In  
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7 355 the first double-blind, placebo-controlled, 26-week study of 804 participants, 49% of patients  
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9 356 treated with linaclotide exhibited  $\geq 30\%$  improvement in abdominal pain (corresponding to a 2.1-  
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11 357 point decrease) and 48% experienced an increase of  $\geq 1$  in weekly CSBMs (corresponding to a  
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13 358 2.2-point decrease) for at least six of the 12 treatment weeks.[9] Moreover, linaclotide treatment  
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15 359 resulted in increases in spontaneous bowel movements (SBMs) per week by 3.8 and CSBMs  
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17 360 per week by 2.2. In the second pivotal multicenter, double-blind, placebo-controlled study with  
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19 361 800 patients with IBS-C treated over 12 weeks, linaclotide resulted in significant improvements  
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21 362 in abdominal pain (1.9-point worst abdominal pain improvement), bloating (1.9-point  
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23 363 improvement), SBMs per week (+3.9 frequency), and CSBMs per week (+2.3 frequency).[13] In  
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25 364 both the RCTs and the current NIS setting, improvements in IBS-C symptoms were  
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27 365 demonstrated for linaclotide immediately following therapy initiation, and were sustained  
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29 366 throughout treatment duration. Therefore, we can deduce that the NIS results under routine  
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31 367 clinical settings in Europe, including those in the current study, are in agreement with the RCT  
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33 368 findings from the US.

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37 369 Global tolerability of linaclotide treatment was assessed as “good” or “excellent” in  $>75\%$   
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39 370 patients by their treating physicians in both countries in the current study. Moreover, physician  
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41 371 satisfaction with linaclotide therapy was evaluated on a 0-10 scale (“very satisfied” to “totally  
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43 372 unsatisfied”), with scores of 2.9 (“good” satisfaction) after 4 weeks in Austria and 4.6  
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45 373 (“moderate” satisfaction) after 16 weeks in Switzerland. In comparison, 45% and 52% of  
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47 374 patients treated with linaclotide noted satisfaction with linaclotide in the two RCTs, while 62% of  
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49 375 treating physicians rated the effectiveness of linaclotide as “good” or “excellent” in Germany in a  
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51 376 recent NIS.[9,13,16] Previously, an 18-month long-term safety study demonstrated similar  
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53 377 patient satisfaction between linaclotide-treated patients who experienced diarrhea as compared  
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3 378 to those who did not, and >85% reported moderate satisfaction during the treatment period,  
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5 379 indicating a high degree of treatment satisfaction irrespective of AEs.[26]  
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8 380 Diarrhea has previously been reported as a potential consequence of linaclotide-mediated  
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10 381 increase in GI transit and fluid secretion, and as such, was the most commonly reported AE  
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12 382 during this study (7% of patients in Austria and 15% of patients in Switzerland). All events were  
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14 383 mild or moderate in severity. In the Phase III RCTs, diarrhea was reported by 19.5% of patients  
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16 384 in the study by Chey *et al.*, and by 19.7% in the study by Rao *et al.*[9,13] The discrepancy in  
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18 385 diarrhea rates between this NIS and the previous RCTs may be due to the difference in  
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20 386 reporting methods. In fact, all diarrhea AEs, regardless of treatment relatedness, were reported  
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22 387 in the two RCTs, while only adverse drug reactions were reported in this NIS. Additionally, the  
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24 388 lower incidence of adverse drug reactions reported in this NIS may be due to underreporting of  
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26 389 AEs already described in the summary of product characteristics by physicians.[27] Finally, the  
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28 390 impact of concomitant laxative use on diarrhea cannot be discounted.  
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32 391 Treatment options for IBS-C are limited, with traditional therapies showing limited effectiveness  
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34 392 in improving symptoms and quality of life, and only four pharmacologic agents are approved for  
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36 393 use. One such FDA-approved agent is lubiprostone, a chloride channel activator that was  
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38 394 shown to improve IBS-C symptoms in two RCTs; however, lubiprostone is not approved for  
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40 395 treatment in men due to limited efficacy.[28] Recently, plecanatide, a GC-C receptor agonist in  
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42 396 the same drug class as linaclotide, was approved for the treatment of IBS-C based on data from  
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44 397 two RCTs, with a comparable safety and efficacy profile as linaclotide RCTs; however, no  
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46 398 evidence from real-life clinical settings currently exists for plecanatide.[29,30] Another FDA-  
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48 399 approved agent for IBS-C is tegaserod, a prokinetic agent that was approved in 2002 but was  
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50 400 withdrawn from the market in 2007 due to increased cardiovascular risks.[31] The FDA recently  
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52 401 approved its reintroduction for use in adult women <65 years of age with IBS-C.[32] Overall, the  
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54 402 present data confirm RCT findings in a real-world setting, showing that linaclotide is an effective  
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3 403 and satisfactory treatment for the management of IBS-C, a disease for which there are few  
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5 404 effective therapeutic options.  
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8 405 Some limitations are associated with this study, which necessitate caution when interpreting the  
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10 406 findings. The main limitations are the sample size and differing study durations between the two  
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12 407 countries, which only allowed compilation of 4 weeks of data. Another limitation is that  
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14 408 satisfaction with linaclotide was a physician-measured outcome, as compared to a patient-  
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16 409 measured outcome in the clinical trials, which may lead to potential bias. The FDA's composite  
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18 410 primary endpoint for IBS-C (responder: improvement of  $\geq 30\%$  in average daily worst abdominal  
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20 411 pain score and increase of  $\geq 1$  CSBMs from baseline, both in the same week for at least 50% of  
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22 412 weeks assessed) was used in the two clinical trials of linaclotide to determine efficacy.[9,13] In  
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24 413 the present study, the lack of a composite primary endpoint may have led to inflation in the  
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26 414 efficacy of linaclotide when compared to the clinical trials. As the diagnosis of moderate-to-  
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28 415 severe IBS-C was determined by the treating physician without strict diagnosis criteria, selection  
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30 416 bias may have occurred. In addition, as this was an NIS without a placebo control, the statistical  
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32 417 analyses are descriptive and explorative, and no statistical hypotheses were pre-specified.  
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34 418 Nevertheless, to the best of our knowledge, no real-world studies have been conducted  
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36 419 evaluating IBS-C treatments in the Alpine region, and observational studies were thus  
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38 420 undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in  
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40 421 various European countries, with data recently published from Sweden,[33] the UK,[34] and  
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42 422 Germany.[16] Our current findings suggest that linaclotide is safe and effective in reducing  
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44 423 major symptoms of IBS-C in routine clinical practice in Austria and Switzerland. These data  
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46 424 confirm the previously reported results from two randomized Phase III clinical trials that  
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48 425 collectively demonstrate the efficacy and safety of linaclotide treatment for the management of  
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50 426 patients with IBS-C with moderate-to-severe abdominal symptoms.  
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525 **TABLES**526 **Table 1** Patient baseline demographics and characteristics

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
Female, n (%)	71 (82.6)	40 (76.9)
Mean age, years	51.3	49.2
Mean BMI, kg/m <sup>2</sup>	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)
<b>Laxatives, n (%)</b>	22 (25.6)	13 (25.0)
<b>Osmotic, n (%)</b>	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)
<b>Bulk-forming, n (%)</b>	0	5 (9.6)
Sterculia	0	4 (7.7)
Ispaghula (psylla seeds)	0	1 (1.9)
<b>Stimulant, n (%)</b>	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

Pohl *et al.*, Linaclotide in IBS-C – The Alpine Study

<b>Stimulant/stool softener, n (%)</b>	0	2 (3.9)
Glycerol	0	2 (3.9)
<b>Stool softener, n (%)</b>	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 ( $\pm$ 2.1)	5.4 ( $\pm$ 2.7)
Patients experiencing bloating at baseline, n (%)	81 (95.3)	48 (94.1)
Mean intensity score of bloating at baseline (SD)	5.8 ( $\pm$ 2.4)	5.6 ( $\pm$ 2.7)
Mean number of bowel movements/week (SD)	2.1 ( $\pm$ 1.3)	2.1 ( $\pm$ 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)

527 % are calculated from total number of patients providing data for that outcome. Laxatives reported by type and chemical substance.

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

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



530 **Table 2** Reasons for discontinuing linaclotide

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
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)

531 Austria: Seven patients reported two reasons each.

532 Switzerland: Four patients reported two reasons each.

533 **Table 3** Use of concomitant medications

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
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)

534 Concomitant medications reported by anatomical main group.

535 **Table 4** Summary of safety

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
Total AEs	16	15
Serious AEs	0	0
Patients with $\geq 1$ 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)

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

537 \*Two abdominal distension events reported for one patient.

538 AE, adverse event.

**539 FIGURE LEGENDS**

540 **Figure 1** Effect of linaclotide treatment on (A) abdominal pain, (B) bloating, and (C) frequency of  
541 bowel movements in all patients. Visit 1 and visit 2 refer to baseline and week 4, respectively.

542  $**p < 0.001$  versus visit 1, assessed by Wilcoxon signed-rank test.

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

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

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

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

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559 participants and their families, study investigators, research coordinators, and study staff.

**560 AUTHOR CONTRIBUTIONS**

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

**566 DISCLOSURES**

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

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

**575 DATA AVAILABILITY**

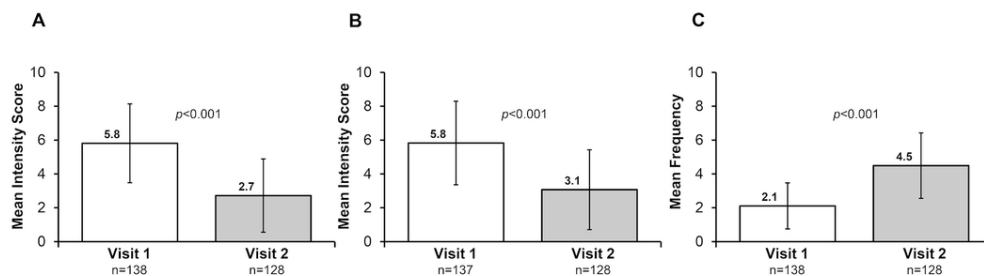
576 Data reported in this manuscript are available within the article. Allergan will share de-identified  
577 patient-level and/or study-level data, including protocols and clinical study reports, for Phase II–  
578 IV trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT.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

Pohl *et al.*, Linaclotide in IBS-C – The Alpine Study

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2  
3 580 European Union and the primary manuscript from the trial must be published prior to data  
4  
5 581 sharing. To request access to the data, the researcher must sign a data use agreement. All  
6  
7 582 shared data are to be used for non-commercial purposes only. More information can be found  
8  
9 583 on <http://www.allerganclinicaltrials.com/>.

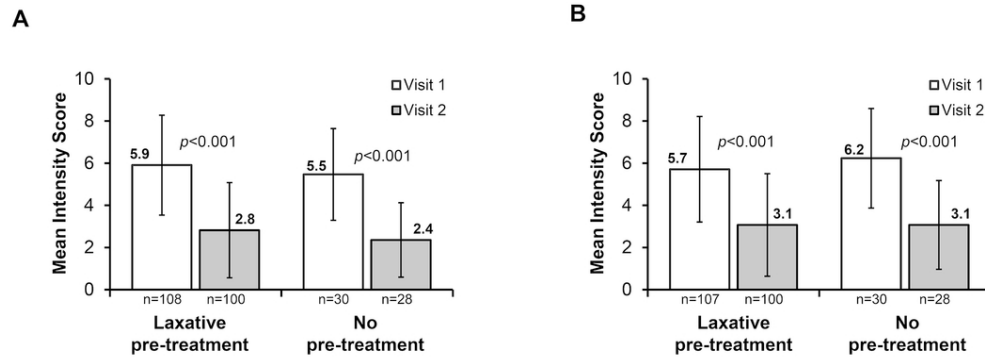
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For peer review only



**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.

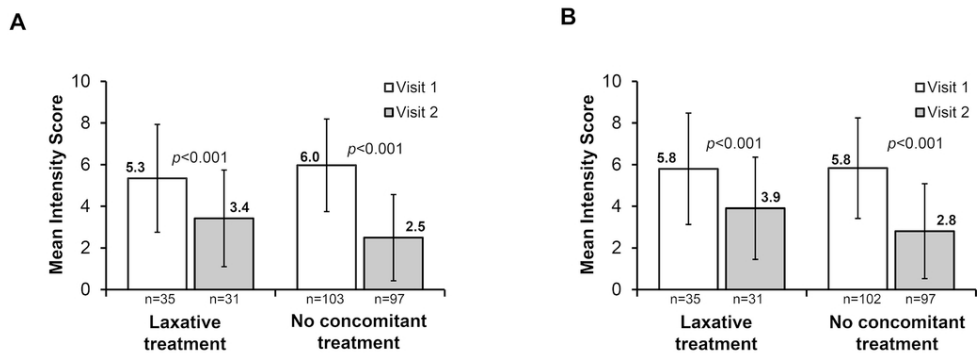
90x25mm (300 x 300 DPI)



**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.

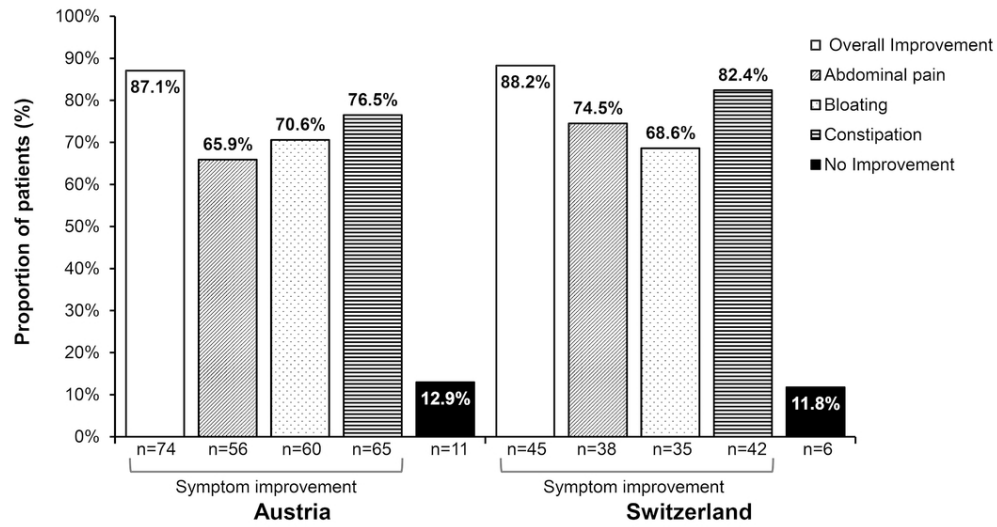
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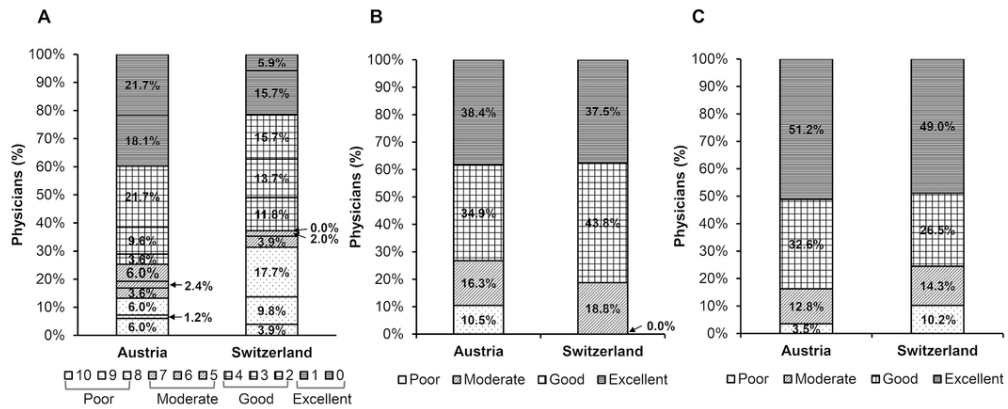
**Figure 3** Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. \*\* $p < 0.001$  versus visit 1, assessed by Wilcoxon signed-rank test.

90x32mm (300 x 300 DPI)



**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].

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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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://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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<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Gastroenterology and hepatology
Keywords:	Irritable bowel syndrome-constipation, linaclotide, real world evidence, non-interventional study, abdominal pain, bloating

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Manuscripts

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4 1 **TITLE PAGE**5  
6  
7 2 **A Multicenter, Non-Interventional Study of the Efficacy and Tolerability of Linaclotide in**  
8 3 **the Treatment of Irritable Bowel Syndrome with Constipation in Primary, Secondary, and**  
9 4 **Tertiary Centers: The Alpine study**  
10  
11 5 -----12  
13 6 **Running Title:** Linaclotide in IBS-C – The Alpine study14  
15  
16 7 Daniel Pohl<sup>1</sup>, Michael Fried<sup>1</sup>, Dominic Lawrance<sup>2</sup>, Elmar Beck<sup>3</sup>, Heinz F. Hammer<sup>4</sup>18  
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46 23 **Keywords:** Irritable bowel syndrome-constipation; IBS-C; linaclotide; real world evidence; non-47  
48 24 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  $\geq 18$  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.

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3 48 **Conclusions:** Patients with IBS-C receiving linaclotide experienced effective treatment of  
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5 49 moderate-to-severe symptoms in routine clinical practice. Linaclotide was safe and well  
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7 50 tolerated and no new safety concerns were raised, supporting results from previous clinical  
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9 51 trials.

## 52 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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

## 62 INTRODUCTION

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

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

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

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3 87 Linaclotide was demonstrated to increase colonic transit and reduce abdominal pain and  
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5 88 constipation in patients with IBS-C in Phase II trials.[11,12] Subsequently, the efficacy and  
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7 89 safety of linaclotide for the treatment of IBS-C was established in two placebo-controlled Phase  
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9 90 III trials that showed improvements in IBS-C symptoms, including abdominal pain and bowel  
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11 91 movements.[9,13]  
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14 92 Linaclotide was approved by the Food and Drug Administration (FDA) and European Medicines  
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16 93 Agency in 2012 for the symptomatic treatment of adults with moderate-to-severe IBS-C.[14,15]  
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18 94 While the efficacy and safety of linaclotide has been established in clinical trial settings, these  
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20 95 may not depict real-life experiences. To address this need, observational studies were  
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22 96 undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in  
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24 97 Europe. In routine clinical practice, linaclotide has recently been shown to be effective in  
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26 98 improving IBS-C symptoms in a post-marketing authorization study conducted in Germany.[16]  
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28 99 Herein, we aimed to document the effectiveness and safety of linaclotide for the treatment of  
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30 100 moderate-to-severe IBS-C in adults under real-life conditions in the Alpine region of Austria and  
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32 101 Switzerland.  
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## 36 102 **METHODS**

### 39 103 ***Study design***

40 104 This was a multicenter, open, observational, non-interventional study (NIS) evaluating the  
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42 105 effectiveness and safety of linaclotide for the treatment of moderate-to-severe IBS-C, in adult  
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44 106 patients under real-life routine clinical practice conditions in Austria and Switzerland. There were  
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46 107 no treatment groups or actions to which patients were randomly assigned. A total of 200  
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48 108 patients were planned for enrollment across 40 sites in each country. The study was conducted  
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50 109 from December 2013 to March 2015 in Austria and from November 2014 to November 2015 in  
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52 110 Switzerland.  
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3 111 The study comprised a 4-week treatment period commencing with visit 1 at treatment initiation  
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5 112 and visit 2 occurring approximately 4 weeks after initiation in Austria. In Switzerland, data were  
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7 113 collected over the course of three visits, at 0, 4, and 16 weeks after treatment initiation.  
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9 114 Linaclotide was administered per the usual therapeutic procedure of the attending physician and  
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11 115 in accordance with the indication for the drug (290 µg once daily, taken at least 30 minutes  
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13 116 before meals).[15]  
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15  
16 117 The study protocols were approved by the local Institutional Review Board or Independent  
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18 118 Ethics Committee of each center (study approval numbers: Austria, 26-279 ex 13/14;  
19  
20 119 Switzerland, KEK-ZH-Nr.2014-0137). The study was conducted in accordance with the  
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22 120 Declaration of Helsinki, applicable local laws and regulations, and International Conference on  
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24 121 Harmonisation E6 Good Clinical Practice guidelines. All participants provided written informed  
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26 122 consent prior to study initiation.  
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### 30 **Participants**

31 124 Eligible patients were aged ≥18 years with a diagnosis of moderate-to-severe IBS-C (diagnosed  
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33 125 by the treating physician), characterized by clinical evidence of relevant interference of  
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35 126 symptoms with well-being and/or daily routines at work or during leisure. The decision to treat a  
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37 127 patient with linaclotide was made solely by the treating physician prior to inclusion in the study.  
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39 128 Patients with known hypersensitivity to the active ingredient or any other component of  
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41 129 linaclotide, suspected or known GI obstruction, or who were pregnant or planning to become  
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43 130 pregnant were excluded from the study.  
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### 47 **Study assessments**

48 132 All relevant data collected during routine treatment with linaclotide were recorded in case report  
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50 133 forms. Patient demographics and medical history were collected, including diagnosis, prior  
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52 134 treatment, and symptoms of IBS-C, comorbidities, and concomitant medications.  
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3 135 The primary effectiveness endpoints included severity of abdominal pain and bloating,  
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5 136 frequency of bowel movements during the week before each visit, general symptom  
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7 137 improvement relative to pre-treatment, physicians' satisfaction with linaclotide therapy,  
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9 138 sensation of incomplete bowel evacuation, change in predominant stool consistency, and  
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11 139 physicians' global assessment of the effectiveness of linaclotide. Changes in the severity of  
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13 140 abdominal pain and bloating were measured using an 11-point numeric rating scale (NRS; 0=no  
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15 141 pain/bloating to 10=worst possible pain/bloating). Physicians' satisfaction with linaclotide  
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17 142 therapy was measured using a 10-point NRS (0=very satisfied to 10=totally unsatisfied).  
18  
19 143 General symptom improvement and improvement in three individual symptoms – abdominal  
20  
21 144 pain, bloating, and constipation – were measured by patient response to simple yes/no  
22  
23 145 questions asked by the physician (e.g., "Have symptoms improved over the last week compared  
24  
25 146 to the time prior to therapy start?"). Frequency of bowel movements during the week before  
26  
27 147 each visit, sensation of incomplete bowel evacuation, and change in predominant stool  
28  
29 148 consistency were patient-reported.  
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31  
32  
33 149 Adverse events (AEs) related to linaclotide treatment or whose relation to linaclotide treatment  
34  
35 150 could not be excluded were documented. AEs assessed by the physician as not related to  
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37 151 linaclotide treatment were not documented. Other safety measures included physicians' global  
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39 152 assessment of the tolerability of linaclotide.  
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### 42 153 **Statistical analyses**

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44 154 Statistical analysis was performed using SAS™ v9.4 software (SAS Institute, Cary, NC). Data  
45  
46 155 were analyzed using descriptive statistics and no hypotheses were pre-specified. To determine  
47  
48 156 whether the pre–post changes of symptoms were statistically significant, the Wilcoxon signed-  
49  
50 157 rank test was applied. Reported *p*-values are two-tailed, using an alpha level of 0.05 to assess  
51  
52 158 statistical significance. Missing data were imputed using the last observation carried forward  
53  
54 159 method. Visit 1 and 2 efficacy data were compiled for both countries, where applicable.  
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## 160 **Patient and public involvement**

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

## 164 **RESULTS**

### 165 **Patient characteristics**

166 A total of 86 patients in 22 sites and 52 patients in nine sites were enrolled in Austria and  
167 Switzerland, respectively. Baseline characteristics were generally comparable between the two  
168 countries. Of the enrolled patients, 71 (82.6%) in Austria and 40 (76.9%) in Switzerland were  
169 female, and the mean age was 51 and 49 years, respectively (**table 1**). The mean body mass  
170 index was 24 kg/m<sup>2</sup> and 23 kg/m<sup>2</sup> in each country. The average time since IBS-C diagnosis was  
171 2.1 years and 5.2 years for patients in Austria and Switzerland, respectively. At baseline, more  
172 than 90% of patients in both countries reported abdominal pain (mean intensity scores of 6.0  
173 and 5.4, respectively) and bloating (mean intensity scores of 5.8 and 5.6, respectively). Patients  
174 in both countries reported a mean of 2.1 bowel movements per week. Prior treatment for IBS-C  
175 was reported by 73 (84.9%) patients in Austria and 49 (94.2%) patients in Switzerland, mainly  
176 consisting of laxatives and dietary fibers, while 33 (38.4%) patients in Austria and 16 (30.8%)  
177 patients in Switzerland received concurrent IBS treatment. Concomitant diseases were reported  
178 by 35 (40.7%) patients in Austria and 10 (19.2%) patients in Switzerland (**table 1**). Collectively,  
179 baseline characteristics of the patients with IBS-C in this study were reflective of the general IBS  
180 patient population (i.e., approximately 70% of IBS patients are typically female, with a high  
181 likelihood of the majority of patients being ≤50 years).

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

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3 184 lack of effectiveness for 13 (15.1%) patients in Austria and adverse events in Switzerland,  
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5 185 reported in 10 (19.2%) patients. Reasons for treatment discontinuation are summarized in  
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7 186 **table 2.**  
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## 10 187 **Effectiveness outcomes**

### 11 188 *Effect of linaclotide treatment on symptoms of IBS-C*

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14 189 Linaclotide was administered over 4 weeks in Austria and 16 weeks in Switzerland, and data  
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16 190 from the initial 4-week treatment periods are compiled in this analysis. Of the 138 enrolled  
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18 191 patients, data were available for 128 patients at week 4. Improvements in abdominal pain,  
19  
20 192 bloating, and bowel movements were observed after 4 weeks of treatment with linaclotide. From  
21  
22 193 a mean intensity score of 5.8 at baseline, abdominal pain was reduced to 2.7 after 4 weeks of  
23  
24 194 treatment in both countries (**figure 1A**;  $p < 0.001$  vs. visit 1; 11-point NRS [0=no pain to 10=worst  
25  
26 195 possible pain]). In Switzerland, continued reduction in abdominal pain was observed at week 16,  
27  
28 196 with a mean intensity score of 2.5 (standard deviation [SD] $\pm 2.0$ ;  $n=51$ ;  $p < 0.0001$  vs. visit 1).  
29  
30 197 Improvements in bloating were also seen after 4 weeks of treatment in both countries; from a  
31  
32 198 baseline mean intensity score of 5.8, the bloating score was reduced to 3.1 at week 4 (**figure**  
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34 199 **1B**;  $p < 0.001$  vs. visit 1; 11-point NRS [0=no bloating to 10=worst possible bloating]), with a  
35  
36 200 mean intensity score of 3.0 (SD $\pm 2.2$ ;  $n=51$ ;  $p < 0.0001$  vs. visit 1) at week 16 in Switzerland.  
37  
38 201 Furthermore, the frequency of bowel movements increased from a mean of 2.1 per week at  
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40 202 baseline to 4.5 at week 4 (**figure 1C**;  $p < 0.001$  vs. visit 1) in both countries, and to 4.7 (SD $\pm 1.6$ ;  
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42 203  $n=51$ ;  $p < 0.0001$  vs. visit 1) at week 16 in Switzerland.  
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47 204 Data were stratified based on patients who received prior IBS-C treatment, and improvements in  
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49 205 IBS-C symptoms were observed within the 4-week treatment period, regardless of prior IBS-C  
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51 206 treatment. Significant reductions from week 1 to week 4 in mean abdominal pain intensity and  
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53 207 mean bloating intensity were seen in patients who had received laxative pre-treatment and in  
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55 208 those who did not receive prior IBS-C treatment (**figure 2A** and **figure 2B**, respectively; all  
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209  $p<0.001$  vs. visit 1). Similar degrees of mean reduction in abdominal pain were seen in patients  
210 who did not and those who received laxative pre-treatment (both 3.1). Furthermore, the effect of  
211 concomitant laxative use with linaclotide was evaluated. Our results showed that significant  
212 reduction was achieved after 4 weeks of treatment in mean abdominal pain intensity (**figure 3A**;  
213 all  $p<0.001$  vs. visit 1) and mean bloating intensity (**figure 3B**; all  $p<0.001$  vs. visit 1), both in  
214 patients who used laxative concomitantly with linaclotide and those who did not. Greater  
215 symptom improvement was observed in those who did not use concomitant treatment (mean  
216 reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9; **figure 3A** and  
217 **3B**; all differences  $p<0.001$  vs. visit 1).

#### 218 *Patient assessment of improvement of IBS-C symptoms*

219 At each respective end-of-treatment period, patients were asked to indicate their sense of  
220 general improvement of symptoms as compared to the pre-treatment period. In Austria, 74  
221 patients (87.1%) reported overall improved symptoms, among which 56 (65.9%) patients  
222 experienced improvements in abdominal pain, 60 (70.6%) had improvements in bloating, and 65  
223 (76.5%) reported improvements in constipation at visit 2 compared to baseline (**figure 4**). In  
224 Switzerland, 45 patients (88.2%) reported overall improved symptoms, consisting of 38 (74.5%)  
225 patients with improvements in abdominal pain, 35 (68.6%) with improvements in bloating, and  
226 42 (82.4%) reporting improvements in constipation after 16 weeks of treatment compared to  
227 baseline (**figure 4**).

#### 228 *Physician assessment of satisfaction and effectiveness of linaclotide therapy*

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

233 was 4.6 (SD±3.2; median 3.0) points after 16 weeks of treatment, indicative of “moderate  
234 satisfaction”, with at least 50% of the 51 total patients rated a score of ≤3.0 by their treating  
235 physicians (**figure 5A**). Furthermore, physicians assessed the global effectiveness of linaclotide  
236 treatment at the end of the treatment periods, and at visit 2, linaclotide effectiveness was  
237 evaluated as “excellent” in 33 patients (38.4%), “good” in 30 patients (34.9%), “moderate” in  
238 14 patients (16.3%), and “poor” in nine patients (10.5%) in Austria. In Switzerland, physicians  
239 assessed linaclotide effectiveness as “excellent” in 18 patients (37.5%), “good” in 21 patients  
240 (43.8%), and “moderate” in nine patients (18.8%), with the effectiveness not rated as “poor” in  
241 any patient after 16 weeks of treatment (**figure 5B**).

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

### 251 *Use of concomitant medications*

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

## 257 **Safety and tolerability**

### 258 *Summary of adverse events*

259 Sixteen AEs were reported in 10 (11.6%) patients in Austria after 4 weeks of treatment and 15  
260 AEs were reported in 12 (23.1%) patients in Switzerland after 16 weeks of treatment (**table 4**).  
261 The most common AE was diarrhea, which occurred in six (7.0%) and eight (15.4%) patients in  
262 Austria and Switzerland, respectively. Drug ineffectiveness was reported as an AE for five  
263 (5.8%) patients in Austria and two (3.9%) patients in Switzerland. AEs leading to treatment  
264 discontinuation occurred in eight (9.3%) patients in Austria and 10 (19.2%) in Switzerland (**table**  
265 **2**). AEs leading to dose reduction occurred in two (2.3%) patients in Austria. The majority of AEs  
266 were mild or moderate in intensity, while severe AEs were reported in two patients (two events  
267 [one abdominal distension and one rectal tenesmus]; 2.3%) in Austria and four patients (five  
268 events [four diarrhea and one urge incontinence]; 7.7%) in Switzerland. An AE was considered  
269 severe if the intensity of the symptoms significantly interfered with the patient's daily activities.  
270 Of all 31 reported AEs, treatment causality was confirmed for 11 AEs reported by eight patients  
271 in Austria (9.3%) and 14 AEs reported by 12 patients in Switzerland (23.1%). No serious AEs  
272 (i.e., AEs that were life-threatening) were reported in either country over the respective 4-week  
273 or 16-week treatment periods.

### 274 *Physician assessment of linaclotide tolerability*

275 Treating physicians assessed the global tolerability of linaclotide treatment, and after 4 weeks of  
276 treatment, linaclotide tolerability was evaluated as “excellent” in 44 patients (51.2%), “good” in  
277 28 patients (32.6%), “moderate” in 11 patients (12.8%), and “poor” in three patients (3.5%) in  
278 Austria. In Switzerland, physicians assessed linaclotide tolerability as “excellent” in 24 patients  
279 (49.0%), “good” in 13 patients (26.5%), “moderate” in seven patients (14.3%), and “poor” in five  
280 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

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3 306 cohort, where the minimal clinically important difference was determined as 2.2 points or a  
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5 307 29.5% reduction in the NRS.[19] Our findings showed that collectively, the mean intensity of  
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7 308 abdominal pain decreased from a baseline NRS level of 5.8 to 2.7 after 4 weeks of linaclotide  
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9 309 treatment, corresponding to a 53% reduction in abdominal pain in both countries. In Austria, the  
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11 310 reduction in mean abdominal pain intensity score was 3.5 points (57%) at 4 weeks, while  
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13 311 reductions of 2.2 points (41%) at 4 weeks and 2.9 points (53%) after 16 weeks were observed in  
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15 312 Switzerland. These reductions are consistent with those previously validated as clinically  
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17 313 relevant change in pain intensity.[19,20]

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20 314 In a recent NIS conducted in Germany, linaclotide treatment resulted in a reduction in mean  
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22 315 pain intensity score of 1.72 points (35%) at 4 weeks and 2.5 points (50%) at 12 months after  
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24 316 treatment initiation.[16] Data from these European real-world studies demonstrate that  
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26 317 improvements in abdominal pain are observed in linaclotide-treated patients within the first  
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28 318 month of treatment initiation and are sustained throughout the respective treatment periods.  
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30 319 Mechanistically, as a GC-C receptor agonist, linaclotide is believed to increase extracellular  
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32 320 cGMP levels, which in turn reduces the firing of pain-sensing visceral afferent fibers, resulting in  
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34 321 an analgesic effect, thus reducing abdominal pain.[21]

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37 322 In addition to improvements in abdominal pain, significant improvements in bloating were also  
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39 323 observed following 4 weeks of treatment with linaclotide. At baseline, >94% of all patients  
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41 324 reported bloating, and an overall reduction of 2.8 points (47%) was observed after the 4-week  
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43 325 treatment period in both countries, which was sustained after 16 weeks of treatment in  
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45 326 Switzerland. Moreover, linaclotide treatment increased the mean frequency of bowel  
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47 327 movements to 4.5 times a week from a mean of 2.1 times a week at baseline in both countries.  
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49 328 These observations are in line with previous animal studies that showed that linaclotide  
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51 329 increases GI transit and fluid secretion via accumulation of intracellular cGMP in a dose-  
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53 330 dependent manner.[22]

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3 331 At study initiation, >84% of patients in this study had received IBS-C pre-treatment, mainly  
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5 332 comprising laxatives or dietary fibers. We found that linaclotide was effective in managing  
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7 333 symptoms of patients, regardless of prior treatment or concomitant medication use. In fact, our  
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9 334 data found that a greater degree of improvement was observed in patients who did not use  
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11 335 concomitant IBS-C treatment as compared to those who used concomitant laxatives (mean  
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13 336 reduction in abdominal pain: 3.5 vs. 1.9; mean reduction in bloating: 3.0 vs. 1.9), suggesting that  
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15 337 laxatives might interfere with the efficacy of linaclotide. Laxatives such as polyethylene glycol  
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17 338 are often used as first-line therapy for patients with IBS-C; however, their effect on  
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19 339 improvements in abdominal pain or bloating are inconsistent.[1,23] A recent consensus report  
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21 340 recommended against the co-administration of linaclotide with laxatives, especially at the  
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23 341 beginning of treatment due to potential diarrheal side effects, and only suggested co-  
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25 342 administration in cases of partial response to linaclotide.[2] How concomitant laxatives may  
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27 343 impact the efficacy of linaclotide is currently unclear. Osmotic laxatives may improve the  
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29 344 frequency and consistency of bowel movements, but have no impact on abdominal pain or  
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31 345 bloating; moreover, some stimulant laxatives (for which there are no randomized controlled trials  
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33 346 [RCTs] in IBS-C) may relieve chronic constipation but result in abdominal pain and cramping.[1]  
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35 347 In real-life settings, some patients may choose to add laxative treatment based on the severity  
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37 348 of constipation, or water-binding agents may be titrated with linaclotide to gradually improve  
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39 349 stool consistency; however, both of these strategies may inadvertently lessen the efficacy of  
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41 350 linaclotide by binding excess fluids. Nonetheless, the present data demonstrate that linaclotide  
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43 351 can effectively manage IBS-C symptoms irrespective of treatment history, and it does not  
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45 352 require co-administration with other IBS-C medications, specifically laxatives.  
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50 353 The results of this study support the findings from pivotal Phase III RCTs that evaluated the  
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52 354 efficacy and safety of linaclotide in IBS-C [9,13,24,25]. Two of the RCTs used the FDA's  
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54 355 responder criteria of improvement of  $\geq 30\%$  from baseline in average daily worst abdominal pain  
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3 356 score and an increase of  $\geq 1$  in complete spontaneous bowel movements (CSBMs) per week. In  
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5 357 the first double-blind, placebo-controlled, 26-week study of 804 participants, 49% of patients  
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7 358 treated with linaclotide exhibited  $\geq 30\%$  improvement in abdominal pain (corresponding to a 2.1-  
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9 359 point decrease) and 48% experienced an increase of  $\geq 1$  in weekly CSBMs (corresponding to a  
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11 360 2.2-point decrease) for at least six of the 12 treatment weeks.[9] Moreover, linaclotide treatment  
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13 361 resulted in increases in spontaneous bowel movements (SBMs) per week by 3.8 and CSBMs  
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15 362 per week by 2.2. In the second pivotal multicenter, double-blind, placebo-controlled study with  
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17 363 800 patients with IBS-C treated over 12 weeks, linaclotide resulted in significant improvements  
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19 364 in abdominal pain (1.9-point worst abdominal pain improvement), bloating (1.9-point  
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21 365 improvement), SBMs per week (+3.9 frequency), and CSBMs per week (+2.3 frequency).[13]  
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25 366 Global tolerability of linaclotide treatment was assessed as “good” or “excellent” in >75%  
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27 367 patients by their treating physicians in both countries in the current study. Moreover, physician  
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29 368 satisfaction with linaclotide therapy was evaluated on a 0-10 scale (“very satisfied” to “totally  
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31 369 unsatisfied”), with scores of 2.9 (“good” satisfaction) after 4 weeks in Austria and 4.6  
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33 370 (“moderate” satisfaction) after 16 weeks in Switzerland. In comparison, 45% and 52% of  
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35 371 patients treated with linaclotide noted satisfaction with linaclotide in the two RCTs, while 62% of  
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37 372 treating physicians rated the effectiveness of linaclotide as “good” or “excellent” in Germany in a  
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39 373 recent NIS.[9,13,16] Previously, an 18-month long-term safety study demonstrated similar  
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41 374 patient satisfaction between linaclotide-treated patients who experienced diarrhea as compared  
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43 375 to those who did not, and >85% reported moderate satisfaction during the treatment period,  
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45 376 indicating a high degree of treatment satisfaction irrespective of AEs.[26]  
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49 377 Diarrhea has previously been reported as a potential consequence of linaclotide-mediated  
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51 378 increase in GI transit and fluid secretion, and as such, was the most commonly reported AE  
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53 379 during this study (7% of patients in Austria and 15% of patients in Switzerland). All events were  
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55 380 mild or moderate in severity. In the Phase III RCTs, diarrhea was reported by 19.5% of patients  
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3 381 in the study by Chey *et al.*, and by 19.7% in the study by Rao *et al.*[9,13] The discrepancy in  
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5 382 diarrhea rates between this NIS and the previous RCTs may be due to the difference in  
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7 383 reporting methods. Additionally, the lower incidence of adverse drug reactions reported in this  
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9 384 NIS may be due to underreporting of AEs already described in the summary of product  
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11 385 characteristics by physicians.[27] Finally, the impact of concomitant laxative use on diarrhea  
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13 386 cannot be discounted.

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16 387 Treatment options for IBS-C are limited, with traditional therapies showing limited effectiveness  
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18 388 in improving symptoms and quality of life, and only four pharmacologic agents are approved for  
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20 389 use. One such FDA-approved agent is lubiprostone, a chloride channel activator that was  
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22 390 shown to improve IBS-C symptoms in two RCTs; however, lubiprostone is not approved for  
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24 391 treatment in men due to limited efficacy.[28] Recently, plecanatide, a GC-C receptor agonist in  
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26 392 the same drug class as linaclotide, was approved for the treatment of IBS-C based on data from  
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28 393 two RCTs, with a comparable safety and efficacy profile as linaclotide RCTs; however, no  
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30 394 evidence from real-life clinical settings currently exists for plecanatide.[29,30] Another FDA-  
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32 395 approved agent for IBS-C is tegaserod, a prokinetic agent that was approved in 2002 but was  
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34 396 withdrawn from the market in 2007 due to increased cardiovascular risks.[31] The FDA recently  
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36 397 approved its reintroduction for use in adult women <65 years of age with IBS-C.[32]

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40 398 Some limitations are associated with this study, which necessitate caution when interpreting the  
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42 399 findings. The main limitations are the sample size and differing study durations between the two  
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44 400 countries, which only allowed compilation of 4 weeks of data. Another limitation is that  
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46 401 satisfaction with linaclotide was a physician-measured outcome, as compared to a patient-  
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48 402 measured outcome in the clinical trials, which may lead to potential bias. The FDA's composite  
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50 403 primary endpoint for IBS-C (responder: improvement of  $\geq 30\%$  in average daily worst abdominal  
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52 404 pain score and increase of  $\geq 1$  CSBMs from baseline, both in the same week for at least 50% of  
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54 405 weeks assessed) was used in the two clinical trials of linaclotide to determine efficacy.[9,13] In



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3 406 the present study, the lack of a composite primary endpoint may have led to inflation in the  
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5 407 efficacy of linaclotide when compared to the clinical trials. As the diagnosis of moderate-to-  
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7 408 severe IBS-C was determined by the treating physician without strict diagnosis criteria, selection  
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9 409 bias may have occurred. In addition, as this was an NIS without a placebo control, the statistical  
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11 410 analyses are descriptive and explorative, and no statistical hypotheses were pre-specified.  
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13 411 Nevertheless, to the best of our knowledge, no real-world studies have been conducted  
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15 412 evaluating IBS-C treatments in the Alpine region, and observational studies were thus  
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17 413 undertaken to evaluate the effectiveness and safety of linaclotide in real-world settings in  
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19 414 various European countries, with data recently published from Sweden,[33] the UK,[34] and  
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21 415 Germany.[16] Our current findings suggest that linaclotide is safe and effective in reducing  
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23 416 major symptoms of IBS-C in routine clinical practice in Austria and Switzerland. These data  
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25 417 support the previously reported results from two randomized Phase III clinical trials that  
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27 418 collectively demonstrate the efficacy and safety of linaclotide treatment for the management of  
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29 419 patients with IBS-C with moderate-to-severe abdominal symptoms.  
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518 **TABLES**519 **Table 1** Patient baseline demographics and characteristics

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
Female, n (%)	71 (82.6)	40 (76.9)
Mean age, years	51.3	49.2
Mean BMI, kg/m <sup>2</sup>	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)
<b>Laxatives, n (%)</b>	22 (25.6)	13 (25.0)
<b>Osmotic, n (%)</b>	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)
<b>Bulk-forming, n (%)</b>	0	5 (9.6)
Sterculia	0	4 (7.7)
Ispaghula (psylla seeds)	0	1 (1.9)
<b>Stimulant, n (%)</b>	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

Pohl *et al.*, Linaclotide in IBS-C – The Alpine Study

<b>Stimulant/stool softener, n (%)</b>	0	2 (3.9)
Glycerol	0	2 (3.9)
<b>Stool softener, n (%)</b>	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 ( $\pm 2.1$ )	5.4 ( $\pm 2.7$ )
Patients experiencing bloating at baseline, n (%)	81 (95.3)	48 (94.1)
Mean intensity score of bloating at baseline (SD)	5.8 ( $\pm 2.4$ )	5.6 ( $\pm 2.7$ )
Mean number of bowel movements/week (SD)	2.1 ( $\pm 1.3$ )	2.1 ( $\pm 1.4$ )
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)

520 % are calculated from total number of patients providing data for that outcome. Laxatives reported by type and chemical substance.

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

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



523 **Table 2** Reasons for discontinuing linaclotide

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
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)

524 Austria: Seven patients reported two reasons each.

525 Switzerland: Four patients reported two reasons each.

526 **Table 3** Use of concomitant medications

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
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)

527 Concomitant medications reported by anatomical main group.

528 **Table 4** Summary of safety

	<b>Austria (N=86)</b>	<b>Switzerland (N=52)</b>
Total AEs	16	15
Serious AEs	0	0
Patients with $\geq 1$ 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)

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

530 \*Two abdominal distension events reported for one patient.

531 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  $2.9 \pm 3.0$  points ["good" satisfaction]; Switzerland, mean  $4.6 \pm 3.2$  points ["moderate" satisfaction].

## 550 **ACKNOWLEDGMENTS**

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## 554 **AUTHOR CONTRIBUTIONS**

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

## 560 **DISCLOSURES**

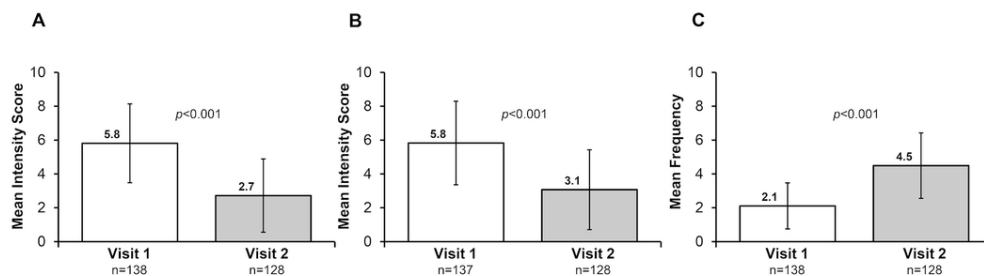
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### 565 ***Competing interest statement***

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

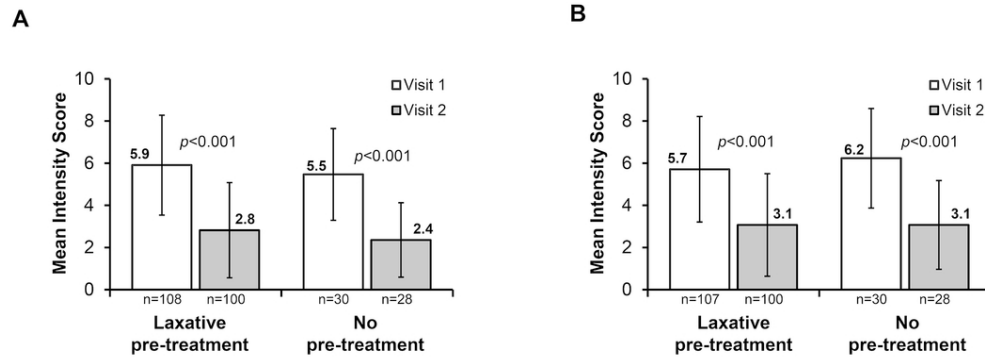
**571 DATA AVAILABILITY**

572 Data reported in this manuscript are available within the article. Allergan will share de-identified  
573 patient-level and/or study-level data, including protocols and clinical study reports, for Phase II–  
574 IV trials completed after 2008 that are registered on ClinicalTrials.gov or EudraCT. The  
575 indication studied in the trial must have regulatory approval in the United States and/or  
576 European Union and the primary manuscript from the trial must be published prior to data  
577 sharing. To request access to the data, the researcher must sign a data use agreement. All  
578 shared data are to be used for non-commercial purposes only. More information can be found  
579 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.

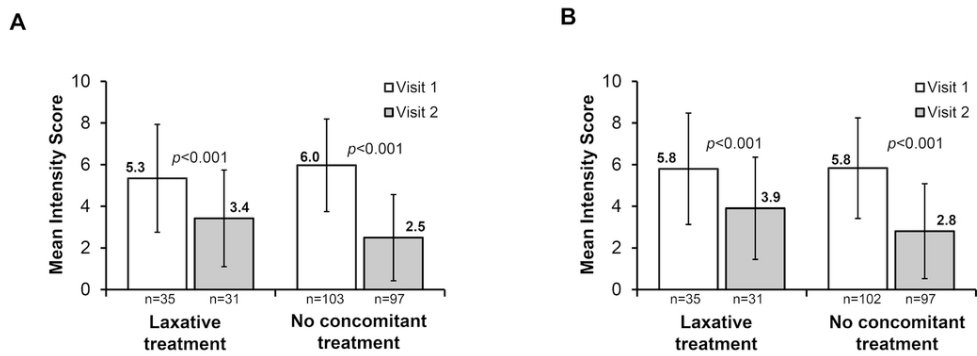
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**Figure 2** Effect of linaclotide treatment in patients with and without prior treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively.  $**p < 0.001$  versus visit 1, assessed by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

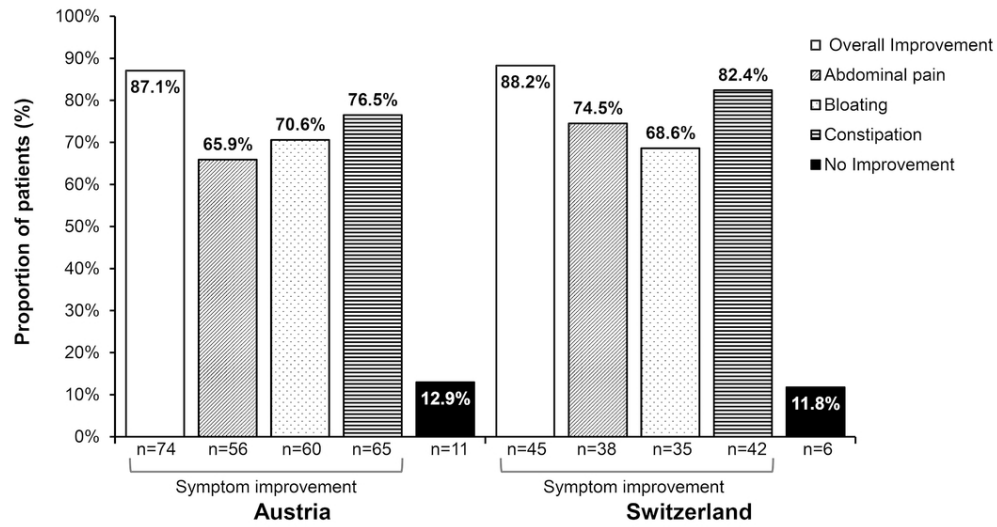
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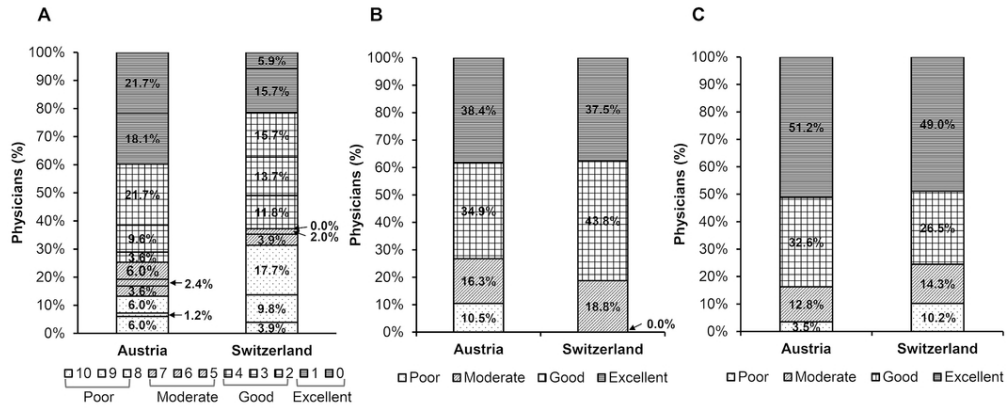
**Figure 3** Effect of linaclotide treatment in patients with and without concomitant treatment for IBS-C on (A) abdominal pain and (B) bloating. Visit 1 and visit 2 refer to baseline and week 4, respectively. \*\* $p < 0.001$  versus visit 1, assessed by Wilcoxon signed-rank test.

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**Figure 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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## 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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).