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Efficacy of Prucalopride for Chronic Idiopathic Constipation: An Analysis of Participants With Moderate to Very Severe Abdominal Bloating

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INTRODUCTION: This *post hoc* analysis evaluated the effect of prucalopride on abdominal bloating in participants with chronic idiopathic constipation (CIC) who had moderate to very severe bloating at baseline.

METHODS: Data from 6 phase 3/4 studies of prucalopride in participants with CIC were pooled. Abdominal bloating was assessed weekly using a 5-point scale (0–4).

RESULTS: The proportion of bloating responders (≥ 1 -point improvement in abdominal bloating score at week 12) was higher in participants treated with prucalopride (62.1%) vs placebo (49.6%).

DISCUSSION: The prucalopride arm had a higher proportion of bloating responders vs placebo in this study population.

SUPPLEMENTARY MATERIAL accompanies this paper at <http://links.lww.com/AJG/C227>, <http://links.lww.com/AJG/C228>, <http://links.lww.com/AJG/C229>

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INTRODUCTION

Chronic idiopathic constipation (CIC) is characterized by symptoms of difficult, infrequent, or incomplete defecation (1). Patients with CIC commonly experience abdominal bloating (2), which is often reported as one of the most bothersome symptoms (3). Approximately 30% of patients with CIC who report abdominal bloating continue to experience this symptom despite receiving prescription treatment (2). Prucalopride is a selective, high-affinity serotonin type 4 receptor agonist indicated for the treatment of CIC in adults (4,5). In addition to improving constipation-related symptoms, prucalopride also improves abdominal bloating in clinical studies of CIC (5). This correlates with improvements in the patient health-related quality of life (HRQOL) (5). This *post hoc* analysis of data from 6 clinical trials aimed to evaluate the effect of prucalopride on abdominal bloating and the HRQOL in a subset of participants with CIC with moderate to very severe bloating at baseline.

METHODS

Data from 5 phase 3 and 1 phase 4, randomized, double-blind, placebo-controlled trials of prucalopride (2 mg once daily for 12 or 24 weeks), from baseline to week 12, were pooled (ClinicalTrials.gov identifiers: NCT00488137 (6), NCT00483886 (7), NCT00485940 (8), NCT01147926 (9), NCT01116206 (10), and NCT01424228 (11)). The Patient Assessment of Constipation Symptoms questionnaire (12), which measures the severity of 12

symptoms (including abdominal bloating) using a 5-point scale (0, none; 1, mild; 2, moderate; 3, severe; and 4, very severe) was a secondary endpoint in each clinical study. The Patient Assessment of Constipation Symptoms scores were assessed at weeks 0, 2, 4, 8, and 12. Participants with a baseline (week 0) abdominal bloating score of moderate (2), severe (3), or very severe (4) were included.

The proportion of bloating responders (defined as participants with an improvement of ≥ 1 point in abdominal bloating score at week 12, compared with baseline) was assessed in the prucalopride and placebo arms. Participants without a bloating score at week 12 were considered nonresponders.

Responder analyses were performed in participants with moderate to very severe bloating at baseline. Participants were further categorized by sex, age (< 65 or ≥ 65 year old), baseline bloating score, and main complaint at baseline (defined as the most commonly reported symptom of CIC). The mean percentage change in abdominal bloating score over time was calculated, and the proportion of participants with a bloating score of 0–1 (minimal bloating) at week 12 was assessed. To evaluate the impact of abdominal bloating severity on the HRQOL, the change from baseline to week 12 in the Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire (13) overall score and subcomponent scores (physical discomfort, dissatisfaction, psychosocial discomfort, and worries and concerns) was evaluated in bloating responders and nonresponders. The PAC-QOL scores range

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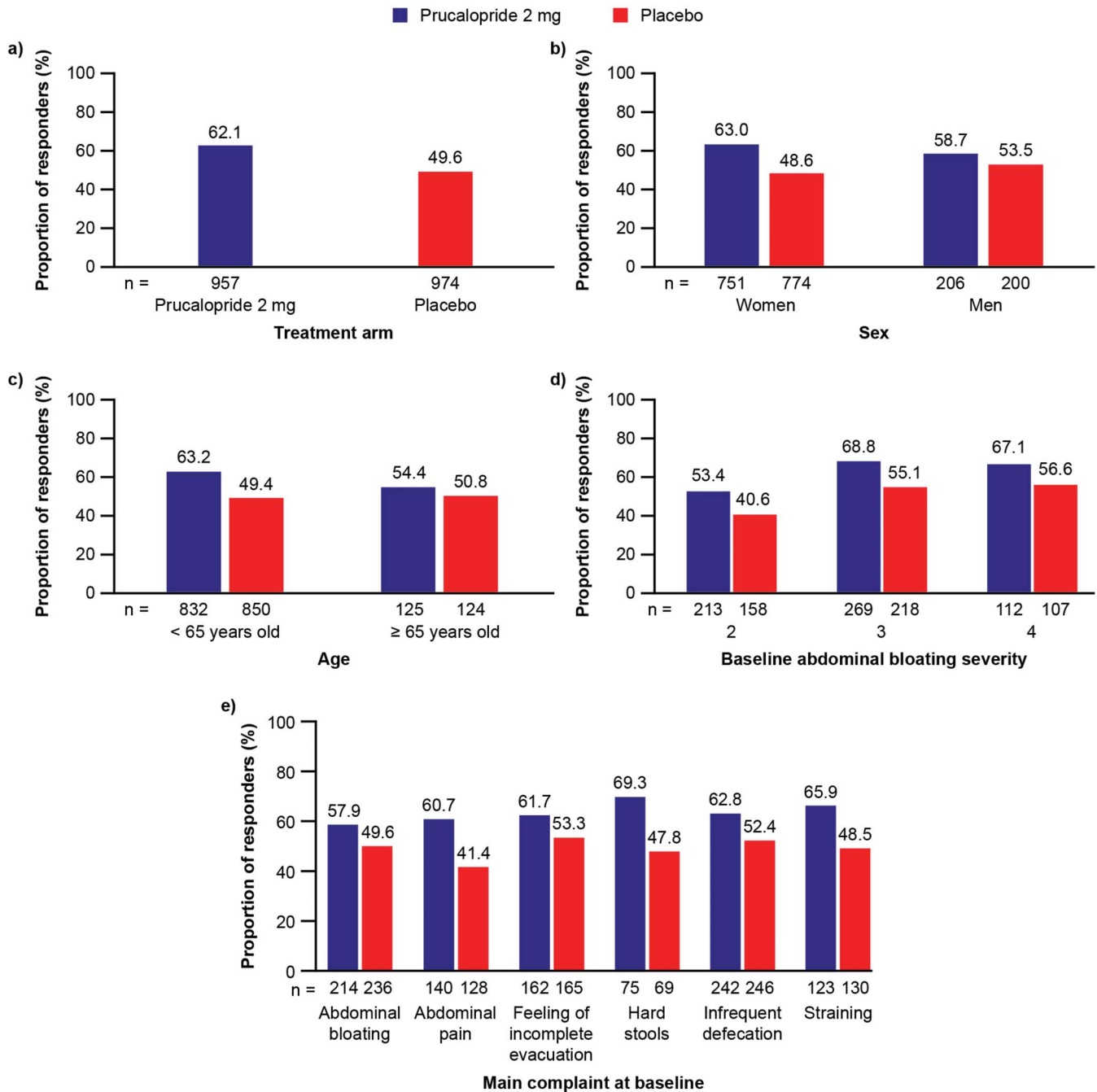


Figure 1. The proportion of abdominal bloating responders (Responders were defined as participants with an improvement of ≥ 1 point in abdominal bloating score from baseline to week 12, as measured by the PAC-SYM questionnaire) at week 12 according to (a) treatment arm, (b) sex, (c) age, (d) baseline severity of bloating (baseline bloating severity was defined according to the PAC-SYM questionnaire), and (e) main complaint at baseline. PAC-SYM, Patient Assessment of Constipation Symptoms.

from 0 to 4, with a higher score indicative of poorer HRQOL. For this analysis, each of the 6 clinical studies were also evaluated separately.

All data are descriptively reported.

RESULTS

Overall, 1,931 of 2,484 participants with CIC (77.7%; prucalopride, n = 957; placebo, n = 974) had moderate to very severe bloating at baseline with a mean (SD) bloating score of 2.8 (0.7).

Among these, most patients had a Global Severity of Constipation score of severe or very severe (65.8%, n = 1,270). Participant baseline characteristics are shown in Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/AJG/C227>.

The proportion of bloating responders at week 12 was higher in the prucalopride arm than in the placebo arm (62.1% vs 49.6%) (Figure 1). Bloating responder rates were also higher in the prucalopride arm than in the placebo arm among women (63.0% vs

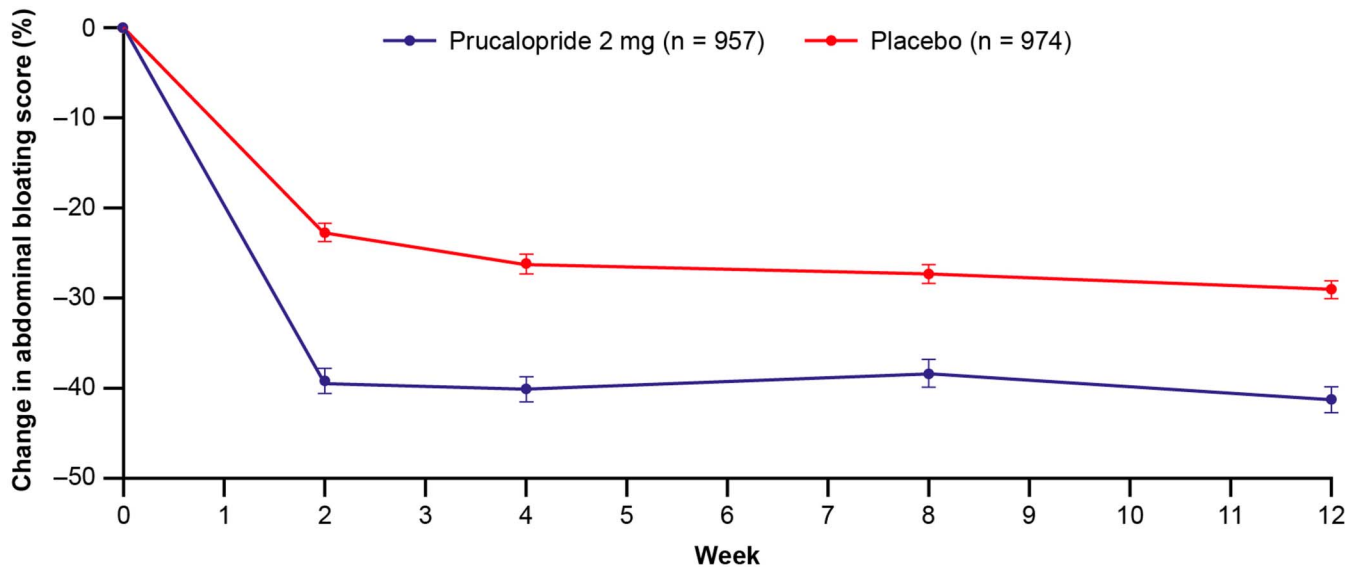


Figure 2. Percentage change in abdominal bloating score (bloating severity was measured on a 5-point scale [0–4] at baseline and weeks 2, 4, 8, and 12 using the PAC-SYM questionnaire) over time in participants with CIC who had moderate to very severe abdominal bloating at baseline. CIC, chronic idiopathic constipation; PAC-SYM, Patient Assessment of Constipation Symptoms.

48.6%), men (58.7% vs 53.5%), participants younger than 65 years of age (63.2% vs 49.4%), participants aged 65 years or older (54.4% vs 50.8%), and irrespective of main complaint at baseline (Figure 1). Differences in the proportions of responders between the prucalopride and placebo arms were comparable for participants with baseline abdominal bloating severity scores of 2, 3, and 4 (12.8%, 13.7%, and 10.5%, respectively) (Figure 1).

Improvements in abdominal bloating were observed beginning at week 2, the earliest measurement time point, and were greater in the prucalopride arm throughout the 12-week measurement period than in the placebo arm (Figure 2). Of participants with baseline bloating scores of 2, 3, or 4, 43.7% had minimal abdominal bloating (a bloating score of 0–1) by week 12 after treatment with prucalopride compared with 30.1% of those who received placebo (see Supplementary Figure 1, Supplemental Digital Content 2, <http://links.lww.com/AJG/C228>). In all 6 clinical studies, abdominal bloating responders had greater improvements at week 12 in the overall PAC-QOL score and sub-component scores than nonresponders (Figure 3). A clinically meaningful difference (>1-point decrease (14)) was observed in the overall PAC-QOL score among responders (difference of -1.1080), but not in nonresponders (difference of -0.1522).

DISCUSSION

This *post hoc* analysis demonstrated that more than 75% of participants with CIC who enrolled in phase 3/4 clinical trials of prucalopride reported at least moderate abdominal bloating at baseline. A greater proportion of participants reported improvement in abdominal bloating with prucalopride compared with placebo, irrespective of age, sex, baseline bloating severity, or main complaint at baseline. Improvements in abdominal bloating with prucalopride occurred early during treatment and were sustained throughout the 12-week treatment period. Bloating responders experienced greater improvements in the HRQOL than nonresponders across all 6 clinical studies. These data highlight the connection between relieving abdominal bloating,

the most bothersome symptom for many patients with CIC (3), and improvement in the overall HRQOL. A key consideration for future trials of patients with CIC could be the inclusion of abdominal bloating as a coprimary endpoint to ensure patient-centric CIC trials going forward.

We acknowledge the descriptive nature of these analyses as a limitation of this study and that treatment-related improvements in other CIC symptoms may have contributed to the improvements in the PAC-QOL scores. However, given the consistency of our observations and that abdominal bloating in patients with CIC is common and correlates with poor HRQOL (3), improvements in bloating may correspond to enhanced HRQOL.

Participants with CIC experiencing moderate to very severe abdominal bloating treated with prucalopride showed greater improvement in abdominal bloating symptoms than participants treated with placebo. Improvements were observed irrespective of participants' age, sex, baseline bloating severity, or main complaint at baseline and were associated with improved HRQOL.

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CONFLICTS OF INTEREST

Guarantor of the article: Kyle Staller, MD, MPH.

Specific author contributions: K.S.: contributed to the planning and conduct of the analysis, interpretation of the data and drafting of the manuscript, and has approved the final submitted draft. J.H.: contributed to the planning and conduct of the analysis, interpretation of the data and drafting of the manuscript, and has approved the final submitted draft. R.K.: contributed to the planning and conduct of the analysis, interpretation of the data and drafting of the manuscript, and has approved the final submitted draft. W.S.: contributed to the planning and conduct of the analysis, interpretation of the data and drafting of the manuscript, and has

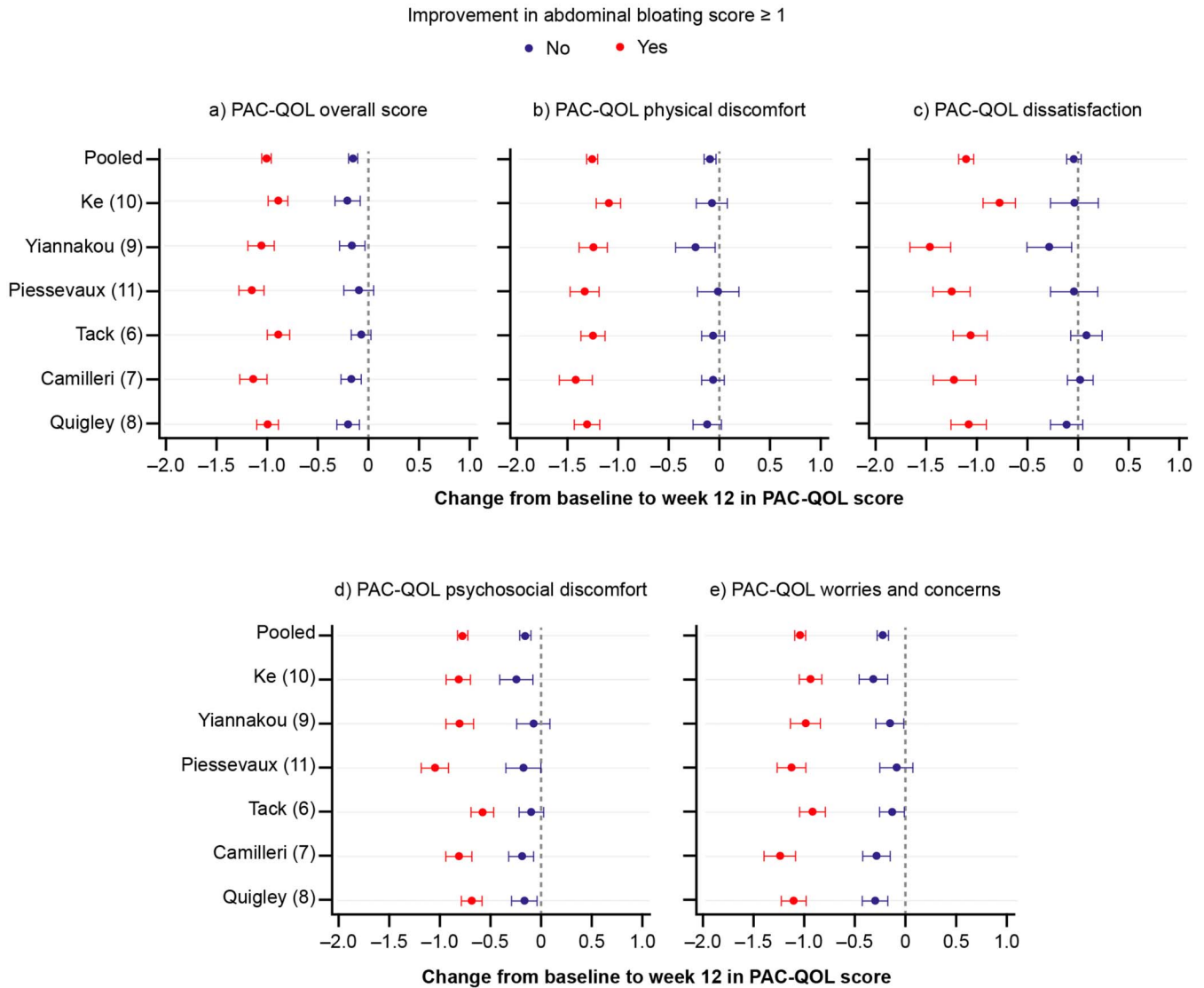


Figure 3. Change from baseline to week 12 in PAC-QOL scores in abdominal bloating responders (responders were defined as participants with an improvement of ≥ 1 point in abdominal bloating score from baseline to week 12, as measured by the PAC-SYM questionnaire) and nonresponders in pooled data from 6 trials and by individual clinical trial. PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assessment of Constipation Quality of Life.

approved the final submitted draft. A.L.: contributed to the planning and conduct of the analysis, interpretation of the data and drafting of the manuscript, and has approved the final submitted draft.

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Potential competing interests: K. Staller has received consultancy fees from Arena, Boston Pharmaceuticals, Gelesis, and Synergy; has received speaker and consultancy fees from Shire, a Takeda company; and has received research fees from AstraZeneca, Gelesis, Ironwood, and Urovant. J. Hinson is an employee of Takeda Development Centre Americas, Inc., and a stockholder of Takeda Pharmaceutical Company Limited. R. Kerstens is an employee of Orion Statistical Consulting BV, which received funding from Shire Human Genetic Therapies, Inc., a Takeda company, for this

analysis. William Spalding is an employee of Takeda Development Centre Americas, Inc, and a stockholder of Takeda Pharmaceutical Company Limited. Anthony Lembo has received research funding and consultancy fees from Shire, a Takeda company, and Takeda, Arena, Ardelyx, Ironwood, Vibrant, Mylan, Bayer, Gelesis, and Orphomed.

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